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Prehospital risk assessment in patients suspected of non-ST-segment elevation acute coronary syndrome: a systematic review and meta-analysis

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ABSTRACT

Objective To review, inventory and compare available diagnostic tools and investigate which tool has the best performance for prehospital risk assessment in patients suspected of non-ST-segment elevation acute coronary syndrome (NSTE-ACS).

Methods Systematic review and meta-analysis. Medline and Embase were searched up till 1 April 2021. Prospective studies with patients, suspected of NSTE-ACS, presenting in the primary care setting or by emergency medical services (EMS) were included. The most important exclusion criteria were studies including only patients with ST-elevation myocardial infarction and studies before 1995, the pretroponin era. The primary end point was the final hospital discharge diagnosis of NSTE-ACS or major adverse cardiac events (MACE) within 6 weeks. Risk of bias was evaluated by the Quality Assessment of Diagnostic Accuracy Studies Criteria.

Main outcome and measures Sensitivity, specificity and likelihood ratio of findings for risk stratification in patients suspected of NSTE-ACS.

Results In total, 15 prospective studies were included; these studies reflected in total 26 083 patients. No specific variables related to symptoms, physical examination or risk factors were useful in risk stratification for NSTE-ACS diagnosis. The most useful electrocardiographic finding was ST-segment depression (LR+3.85 (95% CI 2.58 to 5.76)). Point-of-care troponin was found to be a strong predictor for NSTE-ACS in primary care (LR+14.16 (95% CI 4.28 to 46.90) and EMS setting (LR+6.16 (95% CI 5.02 to 7.57)). Combined risk scores were the best for risk assessment in an NSTE-ACS. From the combined risk scores that can be used immediately in a prehospital setting, the PreHEART score, a validated combined risk score for prehospital use, derived from the HEART score (History, ECG, Age, Risk factors, Troponin), was most useful for risk stratification in patients with NSTE-ACS (LR+8.19 (95% CI 5.47 to 12.26)) and for identifying patients without ACS (LR−0.05 (95% CI 0.02 to 0.15)).

Discussion Important study limitations were verification bias and heterogeneity between studies. In the prehospital setting, several diagnostic tools have been reported which could improve risk stratification, triage and early treatment in patients suspected for NSTE-ACS. On-site assessment of troponin and combined risk scores derived from the HEART score are strong predictors. These results support further studies to investigate the impact of these new tools on logistics and clinical outcome.

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Trial registration number This meta-analysis was published for registration in PROSPERO prior to starting (CRD York, CRD42021254122).

Strengths and limitations of this study

- This systematic review and meta-analysis include all currently available prospective data on the subject of prehospital risk assessment in patients with non-ST-segment elevation acute coronary syndrome.
- Available patient characteristics and diagnostic tools (including recently developed combined risk scores and point-of-care biomarkers) are reviewed and compared in both the setting of primary care as well as emergency medical care.
- Despite strict inclusion and exclusion criteria, heterogeneity was present in our review.
- For none of the included prehospital diagnostic tools, there were prospective intervention and/or randomised controlled studies available.

INTRODUCTION

The suspicion of an acute coronary syndrome (ACS) is one of the main reasons for consultation of emergency medical care.[1–4] Depending on national and regional protocols, patients who are suspected of having an ACS are first seen in primary care by a general practitioner (GP) or by the emergency medical services (EMS). The decision to admit the suspected patient with ACS directly to a tertiary intervention centre, or to transport the patient to a local hospital for observation results from varying risk stratification methods. In general, this prehospital risk assessment and triage is mainly based on

the patient's medical history and physical examination. None or only a limited number of diagnostic tools are used in this process. Often, only an ECG is made by the EMS to rule out a ST-segment elevation myocardial infarction (STEMI). Consequently, no adequate prehospital risk assessment and triage is performed in those without ST-segment elevation on their ECG (NSTE-ACS) and are transferred to a local hospital without onsite interventional options for further diagnostic evaluation.[2]

In the recent years, in-hospital diagnostic algorithm for suspected NSTE-ACS has been developed and improved. The implementation of combined risk scores (CRSs) such as the History, ECG, Age, Risk factors, Troponin (HEART) and the Thrombolysis in Myocardial Infarction (TIMI) scores and new sensitive biomarker assays have substantially improved risk stratification, reduced the delay to diagnosis, shortened stays in the emergency departments and lowered healthcare costs.[5 6] Further improvement of care and cost reduction could be possible when these diagnostic algorithms would be applicable in the prehospital phase. The recent development of point-of-care (POC) analysers for on-site biomarker assessment has accelerated these possibilities of prehospital risk assessment in suspected patients with NSTE-ACS. Improving early risk stratification by GP or ambulance paramedics is important for several medical and economic reasons. Most importantly, due to the absence of reliable prehospital diagnostic tools, an NSTE-ACS is not always recognised, leading to a missed diagnosis in around 2%–5% of consultations.[7] Additionally, the latest European guidelines recommend that high-risk patients with NSTE-ACS receive an early invasive strategy within 24 hours.[8] It is well known that this is associated with shorter ischaemic times and subsequent improved clinical outcomes.[9–11]

On the other hand, the use of additional diagnostic tools could help to definitively rule out an NSTE-ACS in the prehospital setting in chest pain patients with a low suspicion for NSTE-ACS. This is important as only 11%–21% of these patients presenting to an emergency department are finally diagnosed with an NSTE-ACS, in the remaining majority generally no life-threatening condition is found.[12–14] Early risk assessment in these patients with low suspicion could significantly reduce the need of unnecessary diagnostics, referrals to hospitals, and therefore reduce healthcare cost.

Recently, several studies have been performed to investigate several known and new diagnostic tools for prehospital risk assessment in suspected patients with ACS.[15–17] We performed a systematic review and meta-analysis of available prospective data to summarise and compare current available and new diagnostic tools for prehospital risk assessment in patients suspected of NSTE-ACS.

METHODS

Study selection and data extraction

This meta-analysis was published for registration in PROSPERO prior to starting (CRD York, CRD42021254122).

We performed searches in Medline and Embase for all published articles up till 1 April 2021. After identifying articles, we reviewed references from appropriate articles to identify additional references for this systematic review. Full search is shown in online supplemental eAppendix 1.

Titles and abstract for all articles were screened by the primary author (JD) and decisions were checked by a second reviewer (P-JV). If the author identified the article as potentially suitable for inclusion, the full text of the article was reviewed in detail by two authors (JD and P-JV) and selected whether the inclusion criteria were met. Disagreements between reviewers were resolved by the decision of a third independent reviewer. If data were sufficient to generate a 2×2 table, the data were independently extracted, and the methodological quality and eligibility were determined. Bias was evaluated by the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) Criteria.[18]

We included studies that met the following inclusion criteria: (1) patients suspected for NSTE-ACS; (2) prospective study; (3) original data; (4) presenting prehospital (primary care, EMS); (5) prehospital risk assessment or triage; (6) outcome data on in-hospital ACS or major adverse cardiac event (MACE) within 6 weeks after presentation; (7) article published in English, French or German.

The objective of this review was to investigate which patient characteristics and diagnostic tools were used for early risk assessment in an undifferentiated prehospital population suspected of NSTE-ACS, we excluded studies enrolling a specific subpopulation from the general ACS population, studies with less than 100 patients, and studies enrolling only patients with STEMI. Further, we excluded studies from which the data were incomplete, or the endpoints were not focused on diagnostic performance. Studies before 1995, the pretroponin era, were excluded as well.

End points and definitions

The primary end point was the final hospital discharge diagnosis of NSTE-ACS by the treating physician or MACE within 6 weeks. NSTE-ACS refers to non-STEMI or unstable angina pectoris (UAP). MACE was defined in the studies and included at least myocardial infarction.

Data and statistical analysis

For included studies individual data of sample size, number of true positive, true negative, false positive and false negative were extracted separately by two authors (JD and P-JV). When possible, we excluded the patients with STEMI from the data extraction. Sensitivity, specificity, likelihood ratios (LRs) and diagnostics OR (dOR) were calculated from the extracted data by two authors (JD and JZ). The statistical analysis was checked by a third author (MvhV). Extracted data included symptoms, physical examination, risk factors, ECG, biomarkers and CRSs.

Since LRs are an appropriate way to measure and express diagnostic accuracy, our main focus was on this

diagnostic measurement.[19 20] An LR around 1.0 has no proven diagnostic value. A positive LR (LR+) between 1 and 2 as a minimal predictor for making ACS more likely, a LR+ of >2 as a weak predictor for ACS, a LR+ >5 as a moderate to strong predictor and a LR>10 as a very strong predictor. A negative LR (LR−) between 0.5 and 1 as a minimal predictor to make ACS less likely, a LR− of <0.5 as a weak predictor, LR−<0.2 as a moderate to strong predictor and a LR−<0.1 as a very strong predictor.[21]

Summary data for dichotomous findings are reported as weighted average when a finding was evaluated in two studies. When findings were reported in three or more studies, the analyses were performed using R V.4.0.4 (R Foundation for Statistical Computing, Vienna, Austria). Sensitivity, specificity and the dOR analyses were performed using the 'meta' package as was heterogeneity. LRs and bivariate analyses were performed using the 'mada' package.[22]

Statistical heterogeneity was reported as the I^2 for the sensitivity and specificity when findings were evaluated in three studies or more. We considered values between 0% and 30% as low heterogeneity, between 30% and 60% as moderate heterogeneity and 60% or more as considerable heterogeneity.[23]

Patient and public involvement

Patient and public were not involved.

Statement of ethics approval

It was not necessary to engage an ethics committee for this study-level systematic review and meta-analysis.

Data sharing statement

Not applicable.

RESULTS

Of the 1817 unique articles, a total of 15 prospective studies met our inclusion criteria and were included in this systematic review (online supplemental eFigure 1).[15–17 24–35] These studies reflected a total of 26 083 patients. Five studies were performed in setting of primary care by the GP and 10 in the setting of the EMS. Rates of final NSTE-ACS diagnosis ranged in primary care from 5% to 22% (median 11% (IQR, 6%–20%). In the EMS setting, the rates of final ACS diagnosis ranged from 8% to 57% (median 17% (IQR, 12%–20%).

Risk of bias for each included study was scored with the QUADAS tool (online supplemental eAppendix 2). Data on 92 variables related to symptoms, physical examination, risk factors, ECG, biomarkers and risk scores were extracted from the articles. The total number of studies providing data, the total number of patients, sensitivity, specificity, LR+, LR− and dOR are listed in the online supplemental material. All data relevant to the systematic review and meta-analysis are uploaded as online supplemental material (online supplemental eAppendies 3–10).

