Chest Pain in Primary Care: A Systematic Review of Risk Stratification Tools to Rule Out Acute Coronary Syndrome

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VISUAL ABSTRACT

Conflicts of interest: authors report none.

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ABSTRACT

PURPOSE Chest pain frequently poses a diagnostic challenge for general practitioners (GPs). Utilizing risk stratification tools might help GPs to rule out acute coronary syndrome (ACS) and make appropriate referral decisions. We conducted a systematic review of studies evaluating risk stratification tools for chest pain in primary care settings, both with and without troponin assays. Our aims were to assess the performance of tools for ruling out ACS and to provide a comprehensive review of the current evidence.

METHODS We searched PubMed and Embase for articles up to October 9, 2023 concerning adult patients with acute chest pain in primary care settings, for whom risk stratification tools (clinical decision rules [CDRs] and/or single biomarker tests) were used. To identify eligible studies, a combination of active learning and backward snowballing was applied. Screening, data extraction, and quality assessment (following the Quality Assessment of Diagnostic Accuracy Studies-2 tool) were performed independently by 2 researchers.

RESULTS Of the 1,204 studies screened, 14 were included in the final review. Nine studies validated 7 different CDRs without troponin. Sensitivities ranged from 75.0% to 97.0%, and negative predictive values (NPV) ranged from 82.4% to 99.7%. None of the CDRs outperformed the unaided judgment of GP's. Five studies reported on strategies using troponin measurements. Studies using high-sensitivity troponin showed highest diagnostic accuracy with sensitivity 83.3% to 100% and NPV 98.8% to 100%.

CONCLUSION Clinical decision rules without troponin and the use of conventional troponin showed insufficient sensitivity to rule out ACS in primary care and are not recommended as standalone tools. High-sensitivity troponin strategies are promising, but studies are limited. Further prospective validation in primary care is needed before implementation.

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INTRODUCTION

Chest pain often poses a diagnostic challenge for general practitioners (GPs). While chest pain is the hallmark symptom of acute coronary syndrome (ACS), it is often caused by less urgent conditions. It is difficult for GPs to differentiate possible ACS from other causes based on symptoms and physical examination alone. This, unfortunately, results in a low threshold for referral, leading to additional burden and cost on the health care system.[1-3]

Only 1.5% to 3.6% of patients with chest pain in primary care are diagnosed with ACS.[3,4] More often, chest pain is caused by non-cardiac conditions, such as musculoskeletal complaints or gastrointestinal disease.[2] It is thought that risk stratification tools, such as clinical decision rules (CDRs) or troponin point-of-care tests (POCT), could help GPs to make more informed referral decisions when evaluating patients with acute chest pain.

Due to different ACS risks in primary and secondary care, the use of risk stratification tools may differ in these settings, and results from studies in secondary care cannot be assumed to apply to primary care.[5] A systematic review from 2019 that assessed CDRs for coronary artery disease and ACS in primary care, concluded that no CDR demonstrated sufficient sensitivity to rule out ACS.[6] Since then new studies have emerged, and high-sensitivity troponin POCTs became available to prehospital settings. In this systematic review, our aim was to assess the performance of risk stratification tools for ruling out ACS in patients with chest pain in primary care and to provide a comprehensive review of the current evidence.

METHODS

This study is reported in accordance with the 2018 Preferred Reporting Items for a Systematic review and Meta-Analysis of diagnostic test accuracy studies statement.[7] The protocol is available upon request.

Search Strategy and Eligibility Criteria

We searched the electronic databases PubMed and Embase for original articles published in English, up to October 9, 2023. A complete overview of the search is presented in Supplemental Appendix 1. Two authors (S.B., A.M.) identified articles for potential inclusion. A third author (R.E.H.) was available to resolve any disagreements. Eligibility criteria were: (1) adults (aged 18 years or more); (2) acute chest pain; (3) enrollment in primary care; (4) available outcome data for ACS, acute myocardial infarction (AMI), or the composite endpoint of major adverse cardiac events (MACE); and (5) use of diagnostic tools. Diagnostic tools were defined as risk stratification tools constructed by a set of condition-specific findings that are applicable in a primary care setting. Exclusion criteria were: studies conducted in ambulance care or emergency department settings or requiring advanced diagnostic testing (eg, coronary angiography, serial biomarker testing); or cardiac monitoring.

