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Point of Care Tests (POCT): D-Dimer and Troponin

Update 2024

Final report

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Update 2024

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List of abbreviations

ACS ..... Acute Coronary Syndrome
AGREE ..... Appraisal of Guidelines, Research and Evaluation
AMSTAR-2 ..... Assessing the Methodological Quality of Systematic Reviews-2
CADTH ..... Canadian Agency for Drugs and Technologies in Health
CL ..... Central Laboratory
cTnI ..... cardiac Troponin I
cTnT ..... cardiac Troponin T
CTPA ..... Computerized Tomography Pulmonary Angiography
DTA ..... Diagnostic Test Accuracy
DVT ..... Deep Vein Thrombosis
ECG ..... Electrocardiography
ED ..... Emergency Department
EFF ..... Effectiveness
ESC ..... European Society of Cardiology
EUnetHTA ..... European network for Health Technology Assessment
FU ..... Follow Up
GP ..... General Practitioner
hs ..... High-sensitivity
hs-cTn ..... High-sensitivity cardiac troponin
HTA ..... Health Technology Assessment
ICSH ..... International Council for Standardisation in Haematology
IHD ..... Ischemic Heart Disease
INR ..... International Normalised Ratio
LOS ..... Length of Stay ACS Acute Coronary Syndrome
MACE ..... Major adverse cardiac events
MeSH ..... Medical Subject Headings ACS Acute Coronary Syndrome
n. s. ..... not statistically significant
N/A ..... Not Applicable, Not Available
NICE ..... National Institute for Health and Care Excellence
NPV ..... Negative Predictive Value
NSTE-ASC ..... Non-ST-segment elevation acute coronary syndrome
NRCT ..... Non-Randomised Controlled Trial
NSTEMI ..... Non-ST Elevation Myocardial Infarction
PE ..... Pulmonary Embolism
PICO ..... Population – Intervention – Comparison – Outcome
POC ..... Point Of Care
POCT ..... Point of Care Test
PRISMA ..... Preferred Reporting Items for Systematic reviews and Meta-Analyses
PPV ..... Positive Predictive Value
PTS ..... Post-Thrombotic Syndrome
QoL ..... Quality of Life
RCT ..... Randomised Controlled Trial

RACPP..... Rural accelerated chest pain pathway
RR..... Referral Rates
s. s..... statistically significant
SEN..... Sensitivity
SPEC ..... Specificity
SR..... Systematic Review
STEMI ..... ST-Elevation Myocardial Infarction
Tn..... Troponin
Tn-POCT ..... Troponin-Point of Care Testing
TTD ..... Time To Discharge
UA..... Unstable Angina
URL ..... Upper Reference Limit
VTE ..... Venous Thromboembolism

Executive Summary

Aim: In contrast to the 2019 report, the scope of this assessment is limited to primary and community care settings. It addresses the research question whether using the point of care tests (POCT) for D-dimer and troponin (Tn) in symptomatic patients presenting at primary or community care is more effective and/or safer than current diagnostic practice.

Update 2024 of 2019 report on Tn- and D-Dimer-POCT: scope limited to primary care settings

Methods: A systematic literature search was performed (February 2024) in the Cochrane Library, Medline via Ovid, Embase and the International Network of Agencies for Health Technology Assessment Database (INAHTA) for new systematic reviews (SRs) and HTAs reports. The search was limited to studies published in German or English from June 2019 to March 2024. As no the SRs or HTAs was found relevant for the update, a second search was performed in March 2024 for primary studies separately for each POCT applying the same time period and databases and was complemented by a targeted hand search in the Trip and Guidelines Inter-national Network (GIN) databases for clinical guidelines and in the Clinical-Trials.gov registry for ongoing studies.

systematic search in several databases for SR and HTA and for primary studies

hand search for clinical guidelines and ongoing studies

Two independent researchers conducted all steps in the systematic review (study selection, data extraction and review for accuracy, risk of bias assessment). The quality of RCTs was assessed with the Cochrane Risk of Bias 2 (RoB 2) tool for randomized controlled trials (RCTs). The ROBINS-I tool for non-randomised controlled trials (NRCTs) assessed the quality of prospective observational studies. A qualitative synthesis of the evidence was performed. The results were presented in plain text format.

independent study selection, data extraction and review for accuracy, risk of bias assessment by two researchers

Results and discussion:

Tn-POCT: Three studies (1 RCT, 2 observational studies) were identified: none of them investigated high-sensitivity (hs) Tn POCT. When measured and analysed, MACE incidence at 30-day and 1-year follow-ups and hospital admissions were similar, ED referrals were reduced. QoL and patient satisfaction with care were measured only in one study each; results were similar between groups. Diagnostic accuracy of the pre-hospital rule-out strategy, with single time-point POCT Tn measurement, for detecting a 1-year MACE in low-risk patients in a primary care setting was comparable and almost identical to the ED rule-out strategy. In both observational studies, the negative predictive value of a rural accelerated diagnostic chest pain pathway, with two time-points POCT Tn measurements for 30-day MACE, was high (100%).