Symptoms

Symptoms were not predictive for ACS in primary care or in the EMS setting (online supplemental eTable 1). The absence of having chest pain in the ambulance was a minimal predictor for making ACS less likely (LR− 0.61 (0.58–0.63)). Duration of symptoms in primary care until presentation was not appropriate for risk assessment in ACS.

Physical examination

Pain not reproducible by palpation (LR+1.10 (1.02–1.20)) and pallor (LR+1.17 (1.00–1.38)) were minimally predictive for making ACS more likely (online supplemental eTable 2). Reproducing the pain by palpation is a weak predictor for making ACS less likely (LR− 0.47 (0.43–0.51)) in EMS setting.

Cardiovascular risk factors

Of all the cardiovascular risk factors in EMS setting, history of prior coronary disease (LR+2.07 (1.58–2.71)) was the best predictor to make ACS more likely (online supplemental eTable 3). Male gender (LR+1.28 (1.12–1.45), history of angina pectoris (LR+1.27 (1.08–1.49)) or previous acute myocardial infarction (AMI) (LR+1.83 (1.21–2.80)), CABG (LR+1.60 (1.14–2.24) or percutaneous coronary intervention (PCI) (LR+1.49 (1.24–1.78)) were minimal predictors for ACS. For identifying patients less likely to have an ACS, no risk factor when absent conferred an LR− of 0.5 or lower. In primary care, male gender (LR+1.61 (1.34–1.93)) was the only risk factor for making ACS more likely (online supplemental eTable 4).

ECG

A total of three prospective studies investigated the value of ECG, one in primary care and two in EMS.[24 25 34] In all three studies,the ECG was categorised in ischaemic ECG versus abnormal and/or non-ischaemic ECG. In only one study, the exact definition of an ischaemic ECG was mentioned: ST-deviation≥800 µV.[24] Interpreting an ECG as an ischaemic ECG is predictive for ACS in both the EMS setting (LR+2.23 (1.11–5.30)) as in primary care (LR+3.4 (2.15–5.37)). Classifying the ECG as non-ischaemic is a weak predictor for making ACS less likely in primary care (LR− 0.33 (0.17–0.67)) and a minimal predictor in the EMS setting (LR− 0.57 (0.33–0.95)) (table 1). In terms of individual characteristics of the ECG, a Q-wave is a very strong predictor for ACS (LR+24.62 (3.38–179.20)). ST-depression (LR+3.85 (2.58–5.76)) is a better predictor for ACS than T-wave inversion (LR+2.56 (1.50–4.39)) (table 1).

Biomarkers

A total of nine prospective studies investigated the value of biomarkers, four in primary care and five in EMS.[17 24–29 33 34] All blood samples for biomarkers were drawn in the prehospital setting. Most samples were analysed directly prehospital by POC analysers, but in one study the blood sample was analysed after arrival in the hospital.[27] In EMS setting, median time of onset

Table 1 Performance of the ECG for risk assessment in non-ST-elevation acute coronary syndrome

Test	Setting	Studies	Patients	Sensitivity, % (95 CI)	I^2, %*	Specificity, % (95 CI)	I^2, %*	LR+ (95 CI)	LR– (95 CI)	dOR (95 CI)
Ischaemic ECG†[24 25]	EMS	2	1959	58 (45 to 71)	–	74 (59 to 85)	–	2.23(1.11 to 5.30)	0.57 (0.33 to 0.95)	4.03 (0.70 to 23.42)
Ischaemic ECG†[34]	GP	1	243	74 (53 to 88)	–	78 (69 to 84)	–	3.4 (2.15 to 5.37)	0.33 (0.17 to 0.67)	10.20 (3.55 to 29.28)
Q-wave[25]	EMS	1	541	11 (8 to 15)	–	100 (98 to 100)	–	25.36 (3.49 to 184.47)	0.89 (0.12 to 6.50)	28.39 (3.90 to 209.01)
ST-depression[25]	EMS	1	541	42 (36 to 48)	–	89 (84 to 93)	–	3.85 (2.58 to 5.76)	0.65 (0.43 to 0.97)	5.91 (3.68 to 9.49)
T-wave inversion[25]	EMS	1	541	18 (14 to 23)	–	93 (89 to 96)	–	2.56 (1.50 to 4.39)	0.88 (0.52 to 1.51)	2.91 (1.62 to 5.22)

*When the summary measure was from less than three studies, I^2 was not calculated.
†Definition of ischaemic ECG given in one study only; ST-deviation ≥800 µV.
dOR, diagnostic odds ratio; EMS, emergency medical services; GP, general practitioner; LR–, negative likelihood ratio; LR+, positive likelihood ratio.

of complaint to biomarker assessment was 80 min (IQR 59–135 min) and in primary care the median was 600 (IQR 180–600 min). Further details on the prehospital analysed biomarkers are shown in online supplemental eTable 5.

Of the analysed biomarkers in primary care, the heart-type fatty acid binding protein (H-FABP) (LR+7.84 (3.39–20.76)) was moderate to strong for predicting ACS (table 2). POC-troponin (LR+14.16 (4.28–46.90)) was a very strong predictor for ACS. Both were not useful to make an ACS less likely (LR– 0.68 (0.31–1.91) versus LR– 0.71 (0.49–1.02)) (table 3).

In the EMS setting, POC-troponin (LR+6.16 (5.02–7.57)) was a moderate to strong predictor for making ACS more likely that could be interpreted immediately. There was no difference between blood sampled by POC in the EMS and blood analysed in-hospital.

Combined risk scores

CRSs were investigated in eight studies, two in primary care[28 34] and six in EMS.[15 16 31–33 35] In the EMS setting, the used CRSs were all derived from the well-known HEART score.[5] In total five different CRSs were evaluated in this systematic review (table 4). There were minimal differences between the risk scores. These were due to different positivity threshold, risk factors and troponin analysers. In two studies, data and blood were drawn prehospital but analysed after arrival in-hospital.

In the EMS setting, all the CRSs were strong predictors for ACS when classified in the high-risk group. Between the risk scores there was no statistically significant difference (table 4).

In the low-risk group, the modified HEART performed the best in excluding ACS (LR–0.00). Of the CRSs that can be interpreted directly prehospital, preHEART is a very strong predictor in making ACS less likely (LR– (0.05 (0.02–0.15)).

In all primary care studies, the CRSs classified patients in two risk groups (low vs intermediate/high).[28 34] In the EMS setting, this was only the case with the HEAR score and was a weak predictor for making ACS less likely (LR– 0.40 (0.38–0.43)).[33] The Marburg Heart Score (MHS) showed a significant better performance in making ACS less likely when the threshold value was lowered from 2 to 1 (LR– 0.57 (0.47–0.68) versus LR– 0.35 (0.32–0.38)) (table 5). Alternative decision tools used in primary care were the CRS. Scoring a positive answer to the elements resulted in a point that was calculated into a final score. This final score classified the patient into a low-risk group or intermediate-high risk group. CRS 1 had the best performance in making ACS less likely (LR– 0.24 (0.21–0.28)) and outperformed the MHS.

Table 2 Performance of the biomarkers for risk assessment in non-ST-elevation acute coronary syndrome

Assay	Setting	Studies	Patients	Sensitivity, % (95 CI)	I^2, %*	Specificity, % (95 CI)	I^2, %*	LR+ (95 CI)	LR– (95 CI)	dOR (95 CI)
H-FABP[26 28]	GP	2	601	35 (12 to 52)	–	96 (90 to 99)	–	7.84 (3.39 to 20.76)	0.68 (0.31 to 1.90)	11.53 (3.76 to 31.91)
Hs-troponin T[27]	GP	1	115	83 (36 to 100)	–	76 (67 to 84)	–	3.49 (2.40 to 5.09)	0.22 0.15 to 0.32)	15.97 (1.79 to 142.88)
Myoglobin[25]	EMS	1	536	8 (5 to 12)	–	96 (93 to 98)	–	2.07 (0.98 to 4.38)	0.96 (0.45 to 2.02)	2.17 (0.99 to 4.74)

*When the summary measure was from less than three studies, I^2 was not calculated.
dOR, diagnostic odds ratio; EMS, emergency medical services; GP, general practitioner; H-FABP, heart-type fatty acid binding protein; Hs, high-sensitive; LR–, negative likelihood ratio; LR+, positive likelihood ratio.

Table 3 Performance of the point-of-care (POC)-troponin for risk assessment in non-ST-elevation acute coronary syndrome

	Setting	Studies	Patients	Sensitivity, % (95 CI)	I^2, %*	Specificity, % (95 CI)	I^2, %*	LR+ (95 CI)	LR– (95 CI)	dOR (95 CI)
POC-troponin[15 17 25 30 33]	EMS	5	21 484	25 (14 to 40)	96%	96 (94 to 98)	85%	6.16 (5.02 to 7.57)	0.75 (0.62 to 0.92)	8.27 (7.42 to 9.21)
POC-troponin[27 29]	GP	2	311	31 (12 to 59)	–	98 (95 to 99)	–	14.16 (4.28 to 46.90)	0.71 (0.49 to 1.02)	20.01 (4.56 to 87.88)

*When the summary measure was from less than three studies, I^2 was not calculated.
dOR, diagnostic OR; EMS, emergency medical services; GP, general practitioner; LR+, positive likelihood ratio; LR–, negative likelihood ratio.

Compared with GP decision-making without use of a CRS (LR– 0.32 (0.00–0.46)), there is no improvement that makes ACS less likely (table 6).

Making an ACS more likely, decision-making by the GP to refer to the hospital, without using a POC-troponin (LR+2.37 (1.95–3.73)) and using POC-troponin (LR+3.20 (2.14–4.80)) outperformed the CRSs.

Alternative diagnosis

In our systematic review, three studies in the EMS setting described which alternative diagnoses were possible. From these, two studies noted the predictive value of POC-troponin for other diseases,[17 30] one study noted which other causes for chest pain could be classified as low risk.[31] POC-troponin is a moderate to strong predictor for other cardiac-related diseases like myocarditis (LR+8.89 (8.29–9.54)), decompensated heart failure (LR+5.26 (1.88–6.03)), valve disorders/endocarditis (LR+3.29 (2.93–3.69)) and cardiomyopathy (LR+4.80 (4.36–5.29)). For non-cardiac diseases, POC-troponin is a weak to moderate predictor to make pulmonary embolism (LR+3.81 (1.38–4.46)), pneumonia (LR+2.41 (2.13–2.74)) and diseases of the genitourinary system more likely (LR+4.07 (2.66–4.51)). A normal POC-troponin value makes a myocarditis less likely (LR– 0.40 (0.37–0.42)) but is not a strong predictor for other diagnoses. In the modified HEART, 403 patients were classified as low risk for ACS. In this group, two serious non-cardiac diseased (pulmonary embolism, acute pancreatitis) were found.