Table 1. Study and Patient Characteristics of Included Studies (N = 14)

Source, Year	Risk Stratification Strategy	Type of Evaluation	Study Design	Follow Up	Country	Patients, No.
A. Risk stratification tools without troponin						
Grijseels et al,[11] 1995	Grijseels	Derivation	Prospective study	30 days	The Netherlands	906
Grijseels et al,[12] 1996	Grijseels	Validation	Prospective study	30 days	The Netherlands	977
Bruins Slot et al,[1] 2011	Bruins Slot (updated Grijseels rule)	Derivation Internal validation	Diagnostic accuracy study	30 days	The Netherlands	298
Willemsen et al,[13] 2019	H-FABP CDR	Validation Derivation Internal validation	Prospective non-randomized diagnostic study	30 days	The Netherlands	303
Schols et al,[14] 2019	MHS	Validation	Prospective, observational flash-mob study	6 weeks	The Netherlands	243
Kleton et al,[15] 2020	Bruins Slot MHS INTERCHEST Gencer rule	Validation	Retrospective, observational cohort study	6 months	The Netherlands	664
Manten et al,[16] 2022	MHS INTERCHEST	Validation	Retrospective, observational cohort	6 months	The Netherlands	1,433
Wouters et al,[17] 2022	Safety First	Derivation Internal validation	Cross-sectional study	30 days	The Netherlands	2,192
Harskamp et al,[18] 2021	Simplified HEART HEART-GP	Validation	Retrospective, observational cohort	6 months	The Netherlands	664
B. Troponin based risk stratification tools						
Planer et al,[19] 2006	POCT cTnT	Validation	Prospective study	2 months	Israel	349
Tomonaga et al,[20] 2011	3-in-1 POCT	Validation	Clustered, randomized controlled trial	3 weeks	Switzerland	369
Nilsson et al,[21] 2013	POCT cTnT	Validation	Prospective observational study	30 days	Sweden	196
Andersson et al,[22] 2015	hs-cTnT	Validation	Prospective observational study	30 days	Sweden	115
Johannessen et al,[23] 2021	Single troponin HEART-score Modified HEART	Validation	Prospective observational study	90 days	Norway	1,711

ACS = acute coronary syndrome; AMI = acute myocardial infarction; CDR = clinical decision rule; cTnT = cardiac troponin T; HEART = History, ECG, Age, Risk factors and Troponin; H-FABP = heart-type fatty acid–binding protein; hs = high-sensitivity; INTERCHEST = international chest pain prediction; MACE = major adverse cardiovascular events; MHS = Marburg Heart Score; POCT = point of care test.

Outcomes of Interest

Outcomes of interest were the diagnostic test characteristics of the risk stratification tool: sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and overall discriminative properties (C-statistic). Reference diagnoses of interest were ACS, AMI, and MACE. Major adverse cardiac events are typically defined as a composite of death from any cause, ACS, and urgent coronary interventions. When applicable, we reported the performance of risk stratification tools compared with unaided clinical judgement.

Mean Age, y	Female, %	Endpoint	Endpoint Prevalence, %
67.0	46.0	Acute cardiac pathology	46.2
65.6	47.0	Acute cardiac pathology	47.8
66.0	52.0	ACS	22.0
58.3	51.2	ACS	10.6
64.0	47.7	ACS	18.5
48.0	56.9	MACE	4.8
55.0	57.6	ACS	6.8
59.1	55.3	ACS	11.5
48.0	56.9	MACE	4.8
58.6	41.8	ACS	6.9
65.0	42.0	ACS	8.9
66.0	42.0	ACS	6.6
65.0	34.0	ACS	5.2
56.0	48.0	AMI	3.6

Selection Process

For the selection process, we used an open-source machine learning-aided software (ASReview, Utrecht University) for the initial screening of the titles and abstracts. We followed the principles of the SYstematic review Methodology Blending Active Learning and Snowballing (SYMBALS).[8,9] A more complete description of ASReview's methods and evidence, including clarification of our stopping criteria can be found in Supplemental Appendix 2. Selected articles were imported into the Covidence systematic review software (Veritas Health Innovation), for full text screening, quality assessment, and data extraction. After reaching the final subset of articles, those reference lists were then screened for possible additional inclusions.

Quality Assessment and Data Extraction

Two researchers (S.B., A.M.) separately extracted data elements from each study. The quality of the included articles was assessed by S.B. and A.M. using the 4 domains of the Quality Assessment of Diagnostic Accuracy Studies-2 tool: patient selection, index test, reference standard, and flow and timing.[10] Risk of bias and applicability concerns were assessed separately. A third author (R.E.H.) independently reviewed the extracted data and quality assessment for accuracy.

Data Synthesis and Analysis

Extracted data on study and patient characteristics, outcome measures, and follow-up information are presented in Table 1. Diagnostic test characteristics and discriminative properties are shown in Table 2.

