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Review

Point-of-care testing in primary care patients with acute cardiopulmonary symptoms: a systematic review

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Abstract

Background. Point-of-care tests (POCT) can assist general practitioners (GPs) in diagnosing and treating patients with acute cardiopulmonary symptoms, but it is currently unknown if POCT impact relevant clinical outcomes in these patients.
Objective. To assess whether using POCT in primary care patients with acute cardiopulmonary symptoms leads to more accurate diagnosis and impacts clinical management.
Methods. We performed a systematic review in four bibliographic databases. Articles published before February 2016 were screened by two reviewers. Studies evaluating the effect of GP use of POCT on clinical diagnostic accuracy and/or effect on treatment and referral rate in patients with cardiopulmonary symptoms were included.
Results. Our search yielded nine papers describing data from seven studies, on the clinical diagnostic accuracy of POCT in a total of 2277 primary care patients with acute cardiopulmonary symptoms. Four papers showed data on GP use of D-dimer POCT in pulmonary embolism (two studies); two studies on Troponin T in acute coronary syndrome; one on heart-type fatty acid-binding protein (H-FABP) in acute coronary syndrome; one on B-type natriuretic peptide (BNP) in heart failure; one on 3-in-1 POCT (Troponin T, BNP, D-dimer) in acute coronary syndrome, heart failure and/or pulmonary embolism. Only one study assessed the effect of GP use of POCT on treatment initiation and one on actual referral rates.
Conclusion. There is currently limited and inconclusive evidence that actual GP use of POCT in primary care patients with acute cardiopulmonary symptoms leads to more accurate diagnosis and affects clinical management. However, some studies show promising results, especially when a POCT is combined with a clinical decision rule.

Keywords: Diagnosis, general practice, heart, lung, point-of-care testing, primary health care

Introduction

Excluding serious conditions is one of the cornerstones of general practice consultations. General practitioners (GPs) often use diagnostic tests to assist their decision-making process (1). A wide range of point-of-care tests (POCT) is currently available to GPs, but at present only few POCT are widely used by GPs (2). GPs across countries have expressed a desire to use more POCT in their practice, especially to help them diagnose acute conditions like

acute thromboembolic conditions (D-dimers), and heart diseases (Troponin, B-type natriuretic peptide) (2). This is understandable as patients with cardiopulmonary symptoms are often diagnostically challenging for GPs. POCT could assist GPs in diagnosing and treating patients with these symptoms, but GPs have expressed reservations towards using additional POCT as well, including doubts about the reliability of these tests (3). Nonetheless, several studies have shown that the use of POCT may reduce referrals to secondary care or drug prescriptions, and lead to higher patient satisfaction and better adherence to treatment (4–7). GPs generally consider the effectiveness of use of a POCT on the decision-making process as the most important aspect in their consideration to use a POCT (8).

Before advocating a widespread use and implementation of GP use of POCT in patients with acute cardiopulmonary symptoms, it is important to determine if GP use of these tests actually affects clinical outcomes of patients. Therefore, the aim of this systematic review is to assess whether using POCT in primary care leads to more accurate diagnosis and impacts clinical management in patients with acute cardiopulmonary symptoms.

Method

Search strategy

We performed a systematic electronic literature search in four bibliographic databases: PubMed, EMBASE, CINAHL and the Cochrane library. All articles published before October 2014 were included. We searched the databases for articles on (acute) cardiopulmonary disease and point-of-care testing in primary care. We included several free search terms per category as well as MESH terms. The exact search terms for the PubMed search are shown in Box 1. No search limits were applied. We performed a PubMed search update from October 2014 till February 2016. Furthermore, we checked the reference lists of all included articles for other relevant studies. When no full texts were available, e.g. in the case of conference abstracts, we contacted the authors to retrieve a full manuscript when available.

Study selection

After removing duplicates, two reviewers (JS, AS and in search update AS, JC) independently screened titles and abstracts for predefined PICOS criteria on population and intervention (Box 2). In case of disagreement, a third reviewer (JC) independently screened title and abstract and the record was discussed in a consensus meeting. Subsequently, one reviewer (JC) screened and another reviewer (AS) checked the full-texts of the remaining records on all PICOS criteria.

All PICOS criteria were predefined in a study protocol and were defined in more detail during the review process. We excluded all studies that did not agree with the PICOS criteria. During this stage, we decided to also exclude papers on the use of POCT in (acute respiratory)infections, as many articles, including systematic reviews, have been published on this topic (9–11).

Data extraction and analysis

Data extraction was performed by one reviewer (AS) and the extracted results were studied by all authors. When diagnostic accuracy outcomes were not presented in the article, we calculated them when possible. The heterogeneity among studies precluded a meta-analysis. Therefore, we undertook a narrative synthesis of the data to explore the evidence for the clinical effectiveness of GP use of POCT in primary care patients with cardiopulmonary symptoms.

Box 1. Full Pubmed search (1640 hits)