Tn POCT in primary care: 3 studies (1 RCT+ 2 observational studies)

but none used hsTn POCT and two time-points POCT

positive results

Evidence on the clinical utility of high-sensitivity (hs) POC Tn tests in primary care settings is still limited. No new systematic reviews or clinical or diagnostic guidelines were found related to diagnostic accuracy and clinical utility of hs POC Tn tests in primary care settings in low-risk patients suspected with non-ST-segment elevation acute coronary syndrome (NSTE-ASC). No studies with a low risk of bias were found to assess the effectiveness and safety of hs Tn POCTs in combination with a clinical decision rule. Despite equivalent or positive results of the three studies caution is warranted in the interpretation of these results due to the high, serious or critical risk of bias of the studies and the investigation of only non-high-sensitivity Tn POCT.

limited evidence on hsTn POCT

published studies: high, serious or critical risk of bias investigated non-hsTn POCT

D-Dimer POCT in primary care in combination with clinical decision rule

3 studies (all observational studies)

but only few clinical utility outcomes, only test accuracy

plasma vs capillary blood: poor correlation

D-Dimer POCT: Three studies (3 observational studies) were identified: all three studies investigated D-dimer POCTs in combination with a clinical decision rule (the Oudega for DVT and the Wells rule for PE). Two studies measured only a few clinical utility outcomes and have the critical risk of bias. One study, with a serious risk of bias, in adult patients who present to primary care with symptoms suggestive of DVT and PE and who have a low pre-test probability, five quantitative POCTs adequately rule out VTE. These tests have a high sensitivity and a high negative predictive value with a low false negative rate, so the diagnostic accuracy outcomes of these tests, using plasma samples, were comparable to that of a laboratory-based D-dimer test. As the poor capillary-plasma correlation was observed in some of these quantitative POCTs, the capillary whole blood finger sticks feature of certain devices needs to be further improved. Capillary measurement is important in settings or patients where a venipuncture is not widely performed or is very difficult to perform, like in rural general practice and nursing homes.

limited evidence on D-Dimer POCT published studies: serious or critical risk of bias

Evidence on the clinical utility of qualitative POC D-dimer tests in primary care settings is still limited. Only three observational studies with serious or critical risk of bias were found to assess the diagnostic accuracy or clinical utility of D-dimer POCTs in combination with a clinical decision. They are too problematic to provide valid evidence.

insufficient evidence larger studies confirming clinical utility of single-time POCT needed

Conclusion: Further larger studies confirming the clinical utility of single-time-point fingerstick measurement of high-sensitivity POC Tn tests and quantitative D-dimer POCTs in the primary care setting are still warranted, preferably through RCTs with longer follow-up.

Zusammenfassung

Einleitung

Beschreibung der Technologie

Biomarker Tests: Tn & D-Dimer

Die Biomarker Troponin (Tn) und D-Dimer können mittels Testung im Zentrallabor oder mittels Point of Care Tests (POCTs) gemessen werden. POCTs bieten eine schnelle Rückmeldung der Testergebnisse und ermöglichen schnellere Entscheidungen über das Patient*innenmanagement. Sowohl die Probenahme als auch die Datenanalyse werden am gleichen Standort durchgeführt, wodurch Transport- und Verarbeitungsverzögerungen reduziert werden. Tn-POCT und D-Dimer POCT können zur Unterstützung der Diagnose von Patient*innen mit Symptomen verwendet werden, die auf ein akutes Koronarsyndrom (ACS) bzw. eine venöse Thromboembolie (VTE) hinweisen. Beide POC-Diagnostika können sowohl in der Notfallmedizin als auch in der ambulanten Versorgung eingesetzt werden. Tn-POCT kann zudem in anderen präklinischen notfallmedizinischen Settings wie z. B. im Krankenwagen verwendet werden.