RESULTS

Search Results

After deduplication, the initial search yielded 1,204 titles and abstracts eligible for inclusion. Following further screening, 53 articles remained, of which 40 were excluded after full text screening. An update of the search resulted in 1 additional article (Figure 1). Backward snowballing yielded no additional inclusions.

Study and Patient Characteristics

Table 1 displays the characteristics of the 14 included studies. Nine studies derived or validated a CDR and 5 studies validated troponin assays. Study populations ranged from 115 to 2,192 patients, with follow-up periods from 3 weeks to 6 months. An overview of the components of the included CDRs can be found in Supplemental Table 1. Supplemental Table 2 shows troponin assay characteristics and threshold values.

Quality Assessment

Five of the 14 (35.7%) studies showed a high risk of bias in at least 1 of the quality domains. High risk of bias was

Table 2. Diagnostic Accuracy of Risk Stratification Tools for ACS/MAC

Tool	Source, Year	RS Strategy	Subtype	AUC (95% CI)	Sensitivity, %	95% CI
A. Risk stratification tools without troponin						
Grijseels/Bruins Slot rule	Grijseels et al,[11] 1995	Grijseels rule	Derivation	0.72	...	...
	Grijseels et al,[12] 1996	Grijseels rule	Validation	0.70	91.4	(88.5-93.8)
		Aided clinical judgment	GP + Grijseels rule	...	98.3	(96.7-99.3)
	Bruins Slot et al,[1] 2011	Bruins Slot (updated Grijseels rule)[a]	Update of rule	0.66 (0.58-0.73)	97.0	(89.5-99.6)
		GP unaided	GP risk estimate	0.75 (0.68-0.82)	93.4	(85.2-98.3)
	Kleton et al[b],[15] 2021	Bruins Slot (< 5)	External validation for MACE	0.72 (0.63-0.81)	84.4	(67.2-94.7)
		GP unaided	GP risk estimate	...	81.3	(63.6-92.8)
Willemsen CDR	Willemsen et al,[13] 2019	POCT H-FABP	H-FABP	...	25.8	(12.5-44.9)
			H-FABP embedded in CDR	0.78	87.5	(70.1-95.9)
			GP risk estimate	...	75.0	(56.2-87.9)
Marburg Heart Score	Schols et al,[14] 2019	MHS (< 3)	External validation for ACS	0.64 (0.54-0.74)	75.0	(57.5-87.3)
		GP unaided	GP risk estimate	0.71 (0.61-0.80)	86.7	(72.5-94.5)
		Aided clinical judgment	GP + MHS	...	100	(88.0-100.0)
	Kleton et al[b],[15] 2021	MHS (< 2)	External validation for MACE	0.77 (0.69-0.84)	81.3	(63.6-92.8)
		GP unaided	GP risk estimate	...	81.3	(63.6-92.8)
	Manten,[16] 2022	MHS (< 2)	MHS as triage tool for ACS	0.70 (0.65-0.75)	78.6	(69.1-86.2)
INTERCHEST	Kleton[b],[15] 2021	INTERCHEST (< 2)	External validation for MACE	0.85 (0.78-0.92)	87.5	(71.0-96.5)
		GP unaided	GP risk estimate	...	81.3	(63.6-92.8)
	Manten et al,[16] 2022	INTERCHEST (< 2)	INTERCHEST as triage tool for ACS	0.77 (0.73-0.81)	88.8	(80.8-94.3)
Gencer rule	Kleton et al[b],[15] 2021	Gencer rule (< 2)	External validation for MACE	0.72 (0.63-0.81)	84.4	(67.2-94.7)
		GP unaided	GP risk estimate	...	81.3	(63.6-92.8)

ACS = acute coronary syndrome; AMI = acute myocardial infarction; AUC = area under the curve; CDR = clinical decision rule; COV = cut-off value; cTnT = cardiac troponin T; GP = general practitioner; H-FABP = heart-type fatty acid–binding protein; hs = high sensitivity; INTERCHEST = international chest pain prediction; MACE = major adverse cardiovascular events; MHS = Marburg Heart Score; NPV = negative predictive value; POCT = point of care test; PPV = positive predictive value; RS - risk stratification.

Note: We calculated the sensitivity, specificity, PPV, and NPV using 2x2 contingency tables. Note: Some CI values missing in original articles, therefore not shown here.