((((((((((((((point of care) OR point-of-care) OR office) OR bedside) OR near patient) OR POC) OR on-site) OR rapid) OR ultra-rapid)) AND (((((((testing) OR test) OR tests) OR assay) OR assays) OR immunoassay) OR immunoassays))) OR 'Point-of-Care Systems'[Mesh])) AND ((((((((((primary care) OR primary health care) OR general practice) OR family practice) OR general practitioner) OR GP) OR family doctor) OR family physician)) OR (((((‘Primary Health Care'[Mesh] OR 'Physicians, Primary Care'[Mesh])) OR 'Family Practice'[Mesh]) OR 'General Practitioners'[Mesh]) OR 'Physicians, Family'[Mesh])))) AND ((((((((((((((((((((((((cardiopulmonary disease) OR cardiac disease) OR pulmonary disease) OR chest pain) OR chest infections) OR coronary syndromes) OR myocardial infarction) OR thromboembolic event) OR palpitations) OR arrhythmias) OR heart failure) OR pericarditis) OR dyspnoea) OR pulmonary embolism) OR lung embolism) OR pneumonia) OR lower respiratory infection) OR cough) OR bronchitis) OR asthma) OR COPD) OR pleuritis)) OR ((((((((((((((((((‘Pulmonary Heart Disease'[Mesh]) OR 'Heart Diseases'[Mesh]) OR ('Lung Diseases'[Mesh] OR 'Lung Diseases, Obstructive'[Mesh])) OR 'Chest Pain'[Mesh]) OR ('Acute Coronary Syndrome'[Mesh] OR 'Microvascular Angina'[Mesh])) OR ('Myocardial Infarction'[Mesh] OR 'Inferior Wall Myocardial Infarction'[Mesh] OR 'Anterior Wall Myocardial Infarction'[Mesh])) OR 'Thromboembolism'[Mesh]) OR 'Arrhythmias, Cardiac'[Mesh]) OR ('Heart Failure'[Mesh] OR 'Heart Failure, Systolic'[Mesh] OR 'Heart Failure, Diastolic'[Mesh])) OR 'Pericarditis'[Mesh]) OR 'Dyspnea'[Mesh]) OR 'Pulmonary Embolism'[Mesh]) OR ('Pneumonia'[Mesh] OR 'Pneumonia, Bacterial'[Mesh] OR 'Pneumonia, Viral'[Mesh])) OR 'Cough'[Mesh]) OR 'Bronchitis'[Mesh]) OR 'Asthma'[Mesh]) OR 'Pulmonary Disease, Chronic Obstructive'[Mesh]) OR 'Pleurisy'[Mesh]))

Quality assessment

The internal and external validity of the two trails was assessed using the Cochrane Risk of Bias Tool for randomized trails (12). Furthermore, the risk of bias for the diagnostic accuracy outcomes in all studies, was assessed using the QUADAS-2 tool (13). All assessments were performed by one reviewer (AS) and checked for accuracy by a second (JC). Quality criteria for inclusion were not set as we intended to be broad-based and only few studies were included on the basis of eligibility.

Results

Study selection and study characteristics

From 3657 records, we identified 3079 unique records; 3078 from the database searches and one additional record through a conference abstract. We assessed 169 full-text articles for eligibility and nine papers met our inclusion criteria (Figure 1) (14–22). Eight of nine papers were published within the past 5 years. Study characteristics of the included papers and accuracy outcomes are shown in Tables 1 and 2. All studies were prospective and two were randomized trials. The included studies all had domains with high risk of bias using the Cochrane Risk of Bias Tool for both trails and the

Box 2. PICOS criteria

Population
Patients with acute cardiopulmonary conditions/symptoms in primary care in Western/developed countries. Acute cardiopulmonary was defined as acute conditions or symptoms of either the heart, lungs or vascular blood supply of these organs at the height of the chest cavity. For example, we excluded studies on non-chest related conditions like deep venous thrombosis or upper respiratory tract infection. Furthermore, we excluded studies on fairly uncommon diseases in Western countries, e.g. tuberculosis and HIV.

Intervention
All studies that reported on POCT as an intervention. POCT was defined as biomedical tests on patient material, e.g. blood, urine, faeces, performed and analysed at the point-of-care. We excluded tests like electrocardiography, ultrasonography and spirometry.

Comparator
Care as usual; no use of a POCT.

Outcomes
We included studies on clinical effectiveness; clinical diagnostic accuracy and/or effect on treatment and referral rates. We excluded studies on analytical test accuracy or studies with the objective to determine the optimal cut-off value for a POCT.

Study design
Randomized controlled trails and non-randomized controlled trails, e.g. prospective cohort studies.

QUADAS-2 tool for the diagnostic accuracy in all studies (Tables 3 and 4). Main risks of bias for the diagnostic accuracy outcomes were not all patients receiving the same reference standard and some patients were only followed-up without any extra tests done to confirm absence of the index disease.

Clinical diagnostic accuracy

The eligible nine papers described data of seven different studies which showed relevant data on the clinical diagnostic accuracy of GP use of POCT in patients with acute cardiopulmonary symptoms in primary care (Tables 1 and 2). Three papers described the results of one large clinical study (AMUSE-2) evaluating the effect of D-Dimer POCT for pulmonary embolism (14–16). We found one additional study on D-dimer POCT. Hence, four papers showed data on GP use of D-dimer POCT, two studies on GP use of Troponin T, one on GP use of heart-type fatty acid-binding protein (H-FABP), one on GP use of B-type natriuretic peptide (BNP) and one on a 3-in-1 POCT (Troponin T, BNP, D-dimer) (14–22).

Pulmonary embolism

In a prospective cohort study, Geersing *et al.* (14) investigated the diagnostic value of a combination of the Wells clinical decision rule and a D-dimer POCT to safely exclude pulmonary embolism in 598 adult patients clinically suspected of pulmonary embolism. Seventy-three (12%) patients were diagnosed with a pulmonary embolism. This study concluded that pulmonary embolism can be safely and efficiently excluded on the basis of a Wells score of ≤4 combined with a negative D-dimer POCT result, with a positive and negative predictive value (PPV and NPV) of 21.2 and 98.5%, respectively. Using a Wells threshold of <2 was even safer, but this was at the expense of the specificity (Table 2) (14). In a post hoc analysis by Lucassen *et al.* (15), the D-dimer POCT had a higher specificity as a stand-alone POCT compared to the combination of a D-dimer POCT with the Wells, yet it was less safe with a NPV of 96%. A subanalysis of the same study population by Erkens *et al.* (16) showed that a positive Wells rule or a positive D-dimer POCT are not only positively associated with pulmonary embolism, but also with other clinically relevant diseases, for example pneumonia. In another prospective cohort study by Schouten *et al.* (17), wherein 150 patients were entered via the AMUSE-2 study, a NPV of 94% was found when using a combination of the Wells rule (≤4 points) and a D-dimer POCT in 294 elderly ambulatory adults (≥60 years) suspected of having a pulmonary embolism. The NPV and the specificity in this study was considerately lower than in the study from Geersing *et al.* (14) when compared with the same Wells cut-off score. The NPV was also lower when compared to the Wells <2 condition in the study by Geersing and compared to the D-dimer as a stand-alone test by Lucassen. A scenario analyses in the study of Schouten showed that lowering the threshold for the Wells rule did not improve the failure rate (6.3%) (17). The percentage of patients diagnosed with a pulmonary embolism was higher—and the included patients were older—in the study by Schouten (28%) compared to Geersing *et al.* (14) (12%).