DISCUSSION

In this systematic review, we evaluated 15 prospective studies including 26.083 patients to identify patient characteristics and diagnostic tools for prehospital risk assessment in suspected patients with NSTE-ACS. The main

Table 4 Performance of the combined risk scores in emergency medical services setting for risk assessment in non-ST-elevation acute coronary syndrome

Risk level	Studies	Threshold	LR (95 CI)	Troponin analyser
High				
Core-lab PMHP[15]	1	Positive troponin	8.68 (5.04 to 14.93)	In-hospital laboratorium
preHEART[35]	1	7–10	8.19 (5.47 to 12.26)	POC
PMHP[15]	1	Positive troponin	6.70 (3.01 to 14.91)	POC
Modified HEART[31]	1	7–10	4.96 (3.62 to 6.79)	In-hospital laboratorium
HEART[35]	1	7–10	4.84 (3.41 to 6.89)	POC
Intermediate				
Core-lab PMHP[15]	1	≥4	0.61 (0.35 to 1.04)	In-hospital laboratorium
preHEART[35]	1	4–6	1.22 (0.95 to 1.57)	POC
PMHP[15]	1	≥4	1.12 (0.74 to 1.70)	POC
Modified HEART[31]	1	4–6	0.89 (0.66 to 1.18)	Lab
HEART[35]	1	4–6	0.69 (0.49 to 0.98)	POC
Low				
Core-lab PMHP[15 16]	2	0–3	0.08 (0 to 0.17)	In-hospital laboratorium
preHEART[35]	1	0–3	0.05 (0.02 to 0.15)	POC
PMHP[15]	1	0–3	0.26 (0.11 to 0.59)	POC
Modified HEART[31]	1	0–3	0.00	In-hospital laboratorium
HEART[32 35]	2	0–3	0.14 (0.13 to 0.16)	POC

HEART, History, ECG, Age, Risk factors, Troponin; LR, likelihood ratio; PMHP, prehospital modified HEART pathway; POC, point-of-care.

Table 5 Performance of the combined risk scores (CRS) in primary care for risk assessment in non-ST-elevation acute coronary syndrome

CRS	Studies	Threshold for intermediate-high risk group	LR+ (95 CI)	Threshold for low-risk group	LR− (95 CI)	Setting	Elements of CRS
CRS 1[28]	1	2–6	1.82 (1.59 to 2.10)	0–1	0.24 (0.21 to 0.28)	GP	▶ ST-depression ▶ ST-elevation ▶ Dyspnoea ▶ Feeling of pressure chest pain ▶ Absent laterale chest pain left ▶ POC H-FABP +
CRS 2[28]	1	2–5	1.69 (1.47 to 1.96)	0–1	0.36 (0.31 to 0.42)	GP	▶ ST-depression ▶ ST-elevation ▶ Dyspnoea ▶ Feeling of pressure chest pain ▶ Absent lateral chest pain left
CRS 3[28]	1	2–4	1.75 (1.49 to 2.06)	0–1	0.40 (0.34 to 0.46)	GP	▶ Dyspnoea ▶ Feeling of pressure chest pain ▶ Absent lateral chest pain left ▶ POC H-FABP +
CRS 4[28]	1	2–3	1.55 (1.30 to 1.85)	0–1	0.56 (0.47 to 0.67)	GP	▶ Dyspnoea ▶ Feeling of pressure chest pain ▶ Absent lateral chest pain left
MHS[34]	1	≥3	1.34 (1.11 to 1.61)	0–2	0.57 (0.47 to 0.68)	GP	
MHS[34]	1	≥2	1.12 (1.04 to 1.22)	0–1	0.35 (0.32 to 0.38)	GP	
GP probability assessment[34]	1	≥6	1.48 (1.29 to 1.70)	0–5	0.32 (0.28 to 0.37)	GP	
Combined MHS and GP probability assessment[34]	1	1–2	1.30 (1.19 to 1.42)	0	0	GP	

GP, general practitioner; H-FABP, heart-type fatty acid binding protein; LR+, positive likelihood ratio; LR−, negative likelihood ratio; MHS, Marburg Heart Score; POC, point-of-care.

Table 6 Performance of general practitioner (GP) decision-making for risk assessment in non-ST-elevation acute coronary syndrome

Test	Studies	Patients	Sensitivity, % (95 CI)	I^2, %*	Specificity, % (95 CI)	I^2, %*	LR+ (95 CI)	LR– (95 CI)	dOR (95 CI)
GP decision to refer[28 29]	2	371	79 (54 to 100)	–	67 (50 to 75)	–	2.37 (1.95 to 3.73)	0.32 (0.00 to 0.46)	7.50 (0 to 14.45)
GP decision to refer with POC-troponin[29]	1	128	71 (29 to 96)	–	78 (69 to 85)	–	3.20 (2.14 to 4.80)	0.37 (0.25 to 0.55)	8.70 (1.60 to 47.40)
GP immediately suspected a serious condition[34]	1	243	58 (42 to 72)	–	53 (45 to 60)	–	1.22 (0.98 to 1.51)	0.80 0.65 to 1.00)	1.51 0.79 to 2.91)

*When the summary measure was from less than three studies, I^2 was not calculated.
dOR, diagnostic odds ratio; LR+, positive likelihood ratio; LR–, negative likelihood ratio; POC, point-of-care.

finding is that in the prehospital setting several new diagnostic tools are available which could improve early triage and risk assessment in suspected patients with NSTE-ACS, in particular on-site assessment of biomarkers and CRSs derived from the HEART score were very strong for risk assessment in patients with NSTE-ACS.

Symptoms, physical examination and risk factors

In accordance with previous analyses, in the present study no specific variables related to symptoms and physical examination were relevant predictors for an ACS diagnosis. The predictive value of some cardiovascular risk factors in the prehospital setting was as a single variable weak at best. A possible explanation is that in the prehospital setting less objective information is present on previous history of a patient. This was indeed corroborated in a recent analysis comparing prehospital and in-hospital calculated HEART scores.[16] In this study, disagreement between hospital and prehospital HEART score risk classifications was found in approximately 25% of patients, mainly by different scoring of history and cardiovascular risk factors.

ECG

In patients with suspected ACS, the resting 12-lead ECG is the first-line diagnostic tool. Our results indicate that in the prehospital setting only a minority of the studies provided detailed description of the ECG criteria and used definitions. Moreover, the ECG was only a moderate predictor for NSTE-ACS. We expect that a more detailed analysis of ECGs, training of EMS personnel or GPs could improve the performance of ECG in the prehospital setting.

Biomarkers

The advent of POC analysers facilitates the use of established biomarkers in the prehospital setting. Current guidelines state that measurement of the biomarker troponin is mandatory in all suspected ACS patients.[36] Although the included studies used normal troponin I and T assays, the first high-sensitivity assays also became available recently for POC analysers. This can increase diagnostic accuracy and reduce the time to diagnosis.[37] Depending on the type of assay used, assessment of this biomarker is already reliable 3–6 hours after onset of symptoms. The duration of symptoms could differ between different settings and populations. We found that duration of symptoms often is much longer in the primary care setting compared with the EMS setting. This explains why the negative predictive value of POC troponin is much higher in the primary care setting than in EMS setting. Consequently, symptom duration could indeed be too short to rule out an ACS based on a single troponin assessment in the EMS setting. However, the use of POC troponin in a CRS could offer a solution to lower the risk of false negatives. This is supported by the results from our analyses which clearly show that the CRSs are superior to a single troponin for risk assessment in a patient suspected for NSTE-ACS.

Two primary care studies[26 28] examined the diagnostic value of H-FABP, a small protein that is common in cardiac muscle and is released within 2 hours after the onset of ischaemia.[38] Although there are no prehospital studies that compare troponin with H-FABP, several in-hospital studies have compared these biomarkers. Despite of the early release, these studies showed that the predictive value of the H-FABP is moderate when assessed within the time frame of 6 hours after onset of symptoms. Compared with POC-troponin, stand-alone H-FABP showed inferior diagnostic performance.[39–41]

Combined risk scores

International guidelines advise the use of CRSs at emergency departments.[36] Several scores are available that, generally combine elements of history, cardiovascular risk factors, ECG and the biomarker troponin. The advent of POC analysers makes it possible to use these risk scores in the prehospital setting. We found mainly risk scores derived from the well-known HEART score, which were validated for prehospital usage. The results tend to be very promising; for identifying high-risk patients for NSTE-ACS, but especially for excluding ACS for low-risk patients. Compared with a previous systematic review by Fanaroff *et al*[42] in 2015, in-hospital use of the original HEART score shows higher predictive value for high-risk patients in diagnosing ACS, and a similar strong negative predictive value is found for patients classified as low risk.

The better predictive value for the high-risk group in the original, in-hospital HEART score can be explained by the presence of more objective information and the longer time between the onset of symptoms in relation to blood analyses. In this patient population, there exists a considerable probability that the in-hospital troponin value will be positive more often compared with the prehospital setting as explained before.

In the present analysis, the performance of CRSs in the primary care setting was lower as compared with the EMS setting. This is due the fact that different scores were used, and in none a POC troponin. In addition, important differences exist in patient selection and prevalence of ACS, which also could have impacted the results. Finally, the performance of diagnostic tools (in particular ECG) and CRSs depends on the experience and support of each individual physician. In primary care, there are large difference between regions and countries to what extent additional diagnostic tools are used or necessary. In particular in remote areas with no nearby hospitals, the implementation of CRSs could improve acute medical care for suspect patients with ACS.

When evaluating a patient with suspected ACS, life-threatening diagnoses such as aortic dissection and pulmonary embolism should be part of the clinical evaluation and differential diagnosis. These alternative diagnoses are often associated with increased levels of biomarkers or ECG changes as well. So, the question is if the prehospital tested biomarkers and CRS are sufficient to also rule out chest pain due to aortic dissection or pulmonary embolism. Our meta-analysis included three studies that reported life-threatening diagnoses in the different risk groups. In the group of patients classified as low risk for ACS, one pulmonary embolism and one acute pancreatitis occurred. No information regarding aortic dissections was available. These data indicate that although a CRS is a very strong predictor for excluding ACS, the possibility for a severe alternative diagnosis should not be ignored.