[a] Risk of < 10% for ACS was considered low-risk. [b] Kleton et al assessed the diagnostic accuracy of the Bruins Slot rule, Marburg Heart Score, INTERCHEST score, and Gencer rule. Therefore, the study is mentioned 4 times in the table. [c] Study did not provide 2x2 tables to calculate diagnostic test characteristics. [d] Risk threshold range: 0.1-20%.

Specificity, %	95% CI	PPV, %	95% CI	NPV, %	95% CI
...	...	...	...	...	...
36.7	(32.5-41.0)	56.9	(55.2-58.7)	82.4	(77.3-86.5)
17.8	(14.6-21.5)	52.3	(51.2-53.3)	91.9	(84.8-95.9)
9.5	(6.0-14.0)	23.4	(22.3-24.4)	91.7	(72.6-97.9)
19.4	(14.5-25.1)	24.9	(23.3-26.6)	91.8	(80.8-96.8)
43.8	(39.9-47.8)	7.1	(6.1-8.2)	98.2	(96.1-99.2)
79.3	(75.9-82.9)	16.6	(13.7-19.9)	98.8	(97.6-99.4)
96.9	(93.8-98.6)	50.0	(25.5-74.5)	91.6	(87.6-94.5)
52.0	(45.9-58.1)	17.7	(12.3-24.8)	97.2	(92.6-99.1)
67.5	(61.6-73.0)	21.4	(14.5-30.4)	95.8	(91.6-98.0)
44.0	(36.0-52.3)	24.3	(16.9-33.6)	88.0	(78.0-94.0)
41.4	(34.5-48.6)	25.2	(18.7-32.9)	93.2	(85.2-97.2)
23.3	(17.0-31.1)	23.8	(17.5-31.6)	100	(87.7-100)
67.1	(63.3-70.7)	11.1	(9.3-12.3)	98.6	(97.2-99.3)
79.3	(75.9-82.9)	16.6	(13.7-19.9)	98.8	(97.6-99.4)
54.3	(51.6-57.0)	11.2	(10.1-12.5)	97.2	(95.9-98.1)
78.8	(75.4-81.9)	17.3	(14.6-20.3)	99.1	(97.4-99.7)
79.3	(75.9-82.9)	16.6	(13.7-19.9)	98.8	(97.6-99.4)
57.7	(55.0-60.4)	13.3	(12.3-14.5)	98.6	(97.6-99.2)
37.8	(34.0-41.7)	6.4	(5.5-7.5)	98.0	(95.5-99.1)
79.3	(75.9-82.9)	16.6	(13.7-19.9)	98.8	(97.6-99.4)

continues

Table 2. Diagnostic Accuracy of Risk Stratification Tools for ACS/MACE *(continued)*

Tool	Source, Year	RS Strategy	Subtype	AUC (95% CI)	Sensitivity, %	95% CI
A. Risk stratification tools without troponin						
HEART-score variants	Harskamp et al,[18] 2021	Modified HEART	Simplified HEART-score (COV < 2)	0.86 (0.80-0.91)	96.9	(83.8-99.9)
			HEART-GP (COV < 3)	0.90 (0.85-0.95)	96.9	(83.8-99.9)
		GP unaided	GP risk estimate	...	81.3	(63.3-92.8)
Safety First	Wouters et al[c],[17] 2022	Safety First	Derivation	0.79 (0.76-0.81)	N/A	
			Internal-external validation	0.77 (0.74-0.79)	46-98[d]	
B. Troponin based risk stratification tools						
Conventional troponin	Planer et al,[19] 2006	POCT cTnT	Single POCT cTnT	...	20.8	(7.1-42.2)
		GP unaided	GP risk estimate	...	91.7	(73.0-99.0)
		Aided clinical judgment	GP + POCT cTnT	...	95.8	(78.9-99.9)
	Tomonaga et al,[20] 2011	POCT 3-in-1	POCT 3-in-1	...	89.5	(66.7-98.7)
		POCT cTnT	Single POCT cTnT	0.82 (0.69-0.95)	58.8	(32.9-81.6)
		GP unaided	GP risk estimate	...	100	(76.8-100)
	Nilsson et al,[21] 2013	POCT cTnT	Single POCT cTnT	...	28.6	(3.7-71.0)
		GP unaided	GP risk estimate	...	100	(54.1-100)
		Aided clinical judgment	GP + POCT cTnT	...	71.4	(29.0-96.3)
hs-troponin	Andersson et al,[22] 2015	hs-cTnT	Single hs-cTnT	...	83.3	(35.9-99.6)
	Johannessen et al,[23] 2021	hs-cTnT	Single hs-cTnT	0.85 (0.81-0.89)	100	(94.1-100.0)
			HEART-score	0.77 (0.73-0.82)	91.8	(81.9- 97.3)
			Modified HEART-score	0.74 (0.70-0.78)	98.4	(91.2-100.0)