POCT ermöglicht schnelle Diagnostik

Tn-POCT: akutes Koronarsyndrom (ACS)

D-Dimer POCT: venöse Thromboembolie (VTE)

Gesundheitsproblem

akutes Koronarsyndrom (ACS), Myokardinfarkt/ Ischämie

Das akute Koronarsyndrom (engl. acute coronary syndrome = ACS) ist ein Gesundheitszustand, welcher mit verschiedenen Symptomen (v. a. Brustschmerz) einhergeht und im Wesentlichen durch einen verminderten Blutfluss in den Koronararterien (Myokardischämie) verursacht wird. Der Begriff ACS wird für Patient*innen verwendet, bei denen ein myokardialer Infarkt/eine myokardiale Ischämie vermutet oder bestätigt ist. Es gibt verschiedene Arten von ACS wie z. B. Nicht-ST-Hebung Myokardinfarkt (NSTEMI), ST-Hebung Myokardinfarkt (STEMI) oder instabile Angina pectoris.

Zielpopulation für Diagnostik: Patient*innen mit Anzeichen und Symptomen von ACS

Die Zielpopulation für die Anwendung von Tn-POCT sind erwachsene Patient*innen mit Anzeichen und Symptomen von ACS.

venöse Thromboembolie (VTE) umfasst Lungenembolie und tiefe Venenthrombose (TVT)

Venöse Thromboembolien (VTE) sind Erkrankungen, bei denen sich in einer Vene ein Blutgerinnsel (Thrombus) bildet, das sich dann ausdehnt und im Blut wandert (ein sog. Embolus). Ein Venenthrombus tritt am häufigsten in den tiefen Venen der Beine oder des Beckens auf; dies wird dann als tiefe Venenthrombose (TVT) bezeichnet. Der Blutfluss durch die betroffene Vene kann durch das Gerinnsel begrenzt werden, und es kann zu Schwellungen und Schmerzen im Bein führen. Wenn es sich löst und in die Lungenarterien gelangt, dann spricht man von einer Lungenembolie (LE), die in einigen Fällen tödlich verlaufen kann.

Zielpopulation für Diagnostik: Patient*innen mit Anzeichen und Symptomen von VTE

Die Zielpopulation für die Verwendung von D-Dimer POCT sind erwachsene Patient*innen mit geringem bis mittlerem Risiko der TVT oder PE.

Forschungsfragen und Projektziele

Update des 2019 Berichtes zu Tn- und D-Dimer-POCT: beschränkt auf Primärversorgung

Im Gegensatz zu dem Bericht aus dem Jahr 2019 fokussiert diese Bewertung ausschließlich auf die Primärversorgung. Sie adressiert die Fragestellung, ob der Einsatz von Point-of-Care-Tests (POCT) für D-Dimer und Troponin (Tn) bei symptomatischen Patient*innen in der Primärversorgung effektiver und/oder sicherer als die aktuelle diagnostische Praxis ist.

Methoden

Systematische Literatursuche in 4 Datenbanken

nach systematischen Reviews (SR), HTAs und Primärstudien

nach Leitlinien und laufenden Studien

Eine systematische Literaturrecherche wurde im Februar 2024 in der Cochrane Library, Medline über Ovid, Embase und der Datenbank des International Network of Agencies for Health Technology Assessment (INAHTA) durchgeführt, um neue systematische Übersichtsarbeiten (SRs) und Health Technology Assessments (HTAs) zu identifizieren. Die Suche beschränkte sich auf Studien, die zwischen Juni 2019 und März 2024 auf Deutsch oder Englisch veröffentlicht wurden. Da keine relevanten SRs oder HTAs für das Update gefunden wurden, erfolgte im März 2024 eine zweite Suche nach Primärstudien, die separat für jedes POCT für denselben Zeitraum und dieselben Datenbanken durchgeführt wurde und durch eine gezielte Handsuche in den Trip und Guidelines International Network (GIN) Datenbanken für klinische Leitlinien sowie im ClinicalTrials.gov Studienregister für laufende Studien ergänzt wurde.

Studienauswahl, Datenerfassung und Überprüfung, sowie Bias-Risiko Bewertung durch unabhängige Wissenschaftler*innen

Zwei unabhängige Wissenschafter*innen führten alle Schritte der systematischen Übersicht durch (Studienselektion, Datenerfassung und -prüfung, und Bewertung des Bias-Risikos). Die Qualität der randomisierten kontrollierten Studien (RCTs) wurde mit dem Cochrane Risk of Bias 2 (RoB 2) Tool und die Qualität der nicht-randomisierte kontrollierte Studien (NRCTs) mit dem ROBINS-I-Tool bewertet. Eine qualitative Synthese der Evidenz wurde durchgeführt. Die Ergebnisse wurden narrativ präsentiert.

Ergebnisse

Verfügbare Evidenz

Tn-POCT: 3 Studien (1 RCT + 2 Beobachtungsstudien), D-Dimer-POCT: 3 Studien (alle Beobachtungsstudien)

Tn-POCT: Es wurden drei Studien identifiziert (ein RCT und zwei Beobachtungsstudien); keine davon untersuchte hochsensitive (hs) Tn-POCTs.