Further perspective and upcoming studies

Before using these new diagnostic tools in routine practice, more data on safety, efficacy and performance are necessary. More data are needed when these CRSs are used to determine a different triage and/or treatment strategy. Some up-coming studies that will examine whether this early risk stratification and associated referral decisions based on CRS are feasible, are the preHEART3 study (Trialregister.nl, NL7866), PRe-hospital Evaluation of Senstive TrOponin (PRESTO) study,[43] ARTICA trial,[44] FamouS Triage 3 study[45], TRIAGE-ACS study (Clinicaltrials.gov, NCT05243485), and POPular HEART (Clinicaltrials.gov, NCT04851418).

Study limitations

Although we included only prospective studies to improve the overall study quality, this analysis suffers from several limitations inherent to this study design and patient population.

An important limitation of the study was verification bias. There was a variable definition for ACS between the studies, for example, not all studies included UAP and in

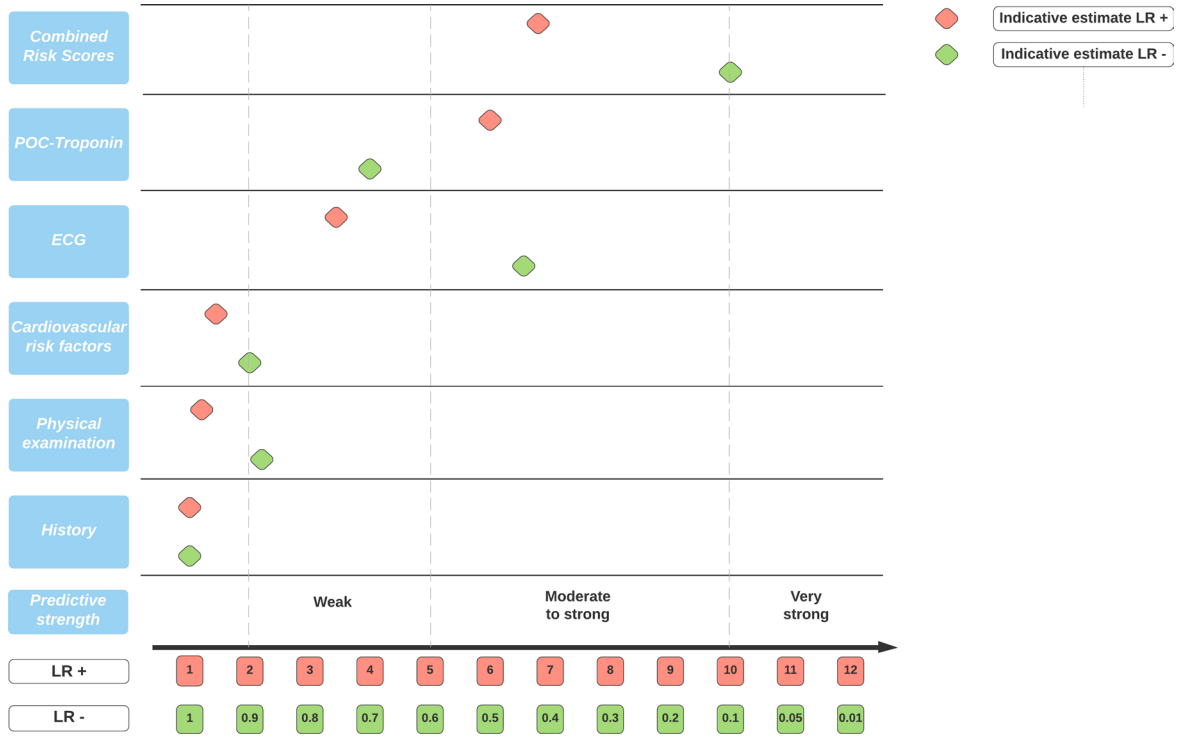

Figure 1 Graphical abstract. It shows the indicative positive and negative likelihood ratio (LR) for each element and how it compares to its predictive value. POC, point-of-care.

some studies some patients were included who developed an STEMI. Although this reflects daily practice, it could have impacted the results.

In the analysis of some variables, heterogeneity was considerable in our meta-analysis (eg, cardiovascular risk factors and POC-troponin measurement in the EMS setting). In POC-troponin, heterogeneity is the result of variation in thresholds between studies. Although this is expected in systematic reviews of diagnostic test accuracy, it is possible this influences our main findings.[46] However, given the small contribution we do not think that the heterogeneity in our meta-analysis alternates the influence of stand-alone risk factors in early risk stratification for ACS.

Another limitation is the lack of well-described patient and additional diagnostic tools data. For example, only one of three studies described their definition of an ischaemic ECG. Therefore, it is difficult to draw conclusions about the diagnostic value of the ECG in this particular population in the prehospital setting. On the other hand, these limited available data are not uncommon for these kind of studies. It is the result of the acute setting in which these patients presents themselves to the GP or the EMS.

Additionally, many of the diagnostic tools were examined in a limited number of studies and study populations. Given the large differences in patient presentation and prevalence of ACS, the performance of the different diagnostic tools could differ when used in a clinical setting or population with different prevalence of ACS.

Finally, not for all diagnostic tools information on false negative results and alternative life-threatening diagnoses were given. Before changing triage and consequent treatment based on these tools, more prospective data are necessary to assess the safety in these rare but important selection of patients.

Conclusion

In the prehospital setting, several new diagnostic tools are available which could improve risk stratification, triage and early treatment in suspected patients with ACS. On-site assessment of biomarkers and CRSs derived from the HEART score showed to be strong predictors for diagnosing patients with a NSTE-ACS and to identify patients without a NSTE-ACS in the EMS setting (figure 1). These promising results underline the importance of new prospective studies in this field.

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Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information.

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Supplemental material

Supplement to: Demandt JPA, Zelis JM, Koks A, et al. Prehospital risk assessment in patients suspected of Non-ST-segment elevation Acute Coronary Syndrome – A systematic review and meta-analysis

Demandt JPA, *et al. BMJ Open* 2022; 12:e057305. doi: 10.1136/bmjopen-2021-057305

eAppendix 1. Full search

Search strategy in MEDLINE:
(ambulance OR pre-hospital OR prehospital OR triage OR paramedics OR ems) AND (ecg OR troponin OR "risk scores" OR POC) AND (acute coronary syndrome OR acs OR nstemi OR "chest pain" OR (acute coronary syndrome [MeSH Terms]) OR (chest pain[MeSH Terms])).

Specific for primary care studies, we performed a second search:
("general practitioner" OR "primary care" OR outpatient) AND (ecg OR troponin OR "risk scores" OR POC) AND (acute coronary syndrome OR acs OR nstemi OR "chest pain" OR (acute coronary syndrome [MeSH Terms]) OR (chest pain[MeSH Terms]))

For our EMBASE search, we added a limitation to exclude all MEDLINE journals and we replaced the MeSH terms with the appropriate Emtree terms.
((ambulance or pre-hospital or prehospital or triage or paramedics or ems).mp. or exp ambulance/) and (ecg or troponin or risk scores or POC).mp. and ((acute coronary syndrome or ACS or NSTEMI or chest pain).mp. or exp non st segment elevation acute coronary syndrome/ or exp acute coronary syndrome/).

In EMBASE we performed a second search as well for additional primary care studies.
(general practitioner OR primary care OR outpatient OR exp general practitioner/ OR primary health care/) and (ecg or troponin or risk scores or POC) and (acute coronary syndrome or ACS or NSTEMI or chest pain or exp non st segment elevation acute coronary syndrome/ or exp acute coronary syndrome/).

eAppendix 2. Quality Assessment Tool for Diagnostic Accuracy Studies (QUADAS) Tool[1]

QUADAS tool: description

1. Was the spectrum of patients representative of the patients who will receive the test in practice?
   Patients presenting in a prehospital setting (EMS, GP) with suspected ACS = yes, retrospective=no

2. Is the reference standard likely to classify the target condition correctly?
   If reference standard in hospital adjudication of ACS, especially NSTEMI or unstable AP; if reference standard is Major Adverse Cardiac Events (MACE), including at least acute myocardial infarction (AMI) =yes

3. Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?
   Adjudicated diagnosis at dismissal. MACE within 6 weeks=yes

4. Did the whole sample or a random selection of the sample, receive verification using a reference standard of diagnosis?

5. Did patients receive the same reference standard irrespective of the index test result?

6. Was the reference standard independent of the index test (i.e., the index test did not form part of the reference standard)?

7. Were the reference standard results interpreted without knowledge of the results of the index test? (Index test results blinded)

8. Were the index test results interpreted without knowledge of the results of the reference standard? (Reference standard results blinded)

9. Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?
   When the test executor had as much info as in clinical practice=yes

10. Were uninterpretable/intermediate test results reported?
    Not reported, numbers are correct=yes

11. Were withdrawals from the study explained?
    Not reported, numbers are correct=yes

Did the study provide a clear definition of what was to be considered a ‘positive’ result?