ACS = acute coronary syndrome; AMI = acute myocardial infarction; AUC = area under the curve; CDR = clinical decision rule; COV = cut-off value; cTnT = cardiac troponin T; GP = general practitioner; H-FABP = heart-type fatty acid–binding protein; hs = high sensitivity; INTERCHEST = international chest pain prediction; MACE = major adverse cardiovascular events; MHS = Marburg Heart Score; NPV = negative predictive value; POCT = point of care test; PPV = positive predictive value; RS - risk stratification.

Note: We calculated the sensitivity, specificity, PPV, and NPV using 2x2 contingency tables.

[a] Risk of < 10% for ACS was considered low-risk. [b] Kleton et al assessed the diagnostic accuracy of the Bruins Slot rule, Marburg Heart Score, INTERCHEST score, and Gencer rule. Therefore, the study is mentioned 4 times in the table. [c] Study did not provide 2x2 tables to calculate diagnostic test characteristics. [d] Risk threshold range: 0.1-20%.

most common in the index test and reference standard domains.[15,16,18-20] Applicability concerns were most frequent in patient selection and index test.[11,12,14] A detailed overview of the risk of bias and applicability assessment can be found in Supplemental Appendix 3.

Risk Stratification Tools

A complete overview of diagnostic test characteristics can be found in Table 2.

Grijseels/Bruins Slot Rule

Grijseels et al developed an algorithm in 1995 which consists of a combination of patient and symptom characteristics and electrocardiogram (ECG) findings.[11,12] Discriminative properties showed C-statistics ranging from 0.70 to 0.72. In 2011, Bruins Slot et al updated the algorithm to a point-based rule with 3 risk categories for ACS.[1] Validation of the updated rule resulted in C-statistics of 0.66 to 0.72, sensitivity of 84.4% to 97.0%, and NPV of 91.7% to 98.2%. When comparing the

Specificity, %	95% CI	PPV, %	95% CI	NPV, %	95% CI
52.4	(48.4-56.3)	9.3	(8.5-10.2)	99.7	(98.0-100)
58.5	(54.6-64.2)	10.6	(9.6-11.7)	99.7	(98.2-100)
79.3	(75.9-82.4)	16.6	(13.7-19.9)	98.8	(97.6-99.4)
...		...		...	
21-93[d]		14-46[d]		93-99[d]	
100	(98.9-100)	100	(47.8-100)	94.5	(93.3-95.5)
72.6	(67.4-77.4)	19.8	(16.6-23.4)	99.2	(96.9-99.8)
72.6	(67.4-77.4)	20.5	(17.5-23.9)	99.6	(97.2-99.9)
92.0	(87.3-95.3)	51.5	(39.3-63.5)	98.9	(96.1-99.7)
93.1	(87.3-96.8)	52.6	(34.5-70.1)	94.5	(90.7-96.8)
78.7	(70.2-84.7)	31.8	(25.4-39.0)	100	(96.6-100)
97.5	(92.3-99.5)	40.0	(11.7-77.1)	95.9	(93.7-97.4)
62.9	(49.7-74.8)	20.7	(15.9-26.5)	100	(91.0-100)
77.7	(69.2-84.8)	15.6	(9.4-24.8)	97.9	(93.6-99.4)
76.2	(67.0-83.8)	16.1	(10.5-23.9)	98.8	(93.3-99.8)
34.5	(32.2-36.8)	5.3	(5.2-5.5)	100	(99.4-100)
52.5	(50.0-54.9)	6.7	(6.1-7.3)	99.4	(98.7-99.8)
38.7	(36.3-41.1)	5.6	(5.3-5.9)	99.8	(98.9-100)

CDR to unaided clinical judgment, GPs categorized patients with and without ACS better.[1,15]

Willemsen CDR

In 2019, Willemsen et al evaluated a heart-type fatty acid–binding protein (H-FABP) POCT.[13] The diagnostic accuracy of H-FABP as standalone test to rule out ACS had a sensitivity of 25.8% and NPV of 91.6%. Using H-FABP with a CDR increased the sensitivity to 87.5% and NPV to 97.2%. Compared with unaided clinical judgment, fewer ACS cases were missed (1.3% vs 2.6%), but there were 13.9% more referrals.