Acute coronary syndrome and heart failure

Two prospective cohort studies by Planer *et al.* (18) and Nilsson *et al.* (19) investigated the diagnostic value of Troponin T in patients with chest pain or other symptoms clinically suggestive of acute coronary syndrome. Planer studied the diagnostic value of Troponin T POCT for the diagnosis of acute myocardial infarction in 349 patients (>30 years) with at least 20 min consecutive chest pain beginning at least 8 h prior to presentation and occurring within the previous 6 days. Of all 349 patients, only 6 (1.7%) were diagnosed with a myocardial infarction, of which one was missed by the Troponin T POCT. They calculated a sensitivity of 83% and a specificity of 100% for a diagnosis of myocardial infarction within 72 h. The PPV and NPV were 100 and 99.7%, respectively. The sensitivity, specificity, PPV and NPV all increased to 100% when the test was combined with the family physician's clinical decision. They concluded that Troponin T POCT had a very high diagnostic value for the evaluation of patients with non-recent onset chest pain in family practice (18).

The results of Nilsson were less positive with regards to the sensitivity and PPV of Troponin T POCT. This prospective cohort study investigated the diagnostic value of GP use of Troponin T POCT in 196 patients (≥35 years) with chest pain, dyspnoea on exertion, unexplained weakness and/or fatigue commenced or worsened during the last 7 days. Of all patients, 128 patients were diagnosed by GPs using a Troponin T POCT. Within the intervention group only 3 (2.3%) patients were diagnosed with a myocardial infarction and 4 (3.1%) with unstable angina. All patients with an unstable angina had a false negative Troponin T POCT, which was also the case in the study by Planer. They calculated a sensitivity of 67%, a specificity of 98%, PPV of 40% and NPV of 99% for acute myocardial infarction among patients with chest pain. When adding unstable angina to the outcome group, both the sensitivity and NPV decreased to 29 and 96%, respectively (19).

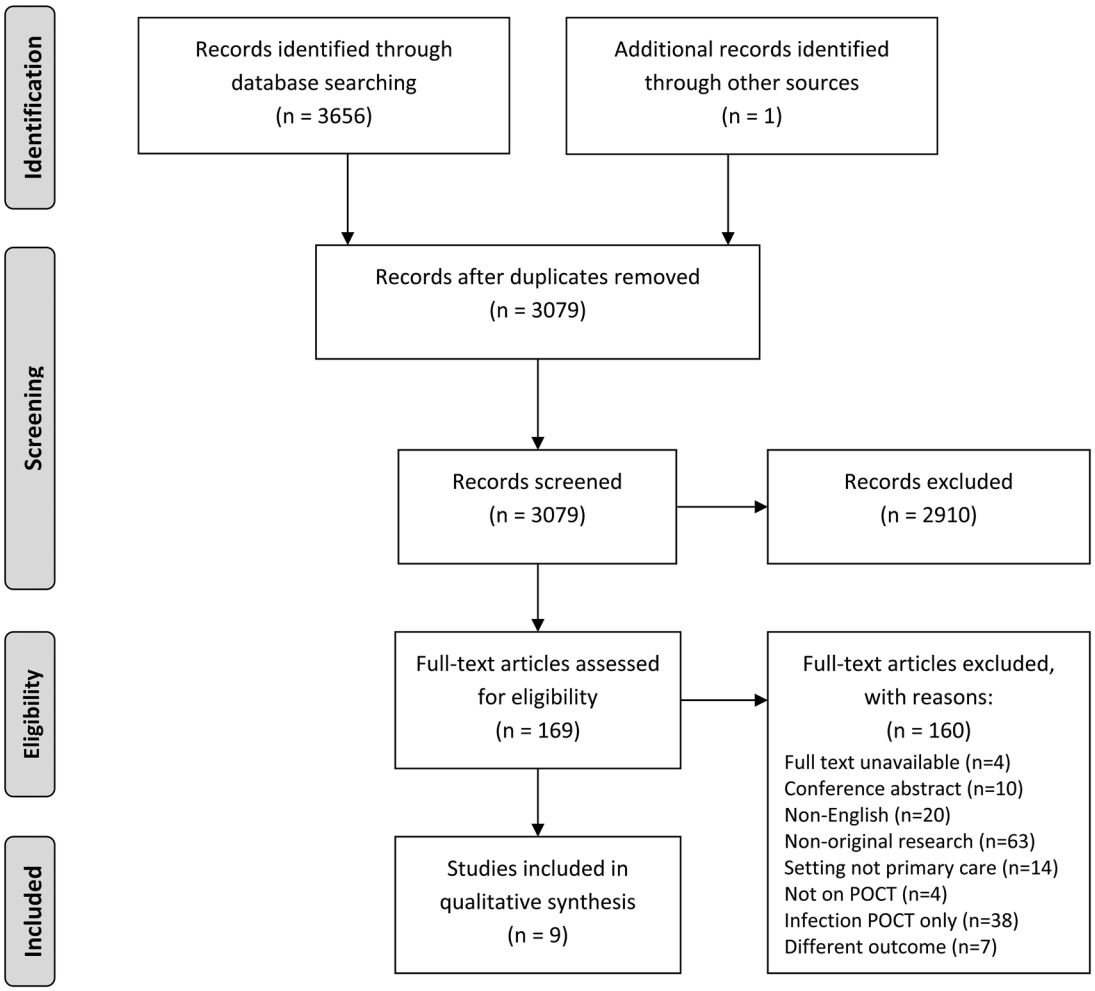

Figure 1. Flow diagram of study selection.