D-Dimer POCT: Es wurden drei Beobachtungsstudien identifiziert. Alle drei Studien untersuchten D-Dimer-POCTs in Kombination mit einer klinischen Entscheidungsregel (die Oudega-Regel für DVT und die Wells-Regel für PE).

Klinische Wirksamkeit und Sicherheit

Tn-POCT: Positive (vergleichbare) Ergebnisse (MACE, Lebensqualität, Krankenhausaufenthalte, diagnostische Genauigkeit) Verringerung unnötiger Notaufnahmebesuche

Tn-POCT: In dem RCT war die 30-Tage- und 1-Jahres-Inzidenz schwerer unerwünschter kardialer Ereignisse (engl. major adverse cardiac events = MACE) niedrig und vergleichbar zwischen der präklinischen Ausschlussstrategie und der Ausschlussstrategie in der Notaufnahme. In zwei Beobachtungsstudien wurde bei Niedrigrisiko-Patient*innen innerhalb von 30 Tagen kein MACE festgestellt. Die RCT zeigte keinen signifikanten Unterschied in der Lebensqualität zwischen den beiden Strategien. Die präklinische Ausschlussstrategie reduzierte signifikant die Anzahl unnötiger Notaufnahmebesuche, ohne die Anzahl der Krankenhausaufenthalte zu beeinflussen. Die diagnostische Genauigkeit der präklinischen Strategie war vergleichbar mit der der Notaufnahme. Der negative prädiktive Wert des diagnostischen Pfades für Brustschmerzen im ländlichen Raum war in beiden Beobachtungsstudien hoch (100%).

D-Dimer POCT: nur wenige Ergebnisse zum klinischen Nutzen, nur Testgenauigkeit

Plasma vs. Kapillarblut: schlechte Korrelation

D-Dimer POCT: Eine Studie untersuchte die 3-Monats-VTE-Inzidenz und Wirksamkeit von zwei klinischen Entscheidungsregeln (engl. clinical prediction rule = CPR) mit D-Dimer-POC-Tests. Bei korrekter Anwendung waren die Ergebnisse gut, aber bei 21% der Patient*innen wurden die CPRs falsch angewendet, was zu einer höheren Fehlerquote führte. Eine andere Studie bewertete die Benutzerfreundlichkeit von fünf neuen D-Dimer-POC-Tests und fand große Unterschiede, wobei die meisten Geräte als einfach zu bedienen eingestuft wurden. Eine dritte Studie zeigte, dass die diagnostische Genauigkeit der

fünf D-Dimer-POC-Tests vergleichbar mit laborbasierten Tests war. Allerdings wurde in einigen Tests eine schlechte Korrelation zwischen Kapillar- und Plasmamessungen beobachtet.

Diskussion

begrenzte Evidenz zu hs Tn-POCT

hohes, ernstes oder kritisches Bias-Risiko der Studien, untersuchten nicht-hs Tn-POCT

Die Evidenz zum klinischen Nutzen von hs POC Tn-Tests in der Primärversorgung ist nach wie vor begrenzt. Es wurden keine neuen SRs und HTAs oder klinische Leitlinien gefunden, die sich auf die diagnostische Genauigkeit und den klinischen Nutzen von hs POC Tn-Tests in der Primärversorgung bei Patient*innen mit geringem Risiko und Verdacht auf akutes Koronarsyndrom ohne ST-Hebung (NSTE-ACS) beziehen. Es wurden keine Studien mit einem geringen Bias-Risiko gefunden, die die Wirksamkeit und Sicherheit von hs Tn-POCTs in Kombination mit einer klinischen Entscheidungsregel bewerten. Trotz äquivalenter oder positiver Ergebnisse der drei Studien sollte die Interpretation dieser Ergebnisse aufgrund des hohen, ernsten oder kritischen Bias-Risikos der Studien und der Untersuchung von ausschließlich nicht-hochsensiblen Tn-POCTs mit Vorsicht erfolgen.

begrenzte Evidenz zu D-Dimer-POCT:

ernstes oder kritisches Bias-Risiko der Studien

Die Evidenz zum klinischen Nutzen von qualitativen POC-D-Dimer-Tests in der primärmedizinischen Versorgung ist nach wie vor begrenzt. Es wurden nur drei Beobachtungsstudien mit ernstem oder kritischem Bias-Risiko gefunden, die die diagnostische Genauigkeit oder den klinischen Nutzen von D-Dimer-POCTs in Kombination mit einer klinischen Entscheidung bewerten. Diese sind methodisch zu problematisch, um eine fundierte Aussage liefern zu können. Da bei einigen der quantitativen POCTs eine schlechte Kapillar-Plasma-Korrelation beobachtet wurde, muss die Funktion der Kapillarblutentnahme mittels Fingerstich bei bestimmten Geräten weiter verbessert werden. Kapillarmessungen sind insbesondere bei Patient*innen wichtig, bei denen eine Venenpunktion sehr schwer durchzuführen ist, oder in Umgebungen, in denen sie nicht weit verbreitet ist, wie in der ländlichen allgemeinmedizinischen Praxis und in Pflegeheimen.