Marburg Heart Score

The Marburg Heart Score (MHS) was developed in 2010 to rule out coronary artery disease.[24] Later, it was evaluated to rule out ACS or MACE in 1 prospective and 2 retrospective studies, with different rule-out thresholds (**Table 1**).[14,15,16]

C-statistics ranged from 0.64 to 0.77, with sensitivity of 75.0% to 81.3%, and NPV of 88.0% to 98.6%. The MHS did not outperform unaided clinical judgement.[14]

INTERCHEST

Like the MHS, the 2017 International Chest pain prediction (INTERCHEST) score was developed to rule out coronary artery disease, and later tested to rule out ACS or MACE. The rule was derived from pooled individual patient data of 5 studies (3,099 patients total).[25] Twofold retrospective validation resulted in C-statistics of 0.77 to 0.85, sensitivity of 87.5% to 88.8%, and NPV of 98.6% to 99.1%.[15,16] Discriminative power was similar to unaided clinical judgement.

Gencer Rule

The Gencer rule was developed in 2010 to rule out coronary artery disease and consists of 7 components.[26] It was validated to rule out MACE in 1 study with a C-statistic of 0.72, sensitivity of 84.4%, and NPV of 98.0%.[15] The performance of the rule was equivalent to unaided clinical judgement.

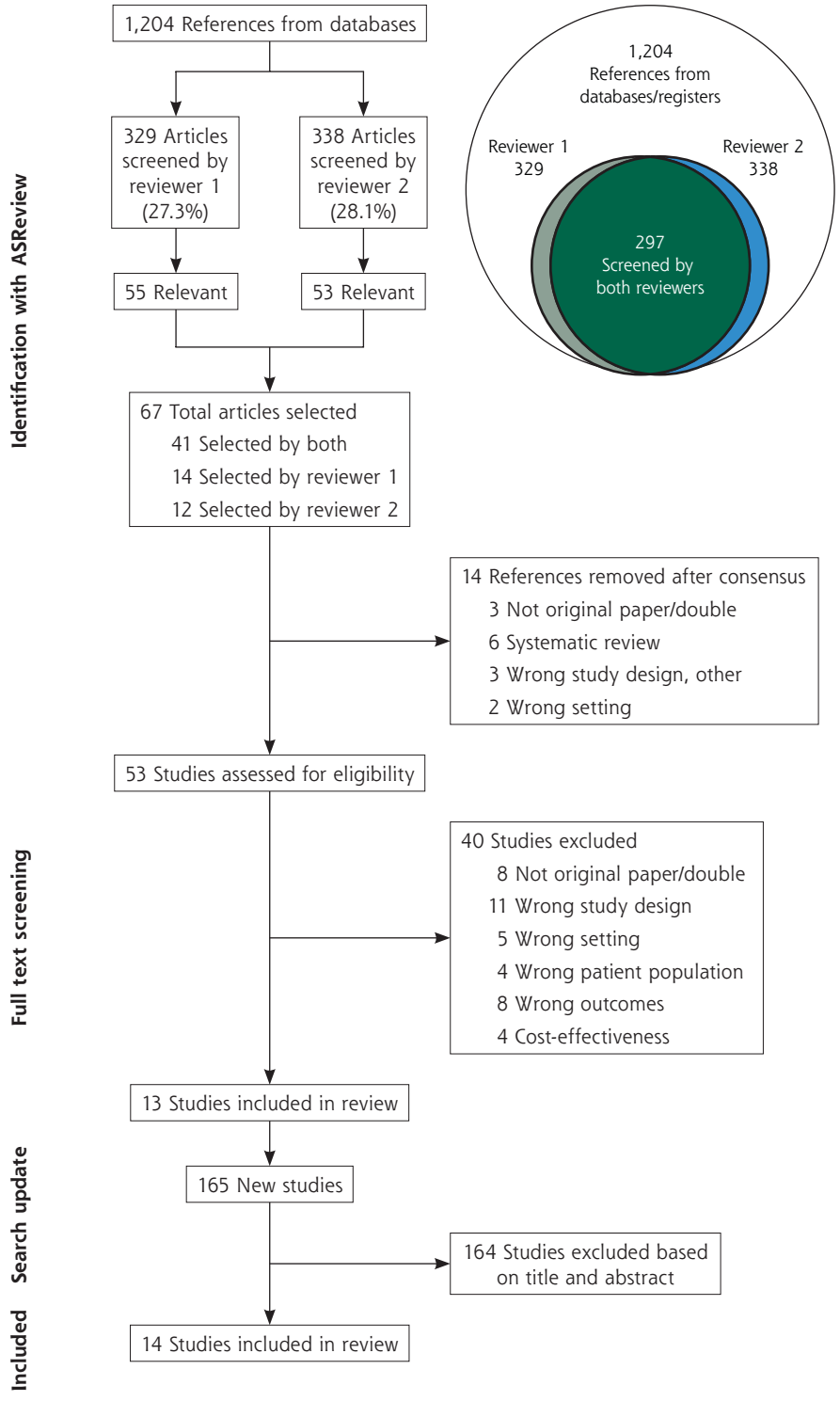
Safety First

Wouters et al in 2022 developed a computerized risk stratification tool for the triage of acute chest pain patients in out-of-hours primary care settings.[17] The tool includes 7 predictors of ACS. After derivation, an internal-external validation technique was used, resulting in a C-statistic of 0.77 to 0.79. The authors did not recommend a cut-off point; however, diagnostic accuracy for various risk thresholds (0.1% to 20%), showed a sensitivity of 46% to 98% and NPV of 93% to 99%.

HEART-Score Variants

The original HEART-score tool (History, ECG, Age, Risk factors, and Troponin), was developed to identify patients at low risk for short-term MACE among patients with acute chest pain in the emergency department.[27] For use in primary care, the original HEART-score was modified.[18] The first variation (simplified HEART-score) simply omits troponin. The second variation, HEART-GP, replaces troponin with the GP's sense of alarm. The modified scores had a C-statistic of 0.86 and 0.90, respectively, sensitivity of 96.9%, and NPV of 99.7% for both versions. Compared with unaided clinical judgment, both scores improved safety, at the cost of additional referrals (simplified HEART had 26% more, and HEART-GP had 4% more).

Figure 1. Flowchart of systematic review of the literature.



ASR = Active learning for Systematic Reviews.