Bruins Slot *et al.* (20) investigated the diagnostic accuracy of H-FABP POCT in 298 patients—with symptoms less than 24 h—suspected of acute coronary syndrome in a prospective cohort study in primary care. In this study substantially more patients were diagnosed with an acute coronary syndrome, 66 of 298 (22%) to be exact, of which 14 (21%) with unstable angina, and 52 (79%) with myocardial infarction, compared to the study population of Planer and Nilsson. By adding H-FABP POCT to the regular diagnostic model for acute coronary syndrome, the area under the receiver operating curve increased from 0.66 to 0.75. The sensitivity, specificity, PPV and NPV of H-FABP were 43, 94, 72 and 83%, respectively, when symptoms occurred no longer than 6 h and 39, 94, 65 and 84%, respectively, when symptoms occurred no longer than 24 h (20).

Burri *et al.* (21) investigated the diagnostic accuracy of BNP-guided diagnosis for heart failure in 323 adult patients presenting with new onset or clearly worsening dyspnoea as their primary symptom in an individually randomized controlled trail. Heart failure was diagnosed in 111 (34%) patients. The BNP-guided diagnostic strategy compared to standard management increased diagnostic accuracy from 33 to 45%. The area under the receiver operating curve for BNP to identify heart failure was 0.87. At the optimal cut-off of 153 ng/l, the sensitivity, specificity, PPV and NPV were 72, 93, 88 and 84%, respectively (21).

Pulmonary embolism, acute coronary syndromes and heart failure

In a multicentre cluster-randomized controlled trial, Tomonaga *et al.* (22) studied the clinical benefit of a 3-in-1 POCT with Troponin T, BNP and D-dimer, compared to conventional diagnosis in 369 patients with potentially cardiovascular chest pain or symptoms. An acute coronary syndrome was diagnosed in 33 (8.9%) patients, heart failure in 51 (13.8%) patients and a thromboembolic event in 24 (6.5%) patients. The diagnoses of acute coronary syndromes, heart failure and thromboembolic events were significantly more correct in the POCT group, with 69.8% correct diagnoses in the POCT group compared to 45.2% in the standard care group. The sensitivity, specificity, PPV and NPV of Troponin T POCT for acute coronary syndrome were 59, 93, 53 and 95%, respectively. GP use of BNP POCT for heart failure had a sensitivity, specificity, PPV, and NPV of 100, 72, 74 and 100% respectively and GP use of D-dimer POCT for thromboembolic conditions 93, 78, 36 and 99%, respectively (22).

Clinical management

Hardly any studies evaluated the actual clinical management when using POCT. With regards to treatment, Burri *et al.* did evaluate the time to appropriate treatment, comparing the intervention group that used a BNP POCT to the control group. GP use of a BNP POCT

Table 1. Characteristics of included articles.

	Population	Intervention	Comparison	Outcome	Design
Geersing *et al.* (14)	*n* = 598 Adults (≥18 years) with clinically suspected pulmonary embolism; symptoms of unexplained (sudden) or deterioration of existing dyspnoea, pain on inspiration or unexplained cough	*n* = 598 Qualitative D-dimer POCT in combination with Wells rule	Wells rule without D-dimer POCT	Diagnostic accuracy	Prospective cohort study
Lucassen *et al.* (15)	*n* = 598 See Geersing *et al.* (14)	*n* = 598 Qualitative D-dimer POCT in combination with Wells rule	D-dimer POCT as stand-alone test	Diagnostic accuracy	Prospective cohort study, post hoc analysis
Erkens *et al.* (16)	*n* = 598 See Geersing *et al.* (14)	*n* = 598 Qualitative D-dimer POCT in combination with Wells rule	—	Frequency of alternative diagnosis	Prospective cohort study, sub-analysis
Schouten *et al.* (17)	*n* = 294 Elderly (≥60) suspected of having a pulmonary embolism (symptoms of unexplained or deterioration of dyspnoea, pain on inspiration or unexplained cough), whom were community dwelling or residing in nursing homes	*n* = 294 Qualitative D-dimer POCT in combination with Wells rule	Standard clinical care	Diagnostic accuracy	Prospective cohort study
Planer *et al.* (18)	*n* = 349 Patients (>30 years) with at least 20 consecutive minutes of chest pain beginning at least 8 h prior to presentation and occurring within the previous 6 days	*n* = 349 Qualitative Troponin T POCT in combination with current daily practice	Standard clinical care	Diagnostic accuracy	Prospective cohort study
Nilsson *et al.* (19)	*n* = 196 Patients (≥35 years) with chest pain, dyspnoea on exertion, unexplained weakness, and/or fatigue commenced or worsened during the last 7 days with no other probable cause than cardiac	*n* = 128 Quantitative troponin T POCT in combination with ECG and clinical evaluation	*n* = 68 ECG and clinical evaluation	Diagnostic accuracy Emergency referrals	Prospective cohort study
Bruins Slot *et al.* (20)	*n* = 298 Patients clinically suspected of an acute coronary syndrome by the GP (e.g. patients with chest pain, or other more 'vague' symptoms prompting a GP to suspect acute coronary syndrome) and complaints lasting for no more than 24 h	*n* = 298 Qualitative H-FABP POCT in combination with current daily practice	Standard clinical care	Diagnostic accuracy	Prospective cohort study
Burri et *al.* (21)	*n* = 323 Patients (≥18 years) presenting with new onset or clearly worsening dyspnoea as their primary symptom	*n* = 163 Quantitative BNP POCT in combination with current daily practice	*n* = 160 Standard clinical care	Diagnostic accuracy Time to appropriate treatment	Individually randomized controlled trial
Tomonaga *et al.* (22)	*n* = 369 Patients presenting with possible cardiovascular chest pain or symptoms within the previous 5 days	*n* = 218 3-in-1 quantitative POCT; Troponin T, BNP, D-dimer POCT in combination with daily practice	*n* = 151 Standard clinical care	Diagnostic accuracy	Cluster-randomized controlled trial

BNP, B-type natriuretic peptide; ECG, electrocardiogram; GP, general practitioner; H-FABP: heart-type fatty acid-binding protein; POCT, point-of-care test.

significantly reduced the time to initiation of appropriate treatment by 12 days. In 66% of patients appropriate treatment was initiated on the day of initial presentation in the BNP POCT group, compared with 53% in the control group.