QUADAS tool: judgement

Study	1	2	3	4	5	6	7	8	9	10	11	A
Van Dongen 2018	Y	Y	Y	Y	Y	N	U	Y	Y	Y	Y	Y
Van Dongen 2020	Y	Y	Y	Y	Y	N	U	Y	Y	Y	Y	Y
Ishak 2018	Y	Y	Y	Y	Y	N	U	U	Y	N	N	Y
Van Dongen 2020	Y	Y	Y	Y	Y	N	U	Y	Y	Y	Y	Y
Bruins Slot 2013	Y	Y	Y	N	Y	Y	Y	Y	Y	N	Y	Y
Andersson 2015	Y	Y	Y	Y	Y	N	Y	Y	Y	N	Y	Y
Schols 2019	Y	Y	Y	Y	U	Y	Y	Y	Y	Y	Y	U
Willemsen 2019	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Nilsson 2013	Y	Y	Y	Y	Y	N	Y	Y	Y	N	Y	Y
Anroedh 2018	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	-
Svensson 2003	Y	Y	Y	Y	Y	N	U	U	Y	N	N	Y
Stopyra 2020	Y	Y	Y	Y	Y	N	U	Y	Y	N	N	Y
Stengaard 2013	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y
Sagel 2021	Y	Y	Y	Y	Y	N	U	Y	Y	N	Y	Y
Rasmussen 2019	Y	Y	U	Y	Y	N	N	Y	Y	N	Y	Y

Y = yes; N = no; U = unclear

eAppendix 3.

eAppendix 3. Study Characteristics					
Source	Study size	Incidence of ACS, No (%)	Clinical Setting	Diagnostic tests	Reference standard
Van Dongen et al.,[6] 2018	700	116 (17)	EMS	Male DM Obesity Family history of CAD Current smoker Previous AMI Previous PCI Previous CABG Previous TIA/Stroke Previous PAV POC- Troponin HEAR score HEART score	30-day MACE: ACS, death, PCI/CABG
Van Dongen et al.,[13] 2019	689	116 (17)	EMS	Core-lab PMHP score Hs-Troponin	30-day MACE: ACS, death, PCI/CABG
Ishak et al.,[14] 2016	1127	192 (17)	EMS	Modified HEART score	Final hospital diagnosis: NSTEMI or uAP
Van Dongen et al.,[15] 2018	700	96 (14)	EMS	HEART score	Final hospital diagnosis: NSTEMI or uAP
Bruins Slot et al.,[10] 2013	298	66 (22)	GP	H-FABP	Final hospital diagnosis: ACS
Andersson, et al.,[8] 2015	115	6 (5)	GP	Hs-Troponin POC-Troponin	Final hospital diagnosis: ACS
Schols et al.,[3] 2019	243	45 (19)	GP	Chest pain Duration of symptoms Worse with excercise Pressure pain Patients assumes cardiac origin of pain History of clinical vascular disease	Final hospital diagnosis: ACS

				Male Pain not reproduced on palpation ECG GP immediately suspected a serious condition MHS GP probability assessment Combines MHS and GP probability assessment	
Willemsen et al.,[4] 2019	303	32 (11)	GP	H-FABP GP decision to refer CRS 1-4	Final hospital diagnosis: ACS
Nilsson et al.,[9] 2012	196	13 (7)	GP	POC-Troponin GP decision to refer GP decision to refer with POC-Troponin	Final hospital diagnosis: ACS
Anroedh et al.,[16] 2018	1421	144 (10)	EMS	ECG	Final hospital diagnosis: NSTEMI or uAP
Svensson et al.,[2] 2002	538	307 (57)	EMS	Pale Nausea Clammy AP Heart failure ECG Myoglobin CK-MB Troponin	Final hospital diagnosis: ACS
Stopyra et al.,[5] 2020	395	74 (19)	EMS	Male DM Obesity Family history of CAD Current smoker Previous AMI Previous PCI Previous CABG Previous TIA/Stroke	30-day MACE: ACS, death

				Previous PAV Hypercholesterolemia Hypertension Prior coronary disease Heart failure PMHP score Core-lab PMHP score	
Stengaard et al.,[7] 2013	985	227 (23)	EMS	Male DM Current smoker Previous AMI Previous PCI Previous CABG Previous smoker POC-Troponin	Final hospital diagnosis: ACS
Sagel et al.,[12] 2021	435	53 (12)	EMS	preHEART score HEART score	3- and 7-day MACE: ACS or death
Rasmussen et al.,[11] 2017	17938	447 (2)	EMS	POC-Troponin	Final hospital diagnosis: NSTEMI

Abbreviations: ACS, Acute Coronary Syndrome; GP, General practitioner; EMS, Emergency Medical Services; DM, diabetes mellitus; AMI, acute myocardial infarction; CABG, Coronary Artery Bypass Grafting; PCI, Percutaneous Coronary Intervention; TIA; Transient ischemic attack, PAV; Peripheral artery disease; AP, angina pectoris; CAD, Coronary artery disease; POC, Point-of-Care; HS, high sensitive; H-FABP; Heart-type Fatty Acid Binding Protein; HEART, History, ECG, Age, Risk Factors, Troponin; PMHP, prehospital modified HEART pathway; CRS, Combined Risk Scores; MHS, Marburg Heart Score; NSTEMI, non-ST-elevation myocard infarct; UAP, unstable angina pectoris; MACE, Major Adverse Cardiac Event

eAppendix 4.

eAppendix 4. Results of individual studies of symptoms

Study	Characteristic	Total no. patients	TP	FP	FN	TN
Svensson et al.,[2] 2006	Chestpain	536	294	213	13	16
	Dyspnoe	536	150	124	157	105
	Nausea	536	114	66	193	163
Schols et al.,[3] 2019	Chestpain	243	39	176	6	22
	Worse with exertion	188	17	69	19	83
	Chestpain feels like pressure pain	212	31	154	8	19
	Patients assumes cardiac origin of pain	242	28	108	17	89
	Symptoms duration <1h	243	39	176	6	22
	Symptoms duration (1-24h)	243	23	15	22	83
	Symptoms duration (>24h)	243	19	63	26	135

Abbreviations: TP, true positives; FP, false positives; FN, false negatives, TN, true negatives

eAppendix 5.

eAppendix 5. Results of individual studies of risk factors						
Study	Characteristic	Total no. patients	TP	FP	FN	TN
Stopyra et al.,[5] 2020	Prior coronary disease	389	37	76	37	239
	Previous PAV	395	4	17	70	304
Van Dongen et al.,[6] 2018	Previous PAV	700	11	20	105	564
Svensson et al.,[2] 2003	Previous AMI	536	160	80	147	149
Stopyra et al.,[5] 2020	Previous AMI	589	28	43	46	472
Van Dongen et al.,[6] 2018	Previous AMI	700	34	116	82	468
Stengaard et al.,[7] 2013	Previous AMI	985	82	206	149	548
Stopyra et al.,[5] 2020	Previous CABG	390	8	27	66	289
Van Dongen et al.,[6] 2018	Previous CABG	700	14	52	102	532
Stengaard et al.,[7] 2013	Previous CABG	985	21	13	210	721
Stopyra et al.,[5] 2020	Previous PCI	395	19	78	55	243
Van Dongen et al.,[6] 2018	Previous PCI	700	42	133	74	451
Stengaard et al.,[7] 2013	Previous PCI	985	73	179	158	575
Stopyra et al.,[5] 2020	Previous TIA/Stroke	395	7	34	67	287
Van Dongen et al.,[6] 2018	Previous TIA/Stroke	700	11	32	105	552
Svensson et al.,[2] 2003	Current smoker	700	30	126	86	458
Stopyra et al.,[5] 2020	Current smoker	395	16	87	58	234
Van Dongen et al.,[6] 2018	Current smoker	700	30	126	86	458
Stengaard et al.,[7] 2013	Current smoker	1084	80	120	151	733
Svensson et al.,[2] 2003	Male gender	536	181	128	126	101
Stopyra et al.,[5] 2020	Male gender	395	43	142	31	179
Van Dongen et al.,[6] 2018	Male gender	700	88	313	28	271
Stengaard et al.,[7] 2013	Male gender	985	170	413	61	341
Svensson et al.,[2] 2003	AP	536	196	115	111	114

Stopyra et al.,[5] 2020	Hypercholesterolemia	395	26	83	48	238
Van Dongen et al.,[6] 2018	Hypercholesterolemia	700	61	214	55	370
Stengaard et al.,[7] 2013	Hypercholesterolemia	985	194	624	37	130
Svensson et al.,[2] 2003	DM	536	58	32	249	197
Stopyra et al.,[5] 2020	DM	395	29	94	45	227
Van Dongen et al.,[6] 2018	DM	700	26	87	90	497
Stengaard et al.,[7] 2013	DM	985	38	143	193	611
Svensson et al.,[2] 2003	Heart failure	536	68	57	239	172
Stopyra et al.,[5] 2020	Heart failure	389	14	40	59	276
Svensson et al.,[2] 2003	Hypertension	536	107	57	200	172
Stopyra et al.,[5] 2020	Hypertension	389	55	201	18	115
Van Dongen et al.,[6] 2018	Hypertension	700	66	306	50	278
Stengaard et al.,[7] 2013	Hypertension	985	133	405	98	349
Stopyra et al.,[5] 2020	Obesity	383	29	152	45	157
Van Dongen et al.,[6] 2018	Obesity	700	27	113	89	471
Stengaard et al.,[7] 2013	Previous smoker	985	69	208	162	546
Stopyra et al.,[5] 2020	Family history of CAD	395	19	78	55	243
Van Dongen et al.,[6] 2018	Family history of CAD	700	47	277	69	307
Schols et al.,[3] 2019	Gender	243	34	93	11	105
	History of clinical vascular disease	243	22	84	23	114

Abbreviations: 95-CI, 95% confidence interval; LR+, positive likelihood ratio; LR- negative likelihood ratio; dOR, diagnostic odds ratio; DM, diabetes mellitus; AMI, acute myocardial infarction; CABG, Coronary Artery Bypass Grafting; PCI, Percutaneous Coronary Intervention; TIA; Transient ischemic attack, PAV; Peripheral artery disease; AP, angina pectoris; CAD, Coronary artery disease; TP, true positives; FP, false positives; FN, false negatives, TN, true negatives

eAppendix 6.

eAppendix 6. Results of individual studies of electrocardiogram findings

Study	Characteristic	Total no. patients	TP	FP	FN	TN
Anroedh et al.,[16] 2018	Ischemic ECG	1421	69	457	75	820
Svensson et al.,[2] 2003	Ischemic ECG	536	52	126	255	103
Schols et al.,[3] 2019	Ischemic ECG	115	17	20	6	72
Svensson et al.,[2] 2003	Q-wave	536	33	1	274	228
	ST-depression	536	129	25	178	204
	T-wave inversion	536	55	16	252	213

Abbreviations: TP, true positives; FP, false positives; FN, false negatives, TN, true negatives

eAppendix 7.

eAppendix 7. Results of individual studies of biomarkers						
Study	Characteristic	Total no. patients	TP	FP	FN	TN
Svensson et al.,[2] 2003	POC-Troponin	536	21	2	286	227
Stengaard et al.,[7] 2013	POC-Troponin	924	73	34	146	671
Stopyra et al.,[5] 2020	POC-Troponin	395	17	11	57	310
Van Dongen et al.,[6] 2018	POC-Troponin	700	43	26	73	558
Rasmussen et al.,[11] 2019	POC-Troponin	17938	640	1175	1026	15097
Andersson et al.,[8] 2015	POC-Troponin	115	2	2	4	107
Nilsson et al.,[9] 2013	POC-Troponin	128	2	3	5	118
Willemsen et al.,[4] 2019	H-FABP	291	8	8	23	252
Bruins Slot et al.,[10] 2013	H-FABP	298	26	14	40	218
Svensson et al.,[2] 2003	CK-MB	536	37	7	270	222
	Myoglobin	536	25	9	282	220
Andersson et al.,[8] 2015	Hs-Troponin	115	5	26	1	83
Abbreviations: TP, true positives; FP, false positives; FN, false negatives, TN, true negatives; POC, Point-of-Care; H-FABP; Heart-type Fatty Acid Binding Protein; HS, high-sensitive						

eAppendix 8.