Conventional Troponin

In a study by Planer et al in 2006, a qualitative cardiac troponin T (cTnT) test was combined with the GP's clinical assessment.[19] The combined strategy resulted in a sensitivity of 95.8% and NPV of 99.6%. The cTnT test as a standalone test showed poor sensitivity (20.8%) and did not outperform unaided clinical judgment.

Tomonaga et al in 2011 compared the use of a 3-in-1 POCT for cTnT, N-terminal pro-B-type natriuretic peptide (NT-proBNP), and D-dimer to usual care in patients with chest pain, dyspnea, or symptoms suggestive for thromboembolic events.[20] The use of this combined POCT test led to more accurate working diagnoses (76% vs 60%) and fewer referrals (30% vs 55% false positives). For ACS, however, the sensitivity was 89.5% compared with 100% in the usual care group, with a NPV of 98.9%, compared with 100%. Sensitivity for troponin as standalone test to rule out ACS was 58.8%, missing 7 out of 17 (41.2%) patients with ACS.

A Swedish study by Nilsson et al in 2013 compared 3 primary care practices that already incorporated the use of cTnT-POCT to 4 practices that did not use cTnT-POCT.[21] Use of cTnT-POCT by GPs reduced hospital referrals (25% vs 43%), but at the expense of sensitivity (71.4% in the practices using cTnT-POCT vs 100% in the control group). Troponin as standalone test showed a sensitivity of 28.6% and NPV of 95.9%, missing 5 out of 7 (71%) patients with ACS.

High-Sensitivity Troponin

In 2015, Andersson et al used the original (stored) samples from the study by Nilsson et al in 2013 to measure high-sensitivity (hs) cTnT and compare the diagnostic outcomes with the outcomes for conventional troponin.[22] They found a sensitivity of 83.3% compared with 33.3%, missing 1 out of 6 (17%) patients with ACS. This came at the expense of specificity (76.2% vs 97.5%) and thus led to additional referrals (23% vs 2% false positives).

Lastly, in 2021, Johannessen et al validated 3 strategies to rule out AMI using hs-cTnT in a primary care emergency outpatient clinic in Norway.[23] The first was a single hs-cTnT rule-out strategy. High sensitivity cTnT was measured at presentation and AMI was ruled out if hs-cTnT was below the limit of detection (ie, very low). No AMI were missed and sensitivity and NPV were 100% with a C-statistic of 0.85. The second and third strategies were the original HEART-score and a modified HEART-score with lower hs-cTnT thresholds. The modified HEART-score outperformed the original HEART-score (sensitivity 98.4% vs 91.8% and NPV 99.8% vs 99.4%), but not the single hs-cTnT rule out strategy.