Only one study evaluated the effect of GP use of a POCT on actual referral rates to secondary care. The Nilsson study had emergency referrals within 30 days of study enrolment as primary outcome. Patients managed by physicians using Troponin T POCT were referred in 25% of cases compared to 43% of patients managed by physicians without POCT. However, two patients who were not referred in the Troponin T POCT group were judged as missed cases, with one having an acute myocardial infarction and one unstable angina. Therefore, Nilsson et al concluded that the use of Troponin T POCT in patients with chest pain including those with acute chest pain may reduce emergency referrals, but probably at the cost of an increased risk to miss patients with an acute myocardial infarction or unstable angina (19). In all of the other included studies actual referral rates were not determined, although some studies—including

Table 2. Clinical diagnostic accuracy of used tests in included studies

	Diagnosis	Final diagnosis in total study population (%)	Diagnostic intervention (cut-off)	Reference standard	Sens	Spec	PPV	NPV	Patients with a negative test result *n*/*N* (%)	Patients with a *false* negative test result *n*/*N* (%)
Geersing *et al.* (14)	Pulmonary embolism[a]	73 of 598 (12.2)	Wells ≤4 + D-dimer POCT (80 ng/ml)	Composite reference standard[c]	95	51	21	99	272/598 (45)	4/272 (1.5)
			Wells <2 + D-dimer POCT (80 ng/ml)		97	32	20	99	168/598 (28)	2/168 (1.2)
Lucassen *et al.* (15)	Pulmonary embolism	73 of 598 (12.2)	D-dimer POCT, stand-alone (80 ng/ml)	Composite reference standard[c]	84	62	24	96	339/598 (57)	12/339 (3.5)
Schouten *et al.* (17)	Pulmonary embolism	83 of 294 (28.2)	Wells ≤4 + D-dimer POCT (80 ng/ml)	Composite reference standard[c]	94	38	37	94	85/294 (29)	5/85 (5.9)
Planer *et al.* (18)	Myocardial infarction	6 of 349 (1.7)	Troponin T POCT (0.08 µg/l)	Common practice, including follow-up only	83	100	100	99.7	344/349 (99)	1/344 (0.3)
	Myocardial infarction + unstable angina	24 of 349 (6.9)			21	100	100	94	344/349 (99)	19/344 (5.5)
Nilsson *et al.* (19)	Myocardial infarction	8 of 196 (4.1)	Troponin T POCT (0.03 µg/l)	Evaluation of hospital records, ECG and GP's clinical evaluation or telephone interviews	67	98	40	99	123/128 (96)	1/123 (0.8)
	Myocardial infarction + unstable angina	13 of 196 (6.6)			29	98	40	96	123/128 (96)	5/123 (4.1)
Bruins Slot *et al.* (20)	Acute coronary syndrome[b] (symptoms <6 h)	53 of 209 (25.4)	H-FABP POCT (7 ng/ml)	ECG, cardiac biomarkers, creatinine kinase-myocardial band and follow-up in all patients, including hospital records in referred patients	43	94	72	83	177/209 (85)	30/177 (16.9)
	Acute coronary syndrome[b] (symptoms <24 h)	66 of 298 (22.1)			39	94	65	84	258/298 (87)	40/258 (15.5)
Burri *et al.* (21)	Heart failure	111 of 323 (34.4)	BNP POCT (153 ng/l)	Follow-up at 12 months using all information relating to the individual patient	72	93	88	84	—	—
Tomonaga *et al.* (22)	Acute coronary syndrome[b]	33 of 369 (8.9)	Troponin T POCT (0.1 ng/ml)	Follow-up at 3 weeks; reassessment of working diagnosis also using specialist/hospital reports when patients required additional specialist visits/ hospitalization	59	93	53	95	128/147 (87)	7/128 (5.5)
	Heart failure	51 of 369 (13.8)	NT-proBNP POCT (125 pg/ml)		100	72	74	100	28/70 (40)	0/28 (0)
	Thromboembolic event	24 of 369 (6.5)	D-dimer POCT (0.5 µg/ml)		93	78	36	99	82/118 (69)	1/82 (1.2)

NPV, negative predictive value; PPV, positive predictive value; Sens, sensitivity; Spec, specificity.

[a]Of which one case of deep vein thrombosis during 3 months of follow-up.

[b]Acute coronary syndrome: myocardial infarction and unstable angina.

[c]Composite reference standard: diagnostic strategy based on current guidelines and routine care, including spiral computed tomography, ventilation-perfusion scan, pulmonary angiography, leg ultrasonography and/or 3 months' follow-up only.

Table 3. Risk of bias of randomized controlled trails

	Random sequence generation	Allocation concealment	Blinding of participants and researchers	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Burri *et al.* (21)	☺	☺	☹	☺	?	?	☹
Tomonaga *et al.* (22)	?	?	☹	☹	☺	☺	?

☺, low risk of bias; ☹, high risk of bias; ?, unclear risk of bias.

Table 4. Risk of bias regarding diagnostic accuracy (QUADAS-2)[a]

	Patient selection	Index test	Reference standard	Flow and timing
Geersing *et al.* (14)	☺	☹	☹	☹
Lucassen *et al.* (15)	☺	☹	☹	☹
Schouten *et al.* (17)	?	☹	☹	☹
Planer *et al.* (18)	☹	?	☹	☹
Nilsson *et al.* (19)	?	☺	☹	☹
Bruins Slot *et al.* (20)	☺	☹	☺	☺
Burri *et al.* (21)	☺	☹	?	?
Tomonaga *et al.* (22)	☺	☺	☹	☹

☺, low risk of bias; ☹, high risk of bias; ?, unclear risk of bias.
[a]There were no concerns regarding applicability in any of these studies.

those on D-dimer POCT—tried to estimate the number of avoidable referrals to secondary care through scenario analyses.

Discussion

Summary

Only few prospective studies evaluating the effect of GP use of POCT on clinical diagnostic accuracy and clinical management in primary care patients with cardiopulmonary symptoms have been performed. All studies were considered at high risk of bias. As such, we currently have insufficient and inconclusive evidence to conclude that GP use of POCT in primary care patients with acute cardiopulmonary symptoms leads to more accurate diagnosis and impacts clinical management. Evidence from a large prospective study on GP use of D-dimer POCT suggests more accurate diagnosis when combining the use of a POCT with a clinical decision rule. As expected, heterogeneity among studies was high and therefore we were unable to perform a meta-analysis.