eAppendix 8. Results of individual studies of Combined Risk Scores

Study	Characteristic	Risk	TP	FP	FN	TN
Stopyra et al.,[5] 2020	Core-lab PMHP	High	50	25		
		Intermediate	24	172		
		Low	0	172		
	PMHP	High	17	11		
		Intermediate	50	193		
		Low	7	117		
Sagel et al.,[12] 2021	preHEART	High	55	56		
		Intermediate	117	797		
		Low	4	614		
	HEART	High	67	122		
		Intermediate	51	648		
		Low	5	315		
Ishak et al.,[14] 2018	Modified HEART	High	116	114		
		Intermediate	76	418		
		Low	0	403		
Willemsen et al.,[4] 2019	CRS 1	High - Low	28	130	4	141
	CRS 2	High - Low	26	130	6	141
	CRS 3	High - low	25	121	7	150
	CRS 4	High - Low	22	120	10	151
Schols et al.,[3] 2019	MHS	Cut-off value 2	27	84	9	66
	MHS	Cut- off value 1	34	126	2	24
	GP probability assessment	High - Low	36	116	6	82
	Combined MHS & GP probability assessment	High - Low	36	115	0	35

Abbreviations: TP, true positives; FP, false positives; FN, false negatives, TN, true negatives; CRS, Combined Risk Scores; HEAR, History, ECG, Age, Risk Factors; POC, Point-of-Care; H-FABP, Heart-type Fatty Acid Binding Protein; MHS, Marburg Heart Score; GP, general practitioner

eAppendix 9.

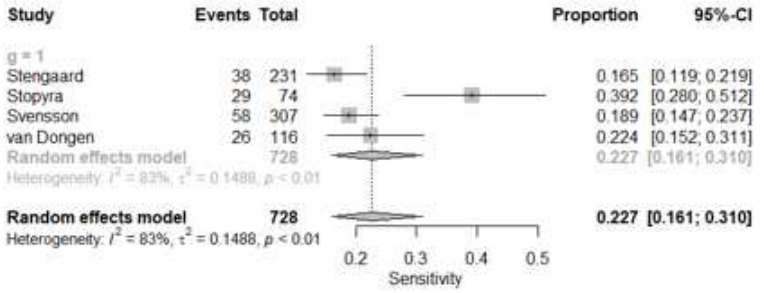
eAppendix 9. Results of individual studies of general practitioner decision making

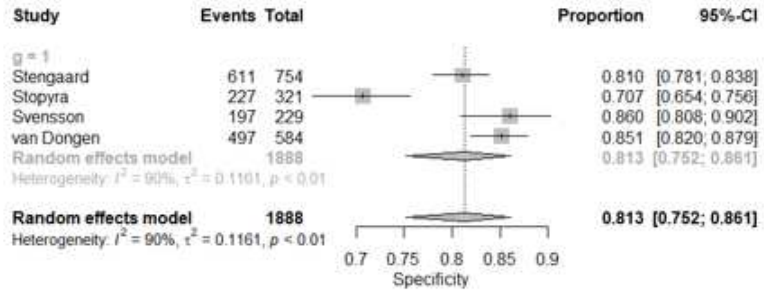
Study	Characteristic	Total no. patients	TP	FP	FN	TN
Willemsen et al.,[4] 2019	GP decision to refer	303	24	88	8	183
Nilsson et al.,[9] 2013	GP decision to refer	68	6	23	0	39
	GP decision to refer with POC-Troponin	128	5	27	2	94
Schols et al.,[3] 2019	GP immediately suspected a serious condition	243	26	94	19	104

Abbreviations: TP, true positives; FP, false positives; FN, false negatives, TN, true negatives; GP, General Practitioner; POC, Point-of-Care