DISCUSSION

This systematic review provides an overview of the evidence on risk stratification tools for acute chest pain in primary care. Seven CDRs with variable diagnostic properties have been evaluated. Some may improve safety (ie, modifications of the HEART-score), but at the expense of more referrals. None of the CDRs demonstrated superiority over unaided GP assessment. In studies evaluating strategies using troponin we found promising results among those that used high sensitivity troponin assays, either as a standalone tool, or incorporated into a CDR, however, further study is needed.

Strengths and Limitations

This systematic review is an extensive and up-to-date overview of risk stratification tools for acute chest pain in primary care. It will aid GPs in their decision for referral and additional testing. A strength of this review is the inclusion of relatively new strategies using hs-troponin. A limitation is the considerable heterogeneity of the included studies, particularly in patient selection, (a delayed-type) reference standard, and follow-up intervals. Furthermore, several of the included studies were limited by small sample sizes (7 had fewer than 500 patients) and low ACS prevalence. This automatically generates high NPVs and might cause overestimation of the tool's performance if the sensitivity is not taken into consideration. Finally, we only included articles in English in the review, which might introduce language bias.

Interpretation of Results

Prior international research indicates that a 1% miss rate is considered acceptable for ACS and MACE.[28,29] Additionally, a risk stratification tool also needs to be efficient. Other research found that Dutch GPs would accept 25-50 unnecessary referrals for every patient with ACS.[28] Assuming an ACS prevalence of 5%, a specificity of at least 50% is needed. Among the studied CDRs, none met the desired sensitivity and specificity. Only the modified HEART-scores may approach these requirements, but they need further validation. Hence, we cannot recommend currently available CDRs as standalone tools to rule out ACS.

Conventional troponin as a standalone test did not meet the desired diagnostic accuracy, and its use seems to be outdated since the introduction of hs-troponin assays. The studies using hs-troponin measurement show the most promising results with sensitivities up to 100%. Although the study by Andersson reported a lower sensitivity (83%) for their single measurement rule-out strategy, this might be due to using a hs-cTnT threshold below the 99th percentile.[22] In contrast, the study by Johannessen used a much lower threshold below the limit of detection with 100% sensitivity.[23] The European Society of Cardiology guidelines underline the necessity of a very low threshold to rule out ACS by a single hs-troponin measurement and report assay specific thresholds.[30]

The One-hoUr Troponin in a low-prevalence population of Acute Coronary Syndrome (OUT-ACS) study (published in 2020), prospectively validated the European Society of Cardiology 0/1-hr algorithm, including hs-troponin, to rule out AMI in primary care.[30,31] Although this strategy approaches both desired sensitivity and specificity (98.4%

and 79.4%), the algorithm requires serial troponin tests and observation of patients, which is often not possible in primary care settings.

Finding a tool that exceeds the GP's accuracy might be challenging, since unaided clinical judgment is already reasonably good with a sensitivity 75% to 100% and specificity 18% to 79%.[1,13-15,19,20] Best diagnostic accuracy might therefore be achieved by combining the GP's risk assessment with a stratification tool instead of risk stratification tools as standalone tests.

Future Research

Results for risk stratification strategies using hs-troponin are promising, but require further prospective validation, since studies in primary care are limited.[22,23] Although hs-troponin strategies are extensively researched and found to be safe in emergency department settings, results cannot be automatically transferred to primary care due to the lower pre-test probability for ACS.[5] While the CDRs did not meet the desired test accuracy to rule out ACS, a combination of a CDR with hs-troponin measurement might offer optimal results. Such strategies are currently under research in primary care practices (Pijn op de borst-HELP[32]) and out-of-hours primary care (HEART-GP[33]).

Variations in health care systems across countries may influence the applicability of risk stratification tools. All but 1 of the included studies were conducted in Europe, where GPs often function as gatekeepers to secondary care. These rule-out strategies, however, could also benefit countries with other primary care structures, such as the United States or countries with large rural regions, where specialized care is scarce and diagnostic options are limited, especially since cardiac monitoring is not required. Such changes, however, require cultural and organizational changes.

Finally, pre-hospital care comprises both primary care and ambulance services and we advocate for standardized care across the entire continuum. Future research should focus on risk stratification tools that are applicable in the entire pre-hospital care chain, and preferably in line with hospital care. The latter is especially important for strategies using troponin since different assays and thresholds hamper communication between health care providers.

CONCLUSION

Clinical decision rules without troponin or with conventional troponin do not show sufficient sensitivity to rule out ACS in primary care and are not recommended as standalone tools. The first hs-troponin studies in primary care show promising results, but further prospective validation in primary care is needed before recommending its implementation.

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Key words: acute coronary syndrome; chest pain; clinical decision rules; primary health care; troponin

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Supplemental materials

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