Strengths and limitations

This is the first systematic review on the clinical effectiveness of GP use of POCT in primary care patients with acute cardiopulmonary symptoms. We specifically chose to focus on a broad range of cardiopulmonary symptoms and not one specific condition or biomarker, as typical patients in general practice present with symptoms and not diagnoses. Making an accurate clinical decision within a 10–15-min consultation is part of the complexity of general practice. We therefore chose to perform a broad search to not miss any potential studies. We specifically excluded studies performed in secondary care, including those performed at A&E departments, to minimize the risk for spectrum bias. Spectrum bias describes the effect a change in patient case mix may have on the performance of a test (23).

There are several potential limitations of this review. Although we carefully predefined POCT, PICOS criteria and exclusion criteria at the start of the study, some studies were difficult to assess for eligibility because of differences in terminology. Therefore, all records were screened by at least two reviewers and in case of doubt were discussed in a consensus meeting. As all eligible papers of the initial search in four databases were present in PubMed, we decided to only perform the search update in Pubmed.

Comparison with existing literature

The sensitivity and specificity of GP use of D-dimer POCT as a stand-alone test in a primary care population suspected of pulmonary embolism as shown by Lucassen is comparable to the sensitivity of 82.6% and specificity of 60.5% found in a prospective observational study by Runyon *et al.* (24) in a low risk emergency department population of 1193 patients evaluated for pulmonary embolism. However, the NPV was somewhat higher in the low risk emergency department population, i.e. 99.4% (15,24). Knudsen *et al.* (25) evaluated the accuracy of BNP testing for the diagnosis of heart failure in an unselected group of 155 patients with acute dyspnoea in an emergency department setting and found a comparable area under the receiver operating curve for BNP compared to the findings of Burri, ranging between 0.82 and 0.90 depending on age and gender. Two systematic reviews by Bruins Slot *et al.* concluded that H-FABP POCT at a cut-off value of 6.2 or 7 ng/ml does not fulfil the requirements for safe and early diagnosis of acute myocardial infarction in a hospital and pre-hospital setting when used as a stand-alone test (26,27). This is in line with the conclusion of the primary care study by Bruins Slot *et al.* (20). With regards to the clinical value of Troponin POCT in a secondary care population, the literature is inconclusive, which is consistent with the findings of the primary care studies (27).

Implications for research and practice

Limited research has been done with regards to cardiopulmonary POCT in primary care clinical practice. Current clinical research mainly evaluates accuracy of POCT and diagnostic yield, when considering the test-treatment pathway. Only a few studies (also) report on clinical management outcomes, e.g. Nilsson evaluated referral rates to secondary care and Burri evaluated timing of treatment (28). There are several factors that currently hamper the comparison of outcomes of these studies, including different devices, biomarkers and diseases, study populations and study size, cut-off values and (combinations with) clinical decision rules.

Acute cardiopulmonary conditions can have serious clinical consequences and so excluding serious pathology is one of the key objectives of GPs when managing these patients. Therefore, if GP use of a specific POCT is to be advocated, the NPV of that POCT is of major importance. Some POCT may have a high NPV in a secondary care population, but a lower and insufficient NPV in primary care. For that reason, we should not assume that the outcomes of POCT studies in secondary care are automatically applicable to primary care, as previously discussed in terms of spectrum bias (23). Also

within primary care, differences in study population could have a major influence on the usefulness of a POCT, as a small difference in test characteristics might render the use of a cardiopulmonary POCT unsafe in certain populations. Therefore, it is very important to define, in a clinical decision pathway, for which patients the POCT is tested effective and safely applicable.

One should be careful when determining the NPV for a primary care population wherein the incidence of a certain disease is low, because when the study population is of insufficient size the test characteristics cannot be calculated reliably. Nilsson and Planer did calculate the NPV value even with only very few patients having a myocardial infarction. This may have led to an overestimation of the NPV of a Troponin T POCT for myocardial infarction in their study population. It is also important to notice that all patients with an unstable angina in the studies of Nilsson and Planer had a negative Troponin T POCT. By definition, the diagnosis of unstable angina is based on unstable cardiac ischemic symptoms without a rise in biomarkers and therefore in essence no biomarkers should be detectable. On the other hand, the incidence of unstable angina is decreasing as patients diagnosed with unstable angina in the past are now being diagnosed with myocardial infarction due to the lower detection thresholds of modern biomarker tests, e.g. high-sensitive Troponin tests. This illustrates the need for modern POCT to gain equal sensitivity to high-sensitive laboratory tests (29).

The chosen cut-off values have also proven to be important when evaluating POCT. Not all studies use the same cut-off values, which influences test characteristics and study outcomes and it makes comparison among study outcomes difficult. For several biomarkers there is an ongoing debate on the optimal cut-off value. For example, it is suggested that the best NT-proBNP cut-off point to exclude heart failure in an ambulatory population is 280 pg/ml, which showed an area under the ROC curve of 0.94. This same study compared that cut-off value with recommended diagnostic cut-off values applied to their population, which ranged from 50 pg/ml in patients younger than 50 years to 400 pg/ml (NICE guidelines) (30,31). The study by Burri only reported the test characteristic when using the optimal cut-off value (153 pg/ml) for their study population. Not predefining the test threshold, but selecting the optimal cut-off for the study population to optimize test characteristics may lead to an overestimation of test performance, as the test performance of the same POCT in another independent sample of patients is likely to be inferior (32). A similar discussion on the optimal cut-off value can be held for D-dimer POCT in elderly patients, which some believe should be higher than 500 ng/ml (33). The cut-off value for the qualitative D-dimer POCT in the study by Geersing was even lower than 500 ng/ml, to be exact 80 ng/ml. Lower cut-off values for H-FABP and Troponin—when available as POCT—can increase safety by decreasing false negative results (34). Differences in cut-off points also play a role in clinical decisions rules, for example the Wells clinical decision rule. Using a Wells cut-off score of <2 is safer in the exclusion of pulmonary embolism than a score of ≤4, but at the cost of a lower efficiency and specificity (14).