Schlussfolgerung

insuffiziente Evidenz, um den klinischen Nutzen von Tn und D-Dimer POCT in der Primärversorgung zu belegen

Eine einmalige Fingerstick-Messung von hs-Tn POCT in der Primärversorgung könnte die Anzahl unnötiger Besuche in der Notaufnahme sowie die Überfüllung reduzieren. Zudem würde die Verringerung von Krankenhausaufnahmen und Überweisungen in die Notaufnahme einen deutlichen Mehrwert für die Patient*innen bieten. Allerdings ist die Evidenz zur Unterstützung dieser Strategie bisher unzureichend. Ebenso reicht die Evidenz nicht aus, um zu belegen, dass die Implementierung von D-Dimer POCT in Kombination mit einer klinischen Entscheidungsregel in der Primärversorgung der üblichen Versorgung überlegen ist.

Weitere umfangreiche Studien, die den klinischen Nutzen von hs POC-Tn-Tests und quantitativen D-Dimer-POCTs mittels Fingerstich in der Primärversorgung bestätigen, sind weiterhin erforderlich, vorzugsweise durch RCTs mit längerer Nachbeobachtungszeit.

1 Summary of Report 2019

EUnetHTA Bericht 2019

breiter Scope: POCT in Primärversorgung und Notfallversorgung

Leitlinien-Synopse und Overview von Reviews

zu D-Dimer und Troponin POCT

The EUnetHTA assessment 2019 [1, 2] addressed the research question whether using the Point of Care Tests (POCT) for D-dimer and troponin (Tn) in symptomatic patients presenting at ambulatory (primary or community care) or emergency care settings is more effective and/or safer than current diagnostic practice. Subsequently, the following research questions were formulated:

- How do evidence-based guidelines recommend the use of Tn-POCT (position in the diagnostic path, threshold values in different patient populations and settings)? (guideline synopsis)
- How do evidence-based guidelines recommend the use of D-dimer-POCT (position in the diagnostic path, threshold values in different patient populations and settings)? (guideline synopsis)
- What are the clinical benefits of Tn-POCT in the management of symptomatic patients (adults)? (overview of reviews)
- What are the clinical benefits of D-dimer POCT in the management of symptomatic patients (adults)? (overview of reviews)

Description of POCT technology

Beschreibung der Tests:

sehr viele, sehr unterschiedliche Produkte mit unterschiedlichen Charakteristika

quantitative und qualitative Tests

breite Range an analytischer Performanz und technischen Ausprägungen

Anwendungsbereiche: symptomatische Patient*innen unter Verdacht eines akuten Koronarsyndroms und/oder einer venösen Thromboembolie

Erwartungen an POCT: geringere Folgekosten

The biomarkers Tn and D-dimer can be measured using a central laboratory (CL, either in the hospital or non-hospital centred medical laboratories) or by using point-of-care tests. Point of care tests (POCTs), also known as near-patient or bedside testing, are diagnostic tests that are performed near patients rather than in central laboratories [3]. POCTs provide rapid feedback on test results, potentially enabling faster decisions about patient management. Both sampling and data analysis are performed at the same site, reducing transport and processing delays [4, 5].

For Tn-POCT, many different devices were identified, of which most devices measure Tn quantitatively and only a few qualitatively. For D-dimer POCT also, many devices could be identified; half of them measure D-dimer quantitatively, the other half qualitatively. When reviewing the characteristics of the identified devices, it was notable that these are heterogeneous when it comes to both analytic performance (e.g., differences in analytical range and sample size) and further technological characteristics (e.g., as to whether it can be connected to another device on which the diagnostic data can be stored). For D-dimer assays, the commercially available devices vary greatly regarding reference values and clinical cut-offs. Similarly, regardless of whether tested in a CL or at the point of care, Tn assays are neither standardised nor harmonised. That is to say, every assay uses a distinct set of antibodies for capturing and detecting Tn in the blood.