eAppendix 10. Forest plots

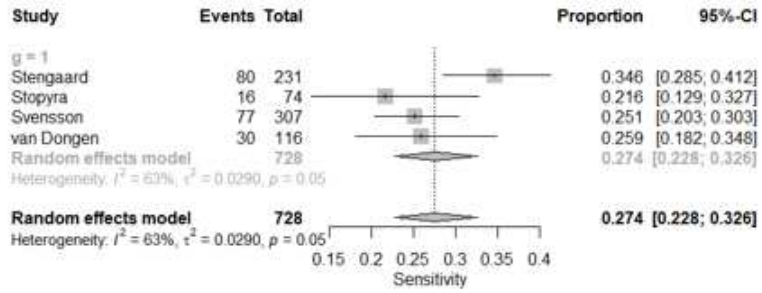
Diabetes Mellitus

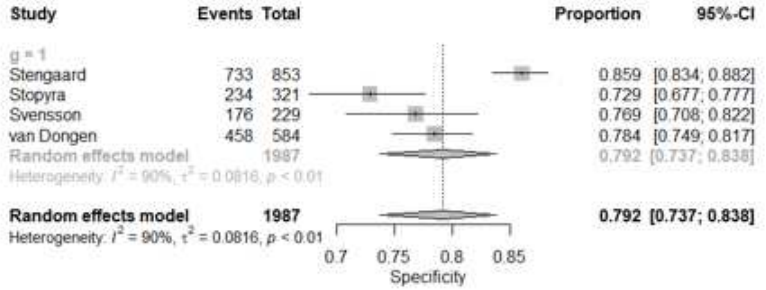




G=1 = Emergency Medical Services setting

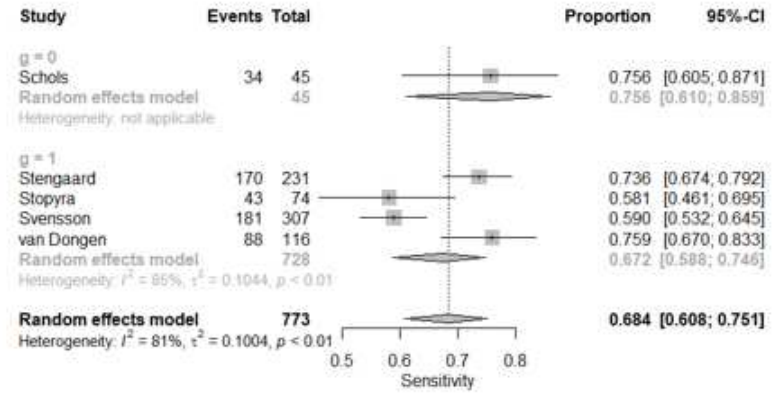
Current smoker

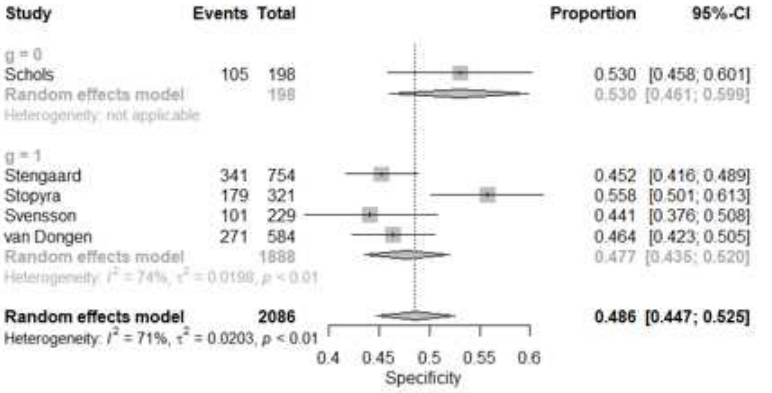




G=1 = Emergency Medical Services setting

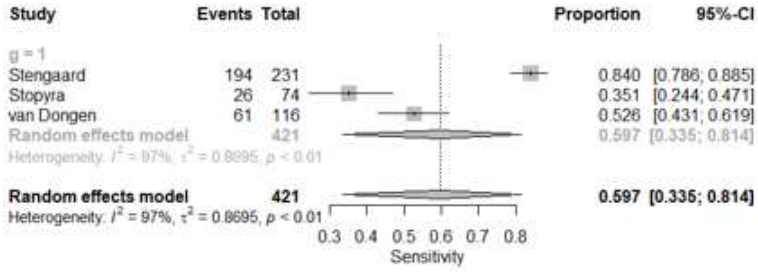
Male gender

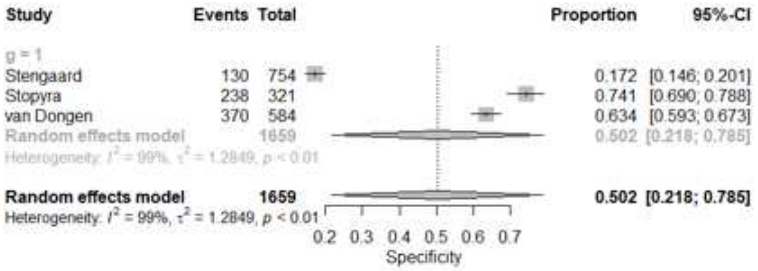




G=1 = Emergency Medical Services setting; G=-0 = General Practitioner setting

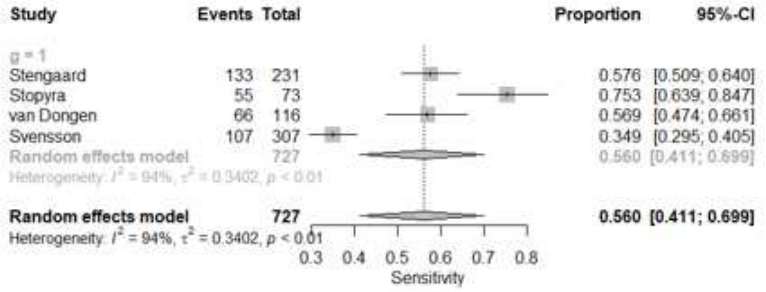
Hypercholesterolemia

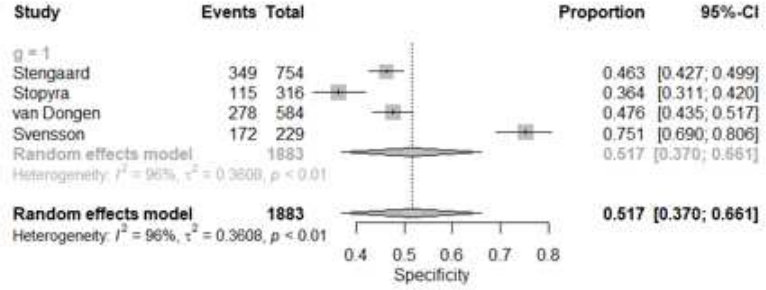




G=1 = Emergency Medical Services setting

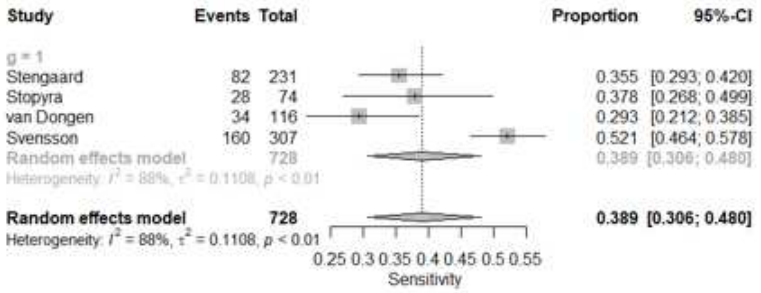
Hypertension

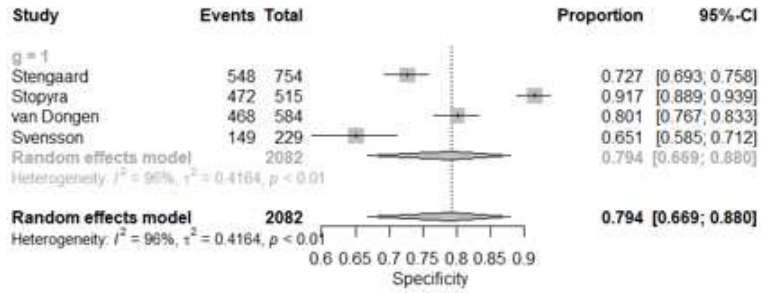




G=1 = Emergency Medical Services setting

Previous AMI

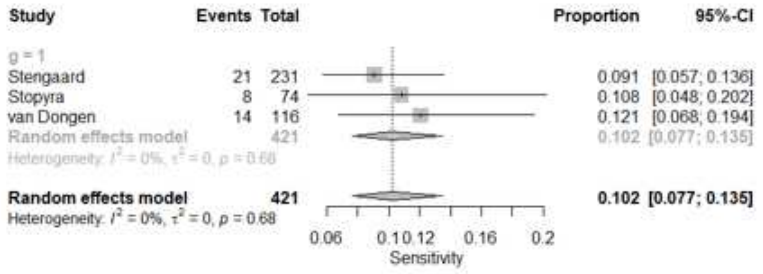


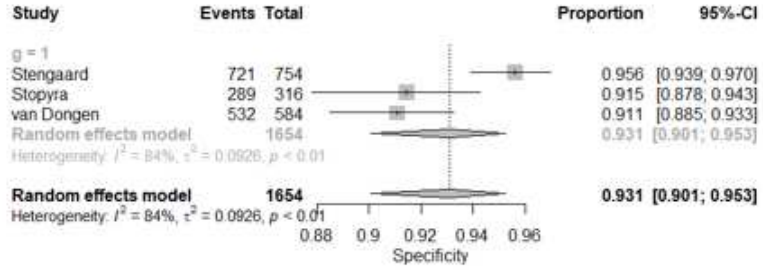


G=1 = Emergency Medical Services setting

AMI = Acute Myocardial Infarction

Previous CABG

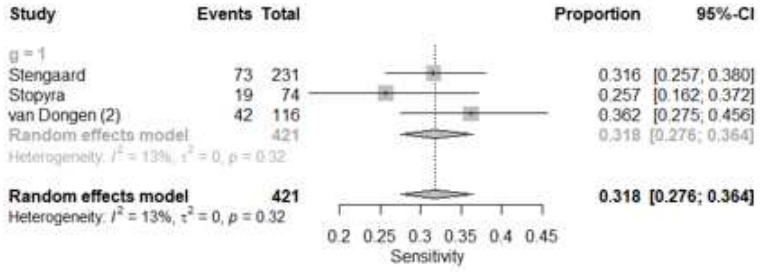


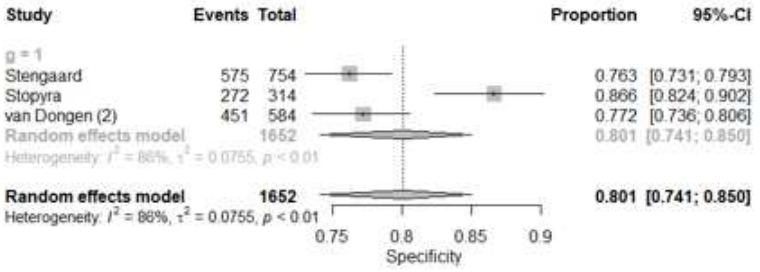


G=1 = Emergency Medical Services setting

CABG = Coronary Artery Bypass Graft

Previous PCI

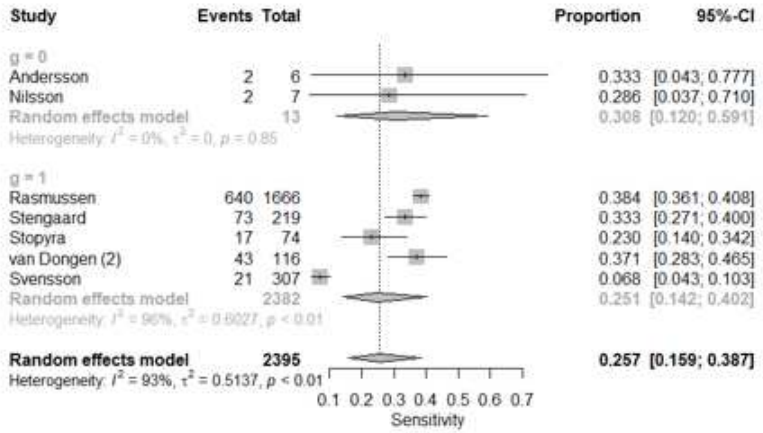


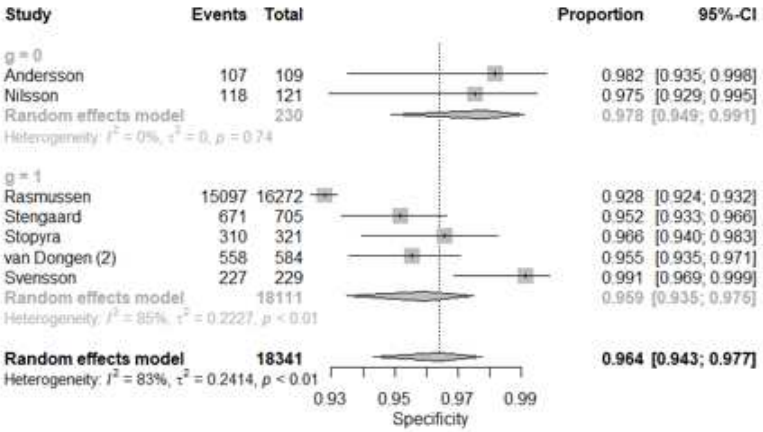


G=1 = Emergency Medical Services setting

PCI = Percutaneous Coronary Intervention

POC Troponin

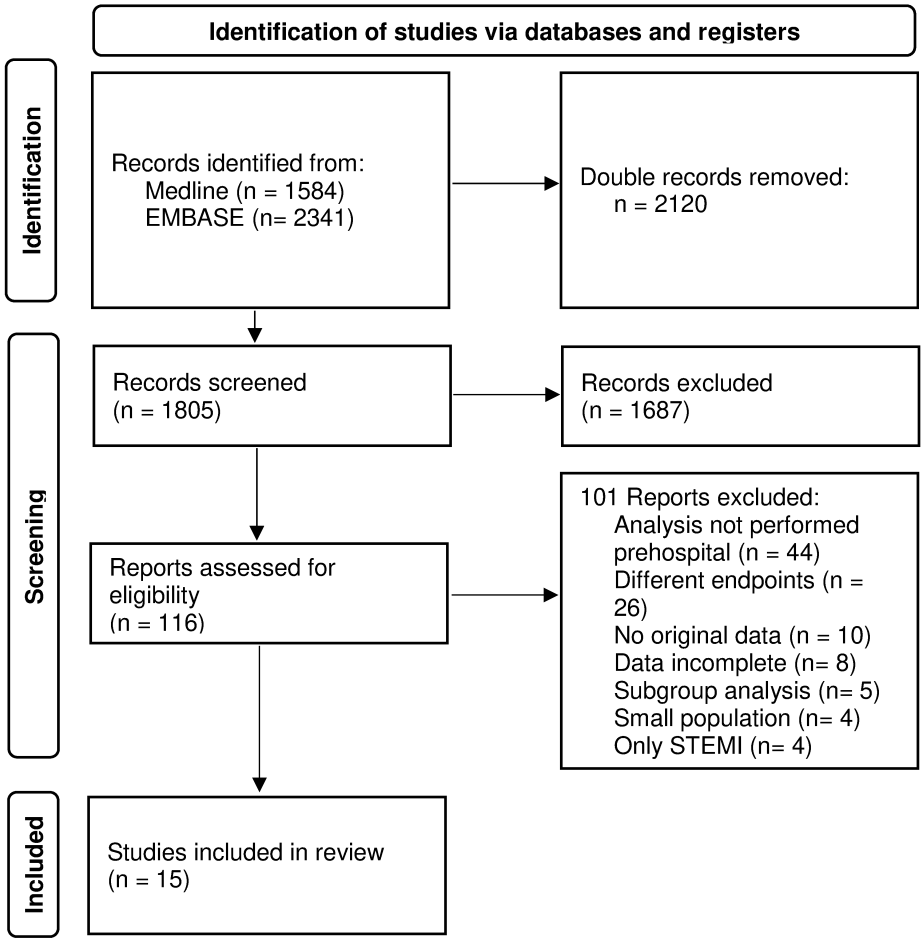




G=1 = Emergency Medical Services setting; G=0 = General Practitioner setting

POC = Point-of-Care

eFigure 1. Flow diagram of study inclusion



eTable 1.