Another factor that complicates comparison among studies is that clinical diagnostic accuracy of a POCT is sometimes presented as a stand-alone test and sometimes combined with a clinical decision rule. With regards to the diagnosis of pulmonary embolism a validated and frequently used clinical decision rule in primary care exists, i.e. the Wells rule, which when combined with the D-dimer POCT has a lower failure rate than the D-dimer POCT as a stand-alone test (14,15,35,36). Such a frequently used and integrated clinical decision rule for the diagnosis of coronary heart disease in primary care does not exist yet. The HEART score for example was developed for patients in an emergency department setting and is not as easily applicable to primary care (37–39). The Marburg Heart Score (MHS), however, may be useful in the initial triage of patients suspected of coronary heart disease in general practice (40–42). Nonetheless, as of yet this clinical decision rule is not commonly used. If a validated cardiac clinical decision rule like the MHS would be added to a Troponin POCT, this would most likely lead to a more effective and safer exclusion of acute cardiac pathology. More research is necessary to investigate whether the combination of the two leads to a high enough NPV to safely exclude cardiac pathology.

Several factors should be taken into consideration when implementing POCT in practice (43). Lack of evidence could lead to limited trust in a POCT, which in turn could lead to referral to secondary care regardless of the test result. If a POCT were to be implemented, physicians should be aware of the risk of non-evidence based testing for other conditions, but also within the cardiopulmonary population—i.e. different duration of symptoms than for which the POCT is proven effective. Therefore, it is very important to incorporate a POCT in a tested clinical pathway and to educate GPs on the use of a new POCT. Further research on the effectiveness of using a POCT panel with more than one cardiopulmonary biomarker, may be useful, especially in primary care, where patients sometimes present with vague or a wide range of symptoms (44).

Conclusion

We conclude that we currently have limited and inconclusive evidence—from prospective and randomized studies with a high risk of bias—that actual GP use of POCT in primary care patients with acute cardiopulmonary symptoms leads to more accurate diagnosis and impacts clinical management. However, some studies show promising results, especially when a POCT is combined with a clinical decision rule, e.g. when GP use of a D-dimer POCT is combined with the Wells clinical decision rule. Further research on the clinical effectiveness of POCT in primary care, preferably in combination with clinical decision rules, is necessary to confirm whether or not POCT could aid GPs in the consultation of patients with acute cardiopulmonary symptoms.

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References

1. Heneghan C, Glasziou P, Thompson M *et al*. Diagnostic strategies used in primary care. *BMJ* 2009; 338: b946.
2. Howick J, Cals JW, Jones C *et al*. Current and future use of point-of-care tests in primary care: an international survey in Australia, Belgium, The Netherlands, the UK and the USA. *BMJ Open* 2014; 4: e005611.
3. Schols AM, van Boekholt TA, Oversier LM, Dinant GJ, Cals JW. General practitioners' experiences with out-of-hours cardiorespiratory consultations: a qualitative study. *BMJ Open* 2016; 6: e012136.