Tn-POCT and D-dimer POCT can be used to aid the diagnosis of patients with symptoms suspected of acute coronary syndrome and venous thromboembolism respectively. Potential advantages of POCT include faster turnaround time, reduced length of stay and reduced unnecessary hospitalisation/further testing.

Health problem and current use of Troponin and D-Dimer Tests

Tn-POCT: The target population for using Tn-POCT is adult patients with signs and symptoms suggestive of "acute coronary syndrome (ACS)". There are different types of acute coronary syndrome, such as non-ST elevation myocardial infarction, ST-elevation myocardial infarction or unstable angina. Acute coronary syndrome is a health condition encompassing a spectrum of signs and symptoms caused by decreased blood flow in the coronary arteries (myocardial ischemia).

Ischemic heart disease is frequent and one of the leading causes of mortality globally. The treatment of myocardial ischemia is time critical, to improve clinical outcomes by reducing treatment delays, ASC complications and mortality. It is, therefore, crucial to rapidly identify the cause of the chest discomfort, which may be described as pain, pressure, tightness, heaviness, or burning, as the leading presenting symptom of suspected acute coronary syndrome, to be able to start appropriate therapy promptly. The primary goal of early evaluation, within 15 minutes after presentation, is to confirm the diagnosis of acute coronary syndrome ("rule-in") or exclude acute coronary syndrome as the cause of the symptoms ("rule-out"). This involves the following steps: initial physical examination and obtaining the patient's medical history, resting electrocardiography (ECG), and finally, cardiac troponin measurement. The standard of care for patients who present with symptoms suggestive of acute coronary syndrome, including those with recurrent symptoms, ischemic electrocardiography changes, or positive cardiac troponins, is admission to the hospital.

Troponin POCT

bei Symptomen von akutem Koronarsyndrom zeitkritisch, da ischämische Herzkrankheit zum Tod führen kann

frühe Diagnostik zum „rule-in" oder „rule-out"

klinische Untersuchung, Ruhe-EKG und Troponin-Test

bei positivem Ergebnis:

sofortige Einweisung ins Krankenhaus

D-dimer POCT: Venous thromboembolism is a condition in which a blood clot (a thrombus) forms in a vein and then dislocates to travel in the blood (an embolus). A venous thrombus most commonly occurs in the deep veins of the legs or pelvis, called a "deep vein thrombosis". The clot can limit blood flow through the affected vein, and it can cause swelling and pain in the leg. If it dislodges and travels to the lungs, to the pulmonary arteries, it is called a "pulmonary embolism". Clinical signs and symptoms of venous thromboembolism are non-specific and often asymptomatic. If deep vein thrombosis is symptomatic, the most common symptoms are leg pain and/or swelling, redness and warmth in the leg, as most DVTs affect the lower-extremity veins. If pulmonary embolism is symptomatic, symptoms include, but are not limited to, dyspnoea, chest pain, pre-syncope or syncope, fever, cough, unilateral leg pain. Venous thromboembolism may be fatal in the acute phase or lead to chronic disease and disability, which affects the patients' long-term quality of life and functional capacity. Venous thromboembolism is frequent, the third most frequent cardiovascular disease. Venous thromboembolism is an escalating public health problem as the incidence of VTE increases with age.

The diagnostic algorithm for both deep vein thrombosis and pulmonary embolism starts with the initial assessment of the pre-test probability. Measurement of D-dimer is the second step; this is usually combined with a clinical prediction score. If the D-dimer test is positive further testing follows, such as ultrasound for the diagnosis of deep vein thrombosis, ventilation-perfusion scan and computed tomography pulmonary angiography for the diagnosis of pulmonary embolism. The standard of care for the treatment of venous thromboembolism is anticoagulation. These drugs "thin" the blood and prevent further clotting.

D-Dimer POCT

bei Symptomen von venöser Thromboembolie (tiefe Venenthrombose oder pulmonale Embolie)

führt zu akuter (mit Todesfolge) oder chronischer Erkrankung

diagnostische Abklärung:

Prüfung der VorTest-Wahrscheinlichkeit, Messung des D-Dimers (in Komb. mit klinischem Vorhersagescore)

bei positivem Ergebnis: Ultraschall, Lungenszintigraphie, CT, Lungenangiographie

Methods of EUnetHTA Report 2019

The EUnetHTA Core Model® was used as a reporting standard.

systematische Suche in 4 Datenbanken

nach systematischen Reviews (SR) und Primärstudien

nach Leitlinien

Search: To identify potentially relevant systematic reviews and meta-analyses, systematic searches in four databases were performed (The Cochrane Library, Centre for Reviews and Dissemination, Embase via Elsevier, Medline via Ovid). Two further searches were conducted in four databases to identify primary studies updating or extending the evidence derived from available systematic reviews (Medline via Ovid, Embase via Elsevier, The Cochrane Library, Cumulative Index to Nursing and Allied Health Literature). To identify relevant clinical practice guidelines, systematic searches were carried out in the Trip database and the Guidelines International Network (G-I-N) database. Also, manual searches were carried out on the websites of the HTA institutes and professional organisations.