eTable 1. Performance of symptoms for risk assessment in non-ST-elevation Acute Coronary Syndrome										
Symptom	Setting	Studies	Patients	Sensitivity, % (95-CI)	I^2, %[a]	Specificity, % (95-CI)	I^2, %[a]	LR+ (95-CI)	LR- (95-CI)	dOR (95-CI)
Chestpain[2]	EMS	1	538	96 (93-98)	-	7 (4-11)	-	1.03 (0.98-1.07)	0.61 (0.58-0.63)	1.70 (0.80-3.61)
Dyspnoe [2]	EMS	1	536	49 (43-55)	-	46 (39-53)	-	0.90 (0.76-1.07)	1.12 (0.94-1.32)	0.81 (0.57-1.14)
Nausea [2]	EMS	1	536	37 (32-43)	-	71 (65-77)	-	1.29 (1.00-1.67)	0.88 (0.68-1.14)	1.46 (1.01-2.11)
Chestpain [3]	GP	1	243	87 (73-95)	-	11 (7-16)	-	0,98 (0.90-1.05)	1.29 (1.11-1.29)	0.81 (0.31-2.14)
Worse with exertion [3]	GP	1	212	47 (30-65)	-	55 (46-63)	-	1.0 (0.79-1.38)	0.97 (0.73-1.28)	1.08 (0.52-2.23)
Chestpain feels like pressure [3]	GP	1	212	79 (64-91)	-	11 (7-17)	-	0.89 (0.81-0.98)	1.87 (1.70-2.05)	0.48 (0.19-1.19)
Patient assumes cardiac origin of pain [3]	GP	1	242	62 (47-76)	-	45 (38-52)	-	1.13 (0.94-1.37)	0.84 (0.69-1.01)	1.36 (0.70-2.64)
Symptoms duration <1h [3]	GP	1	243	87 (73-95)	-	11 (7-16)	-	0.98 (0.90-1.05)	1.2 (1.11-1.29)	0.81 (0.31-2.14)

Symptoms duration (1-24h) [3]	GP	1	243	51 (36-66)	-	42 (35-49)	-	0.88 (0.72-1.08)	1.16 (0.95-1.43)	0.75 (0.39-1.44)
Symptoms duration (>24h)[3]	GP	1	243	42 (28 58)	-	68 (61-75)	-	1.33 (0.97-1.82)	0.85 (0.62-1.16)	1.57 (0.81-3.04)

Abbreviations: 95-CI, 95% confidence interval; LR+, positive likelihood ratio; LR- negative likelihood ratio; dOR, diagnostic odds ratio

[a] When the summary measure was from less than 3 studies, I^2 was not calculated

eTable 2

eTable 2. Performance of physical examination for risk assessment in non-ST-elevation Acute Coronary Syndrome

Test	Setting	Studies	Patients	Sensitivity, % (95-CI)	I^2, %[a]	Specificity, % (95-CI)	I^2, %[a]	LR+ (95-CI)	LR- (95-CI)	dOR (95-CI)
Pale [2]	EMS	1	536	60 (54-65)	-	49 (42-56)	-	1.17 (1.00-1.38)	0.82 (0.70-0.96)	1.43 (1.01-2.02)
Clammy [2]	EMS	1	536	37 (32-43)	-	68 (62-74)	-	1.16 (0.21-1.49)	0.92 (0.72-1.18)	1.26 (0.88-1.81)
Pain not reproducible by palpation [3]	GP	1	210	92 (79-98)	-	16 (11-23)	-	1.10 (1.02-1.20)	0.47 (0.43-0.51)	2.35 (0.68-8.16)
Cardiac murmur [4]	GP	1	250	4 (0-19)	-	91 (86-94)	-	0.41 (0.08-1.91)	1.06 (0.23-4.89)	0.39 (0.05-3.03)

Abbreviations: 95-CI, 95% confidence interval; LR+, positive likelihood ratio; LR- negative likelihood ratio; dOR, diagnostic odds ratio

[a] When the summary measure was from less than 3 studies, I^2 was not calculated

eTable 3

eTable 3. Performance of risk factors in EMS setting for risk assessment in non-ST-elevation Acute Coronary Syndrome

Risk factor	Setting	Studies	Patients	Sensitivity % (95-CI)	I^2, %[a]	Specificity % (95-CI)	I^2, %[a]	LR+ (95-CI)	LR- (95-CI)	dOR (95-CI)
Prior coronary disease [5]	EMS	1	389	50 (38-62)	-	76 (71-80)	-	2.07 (1.58-2.71)	0.66 (0.50-0.86)	3.14 (1.86-5.31)
Previous PAV [5 6]	EMS	2	1095	8 (1-16)	-	96 (92-98)	-	1.93 (0.38-5.53)	0.96 (0.37-2.70)	2.01 (0.33-6.35)
Previous AMI [2 5-7]	EMS	4	2618	39 (31-48)	88%	79 (69-88)	96%	1.84 (1.21-2.80)	0.80 (0.71-0.91)	2.32 (1.34-4.00)
Previous CABG [5-7]	EMS	3	2080	10 (8-14)	0%	93 (90-95)	84%	1.60 (1.14-2.24)	0.96 (0.93-0.99)	1.67 (1.15-2.44)
Previous PCI [5-7]	EMS	3	2080	32 (28-36)	13%	80 (74-85)	86%	1.49 (1.24-1.78)	0.87 (0.81-0.93)	1.71 (1.35-2.17)
Previous TIA/Stroke [5 6]	EMS	2	1095	9 (4-19)	-	93 (86-96)	-	1.30 (0.45-3.21)	0.98 (0.52-2.00)	1.33 (0.37-3.7)
Current smoker [2 5-7]	EMS	4	2618	27 (23-33)	63%	79 (74-84)	90%	1.29 (0.78-2.14)	0.93 (0.80-1.07)	1.39 (0.72-2.68)
Male gender [2 5-7]	EMS	4	2618	67 (59-75)	85%	48 (44-52)	74%	1.28 (1.12-1.45)	0.69 (0.53-0.90)	1.86 (1.39-2.80)

AP [2]	EMS	1	536	64 (58-69)	-	50 (43-56)	-	1.27 (1.08-1.49)	0.73 (0.62-0.85)	1.75 (1.24-2.48)
Hypercholesterolemia [5-7]	EMS	3	2080	60 (34-81)	97%	50 (22-79)	99%	1.23 (0.93-1.61)	0.83 (0.73-0.94)	1.47 (1.04-2.10)
DM [2 5-7]	EMS	4	2618	23 (16-31)	83%	81 (75-86)	90%	1.22 (0.95-1.57)	0.96 (0.89-1.03)	1.29 (0.93-1.80)
Heart failure [2 5]	EMS	2	933	22 (11-30)	-	82 (69-91)	-	1.21 (0.65-2.49)	0.95 (0.56-1.52)	1.27 (0.57-3.2)
Hypertension [2 5-7]	EMS	4	2618	56 (41-70)	94%	52 (37-66)	96%	1.14 (1.04-1.25)	0.88 (0.81-0.95)	1.33 (1.10-1.61)
Obesity [5 6]	EMS	2	1095	29 (16-51)	-	70 (45-84)	-	0.99 (0.65-1.62)	1.00 (0.70-1.47)	0.99 (0.40-2.04)
Previous smoker [7]	EMS	1	985	30 (24-36)	-	72 (69-76)	-	1.08 (0.89-1.31)	0.97 (0.80-1.18)	1.12 (0.81-1.55)
Family history of CAD [5 6]	EMS	2	1095	35 (16-50)	-	61 (48-80)	-	0.89 (0.73-1.50)	1.07 (0.69-1.39)	0.82 (0.50-1.92)

Abbreviations: 95-CI, 95% confidence interval; LR+, positive likelihood ratio; LR- negative likelihood ratio; dOR, diagnostic odds ratio; DM, diabetes mellitus; AMI, acute myocardial infarction; CABG, Coronary Artery Bypass Grafting; PCI, Percutaneous Coronary Intervention; TIA; Transient ischemic attack, PAV; Peripheral artery disease; AP, angina pectoris; CAD, Coronary artery disease

[a] When the summary measure was from less than 3 studies, I^2 was not calculated

eTable 4

eTable 4. Performance of risk factors in primary care for risk assessment in non-ST-elevation Acute Coronary Syndrome

Risk factor	Setting	Studies	Patients	Sensitivity, % (95-CI)	I^2, %[a]	Specificity, % (95-CI)	I^2, %[a]	LR+ (95-CI)	LR- (95-CI)	dOR (95-CI)
Male gender [3]	GP	1	243	77 (61-86)	-	53 (46-60)	-	1.61 (1.34-1.93)	0.46 (0.38-0.55)	3.49 (1.67-7.23)
History of clinical vascular disease [3]	GP	1	243	49 (34-64)	-	58 (50-65)	-	1.15 (0.90-1.48)	0.89 (0.69-1.14)	1.30 (0.68-2.48)

Abbreviations: 95-CI, 95% confidence interval; LR+, positive likelihood ratio; LR- negative likelihood ratio; dOR, diagnostic odds ratio

[a] When the summary measure was from less than 3 studies, I^2 was not calculated

eTable 5.

eTable 5. Additional information about Point-of-Care (POC) analyzers							
Study	Setting	Manufacturer	Assay	Median duration (minutes)	Test result (minutes)	Succes rate (%)	Positive threshold
Van Dongen[6]	EMS	Roche Diagnostics	Troponin T	150	8 – 12	90	0.04 µg/L
Andersson [8]	GP	Roche Diagnostics	Troponin T	600	14	-	0.03 µg/L
Willemsen [4]	GP	FABPulous BV	H-FABP	-	-	-	4 µg/L
Nilsson [9]	GP	Roche Diagnostics	Troponin T	600	14	-	0.03 µg/L
Bruins Slot [10]	GP	Cardiodetect Rennesens GmbH	H-FABP	180	15	89	7 µg/L
Stopyra [5]	EMS	Abbott	Troponin I	-	8-10	-	0.08 µg/L
Svensson [2]	EMS	Cardiac Status Spectral Diagnostics Tests	Myoglobin CK-MB Troponin I	90	15	-	2.91 nmol/L 5 µg/L 0.1 µg/L
Stengaard [7]	EMS	Roche Diagnostics	Troponin T	70	12	90%	0.05 µg/L

Rasmussen [11]	EMS	Roche Diagnostics	Troponin T	55	12	-	0.05 µg/L
Sage[12]	EMS	Abbott	Troponin I	294	8-10	-	0.34 µg/L
Abbreviations: POC, Point-of-Care; HS, high sensitive; GP, General practitioner; EMS, Emergency Medical Services							

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