4. Andreeva E, Melbye H. Usefulness of C-reactive protein testing in acute cough/respiratory tract infection: an open cluster-randomized clinical trial with C-reactive protein testing in the intervention group. *BMC Fam Pract* 2014; 15: 80.
5. Laurence CO, Gialamas A, Bubner T *et al*.; Point of Care Testing in General Practice Trial Management Group. Patient satisfaction with point-of-care testing in general practice. *Br J Gen Pract* 2010; 60: e98–104.
6. Gialamas A, Yelland LN, Ryan P *et al*. Does point-of-care testing lead to the same or better adherence to medication? A randomised controlled trial: the PoCT in General Practice Trial. *Med J Aust* 2009; 191: 487–91.
7. Cals JW, Schot MJ, de Jong SA, Dinant GJ, Hopstaken RM. Point-of-care C-reactive protein testing and antibiotic prescribing for respiratory tract infections: a randomized controlled trial. *Ann Fam Med* 2010; 8: 124–33.
8. Cals JW, Schols AM, van Weert HC *et al*. Point-of-care testing in family practices: present use and need for tests in the future. *Ned Tijdschr Geneeskd* 2014; 158: A8210.
9. Engel MF, Paling FP, Hoepelman AI, van der Meer V, Oosterheert JJ. Evaluating the evidence for the implementation of C-reactive protein measurement in adult patients with suspected lower respiratory tract infection in primary care: a systematic review. *Fam Pract* 2012; 29: 383–93.
10. Falk G, Fahey T. C-reactive protein and community-acquired pneumonia in ambulatory care: systematic review of diagnostic accuracy studies. *Fam Pract* 2009; 26: 10–21.
11. Huang Y, Chen R, Wu T, Wei X, Guo A. Association between point-of-care CRP testing and antibiotic prescribing in respiratory tract infections: a systematic review and meta-analysis of primary care studies. *Br J Gen Pract* 2013; 63: e787–94.
12. Higgins JPT, Altman DG, Gøtzsche PC, *et al*.; Cochrane Bias Methods Group; Cochrane Statistical Methods Group. The Cochrane collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011;343:d5928.
13. Whiting PF, Rutjes AW, Westwood ME *et al*.; QUADAS-2 Group. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. *Ann Intern Med* 2011; 155: 529–36.
14. Geersing GJ, Erkens PM, Lucassen WA *et al*. Safe exclusion of pulmonary embolism using the Wells rule and qualitative D-dimer testing in primary care: prospective cohort study. *BMJ* 2012; 345: e6564.
15. Lucassen WA, Erkens PM, Geersing GJ *et al*. Qualitative point-of-care D-dimer testing compared with quantitative D-dimer testing in excluding pulmonary embolism in primary care. *J Thromb Haemost* 2015; 13: 1004–9.
16. Erkens PM, Lucassen WA, Geersing GJ *et al*. Alternative diagnoses in patients in whom the GP considered the diagnosis of pulmonary embolism. *Fam Pract* 2014; 31: 670–7.
17. Schouten HJ, Geersing GJ, Oudega R, van Delden JJ, Moons KG, Koek HL. Accuracy of the Wells clinical prediction rule for pulmonary embolism in older ambulatory adults. *J Am Geriatr Soc* 2014; 62: 2136–41.
18. Planer D, Leibowitz D, Paltiel O, Boukhobza R, Lotan C, Weiss TA. The diagnostic value of troponin T testing in the community setting. *Int J Cardiol* 2006; 107: 369–75.
19. Nilsson S, Andersson PO, Borgquist L *et al*. Point-of-care Troponin T testing in the management of patients with chest pain in the swedish primary care. *Int J Family Med* 2013; 2013: 532093.
20. Bruins Slot MH, Rutten FH, van der Heijden GJ *et al*. Diagnostic value of a heart-type fatty acid-binding protein (H-FABP) bedside test in suspected acute coronary syndrome in primary care. *Int J Cardiol* 2013; 168: 1485–9.
21. Burri E, Hochholzer K, Arenja N *et al*. B-type natriuretic peptide in the evaluation and management of dyspnoea in primary care. *J Intern Med* 2012; 272: 504–13.
22. Tomonaga Y, Gutzwiller F, Lüscher TF *et al*. Diagnostic accuracy of point-of-care testing for acute coronary syndromes, heart failure and thromboembolic events in primary care: a cluster-randomised controlled trial. *BMC Fam Pract* 2011; 12: 12.
23. Willis BH. Spectrum bias–why clinicians need to be cautious when applying diagnostic test studies. *Fam Pract* 2008; 25: 390–6.
24. Runyon MS, Beam DM, King MC, Lipford EH, Kline JA. Comparison of the Simplify D-dimer assay performed at the bedside with a laboratory-based quantitative D-dimer assay for the diagnosis of pulmonary embolism in a low prevalence emergency department population. *Emerg Med J* 2008; 25: 70–5.
25. Knudsen CW, Riis JS, Finsen AV *et al*. Diagnostic value of a rapid test for B-type natriuretic peptide in patients presenting with acute dyspnoe: effect of age and gender. *Eur J Heart Fail* 2004; 6: 55–62.
26. Bruins Slot MH, Reitsma JB, Rutten FH, Hoes AW, van der Heijden GJ. Heart-type fatty acid-binding protein in the early diagnosis of acute myocardial infarction: a systematic review and meta-analysis. *Heart* 2010; 96: 1957–63.
27. Bruins Slot MH, van der Heijden GJ, Stelpstra SD, Hoes AW, Rutten FH. Point-of-care tests in suspected acute myocardial infarction: a systematic review. *Int J Cardiol* 2013; 168: 5355–62.
28. Ferrante di Ruffano L, Hyde CJ, McCaffery KJ, Bossuyt PM, Deeks JJ. Assessing the value of diagnostic tests: a framework for designing and evaluating trials. *BMJ* 2012; 344: e686.
29. Braunwald E, Morrow DA. Unstable angina: is it time for a requiem? *Circulation* 2013; 127: 2452–7.
30. Verdú JM, Comin-Colet J, Domingo M, *et al*. Rapid point-of-care NT-proBNP optimal cut-off point for heart failure diagnosis in primary care. *Rev Esp Cardiol (Engl Ed)* 2012; 65: 613–19.
31. Hildebrandt P, Collinson PO, Doughty RN *et al*. Age-dependent values of N-terminal pro-B-type natriuretic peptide are superior to a single cut-point for ruling out suspected systolic dysfunction in primary care. *Eur Heart J* 2010; 31: 1881–9.
32. Leeflang MM, Moons KG, Reitsma JB, Zwinderman AH. Bias in sensitivity and specificity caused by data-driven selection of optimal cutoff values: mechanisms, magnitude, and solutions. *Clin Chem* 2008; 54: 729–37.
33. Righini M, Van Es J, Den Exter PL *et al*. Age-adjusted D-dimer cutoff levels to rule out pulmonary embolism: the ADJUST-PE study. *JAMA* 2014; 311: 1117–24.
34. Willemsen RT, van Severen E, Vandervoort PM *et al*. Heart-type fatty acid binding protein (H-FABP) in patients in an emergency department setting, suspected of acute coronary syndrome: optimal cut-off point, diagnostic value and future opportunities in primary care. *Eur J Gen Pract* 2015; 21: 156–63.
35. Wells PS, Anderson DR, Rodger M *et al*. Derivation of a simple clinical model to categorize patients probability of pulmonary embolism: increasing the models utility with the SimpliRED D-dimer. *Thromb Haemost* 2000; 83: 416–20.
36. Wells PS, Ginsberg JS, Anderson DR *et al*. Use of a clinical model for safe management of patients with suspected pulmonary embolism. *Ann Intern Med* 1998; 129: 997–1005.
37. Backus BE, Six AJ, Kelder JC *et al*. A prospective validation of the HEART score for chest pain patients at the emergency department. *Int J Cardiol* 2013; 168: 2153–8.
38. Backus BE, Six AJ, Kelder JC *et al*. Chest pain in the emergency room: a multicenter validation of the HEART Score. *Crit Pathw Cardiol* 2010; 9: 164–9.
39. Six AJ, Cullen L, Backus BE *et al*. The HEART score for the assessment of patients with chest pain in the emergency department: a multinational validation study. *Crit Pathw Cardiol* 2013; 12: 121–6.
40. Bösner S, Haasenritter J, Becker A *et al*. Ruling out coronary artery disease in primary care: development and validation of a simple prediction rule. *CMAJ* 2010; 182: 1295–300.
41. Haasenritter J, Bösner S, Vaucher P *et al*. Ruling out coronary heart disease in primary care: external validation of a clinical prediction rule. *Br J Gen Pract* 2012; 62: e415–21.
42. Haasenritter J, Donner-Banzhoff N, Bösner S. Chest pain for coronary heart disease in general practice: clinical judgement and a clinical decision rule. *Br J Gen Pract* 2015; 65: e748–53.
43. Howick J, Bossuyt PM, Cals JW. Point of care testing in family practice: common myths debunked. *Fam Pract* 2017; 34: 373–375.
44. Harrison A, Amundson S. Evaluation and management of the acutely dyspneic patient: the role of biomarkers. *Am J Emerg Med* 2005; 23: 371–8.