Auswahl der Studien in PRISMA: hochwertige SR und deren Update

Study selection: Searching and study selection occurred separately for each POCT. Two independent researchers for each POCT undertook study selection in accordance with the PRISMA statement. For both POCTs, we identified the most recent and high-quality systematic review from all those identified, which we updated either for publication year (Tn) or by widening the subject of the review (D- dimer).

Qualitätsbeurteilung der Studien: AMSTAR-2 für SR, ROBINS-I für NRCT, AGREE II für Leitlinien

Quality rating: The quality of the eligible studies was assessed using the following tools: For systematic reviews, the AMSTAR-2 checklist was utilised, whilst for non-randomised controlled trials (NRCTs), the quality was assessed using the ROBINS-I tool. The Appraisal of Guidelines, Research and Evaluation (AGREE II) reporting checklist was used to assess the included guidelines' quality.

gewählte Endpunkte: Mortalität, Morbidität, QoL, Patient*innen-management

Selected outcomes: We focused on assessing the effectiveness/clinical utility of these POCT devices. Consequently, we chose mortality/morbidity, quality of life and patient management as outcomes of interest. The latter was split into nine further outcomes: number of hospital admissions, treatment initiation, referral rates, door-to-needle time, turnaround time, time to discharge (TTD), length of stay (LOS), further diagnostic testing, and time to clinical decision. Safety outcomes included side effects/disadvantages.

Datenextraktion durch 2 Wissenschafter*innen

Data extraction and analyses: One researcher extracted the data and another researcher checked the extracted data. The evidence was qualitatively synthesised.

Results Tn-POCT

Ergebnisse zu 15 Tn-POCT Produkten

For Tn-POCT, we identified 15 devices for this assessment, 14 of which measure Tn quantitatively.

verfügbare Evidenz zu Tn-POCT

2 systematische Reviews zu 42 Primärstudien

Available evidence for Tn-POCT: Two systematic reviews were included to evaluate the effectiveness of Tn-POCT, one was a report from the Canadian Agency for Drugs and Technologies in Health (CADTH). These two systematic reviews included a total of 42 primary studies. An update search was conducted on one of the reviews, but no further eligible primary studies were identified. The included systematic reviews reached a moderate to high certainty according to AMSTAR-2.

8 Leitlinien

In addition, eight clinical practice guidelines met our inclusion criteria and were included in the guideline synopsis. Concerning quality (AGREE-II), three guidelines are recommendable and recommendable with modification, respectively. The remaining two guidelines are not fully recommendable.

Clinical effectiveness and safety: Results from the comparison of diagnostic test accuracy (DTA) estimates of the eleven studies included in the CADTH report show that there are significant inconsistencies in estimates measured across settings and there are significant limitations with the study quality (e.g., solely non-comparative studies in the other review). Additionally, evidence found by the CADTH report shows that compared with central laboratory testing (CL), Tn-POCT tended to have a lower sensitivity, lower negative predictive value, higher specificity and higher positive predictive value.

Wirksamkeit und Sicherheit: inkonsistente Ergebnisse bei Testgenauigkeit, geringere Sensitivität, geringerer NPV, höhere Spezifität und höherer PPV im Vergleich zum Zentrallabor

The two systematic reviews included 32 studies investigating the clinical utility of Tn-POCT, of which seven were randomised controlled trials (RCTs). Broadly, the evidence was insufficient to show non-inferiority compared to CL testing when implementing Tn-POCT (if CL testing is onsite or timely available, e.g., in emergency departments). The evidence is also insufficient to show superiority compared to usual care in settings without or delayed CL testing (e.g., certain ambulatory settings and pre-hospital emergency medicine).

insuffiziente Evidenz für Überlegenheit im klinischen Nutzen gegenüber Standarddiagnostik (ohne POCT)

In the **emergency department**, evidence from the CADTH report showed limited evidence that implementing Tn-POCT in the emergency department may reduce turnaround time (reduction in two RCTs), TTD (reduction in two RCTs & one observational study), and LOS (reduction in three RCTs and two observational studies, increase in one RCT). However, the use of Tn-POCT did not statistically change mortality (two RCTs, three observational studies) or adverse events (two RCTs, two observational studies) compared with CL testing up to one year follow-up. Quality of life was also not statistically significantly different up to three months of follow-up (one RCT). Thus, the evidence is insufficient to clearly show non-inferiority of Tn-POCT in comparison to CL testing also in light of the poorer sensitivity and lower negative predictive value as shown above.

im Anwendungssetting: Notfallabteilung (mit Möglichkeit für zeitnahe Labor-Testung)

insuffiziente Evidenz für Nicht-Unterlegenheit bei Endpunkten im Patienten-Management

In **ambulatory (primary and community) care**, insufficient evidence was found indicating the superiority of using a pathway with Tn-POCT compared to usual care (without Tn-POCT) based on the selected clinical utility outcomes: evidence based on one cohort study that was identified by both of the included systematic reviews suggests that implementing Tn-POCT may reduce the referral rates but potentially with an increased risk of missing out on acute myocardial infarction or unstable angina. No evidence was found to conclude that implementing Tn-POCT has a beneficial or harmful effect on mortality/morbidity or health-related quality of life.

im Anwendungssetting: Primärversorgung

insuffiziente Evidenz für Überlegenheit gegenüber Standarddiagnostik bei Mortalität, Morbidität und QoL, ev. geringere Überweisungsraten

In **pre-hospital emergency medicine**, there is also insufficient evidence indicating the superiority of using a pathway with Tn-POCT compared to usual care (without Tn-POCT) in the ambulance based on the selected clinical utility outcomes: The CADTH report found evidence consisting of one RCT showing no difference in hospital admissions and a non-statistical reduction of time from first medical contact to discharge from the emergency department or admission to hospital. The same review found evidence consisting of one non-comparative observational study showing a median turn-around time of 83 minutes (range: 46-187). Concerning the outcome mortality, the CADTH report found evidence based on one RCT showing no difference in death in the next 30 days, but no further information was reported (e.g., exact survival rates or p-values). No evidence was found with regard to the potential effect of implementing Tn-POCT on quality of life.

im Anwendungssetting: ambulante Notfallversorgung

kein Unterschied bei Krankenhauseinweisung, Mortalität

Nebenwirkungen und negative Effekte von falsch-positiven und falsch-negativen Diagnosen durch Tn-POCT

nicht/kaum berichtet

Concerning safety, none of the identified reviews highlighted side effects. However, data on diagnostic accuracy can indirectly indicate whether the harms of false positives and false negatives can be expected. Only one study identified in both systematic reviews directly reported on the harm of discharged patients with acute coronary syndrome: The evidence consisted of one cohort study in the primary care setting that reported a decrease in referrals that, however, may increase the risk of missing outpatients with acute myocardial infarction. Two out of 178 patients in the Tn-POCT group needed but did not receive a referral (referral rate: 25% and 43% of patients managed by physicians using and not using Tn-POCT, respectively). However, the p-value was not reported/available.

8 Leitlinien: 6 für ambulantes Setting keine klaren Empfehlungen für den Gebrauch (optimaler Zeitpunkt, Schwellenwerte, etc.), da Anwender- und Produkt-abhängig

Guideline synopsis: Eight clinical practice guidelines met our inclusion criteria and were included in the guideline synopsis. Six guidelines were developed for the outpatient setting (emergency department, pre-hospital, primary care, ambulance), one guideline was developed for disaster medicine, one guideline did not specifically define the setting but states the guideline is applicable for all cardiac caregivers. None of the included guidelines makes a recommendation regarding the optimal timing of testing, and the diagnostic thresholds and pathways with the reasoning that POCTs continuously and rapidly improve and their performance characteristics are both assay and user dependent.

Experten-Aussagen: Potential von POCT nur dort, wo kein rascher Zugang zu Labortest besteht

Expert consultation (Austria): The experts we consulted believed that Tn-POCT has a theoretical potential value in settings where a CL would not be available or would take too long to supply results. However, there is doubt as to whether such scenarios actually exist in Austria.

5 laufende Studien zu POCT in Notfallabteilung

Upcoming evidence: The search for ongoing studies revealed that five are currently evaluating the use of Tn-POCT in the emergency department. Two of these are RCTs, and three other identified studies are NRCTs. Three studies measure patient management outcomes (e.g., LOS, TTD), and two further studies solely evaluate the clinical performance of these diagnostics.

Results D-dimer POCT

Ergebnisse zu 11 D-Dimer POCT Produkten

For D-dimer POCT, eleven devices were identified, eight of which measure D-dimer quantitatively.

verfügbare Evidenz: 6 systematische Reviews mit bis zu 52 Primärstudien für Update + 2 Studien

Available evidence for D-dimer POCT: Overall, six systematic reviews were identified. The reviews identified between four and 52 primary studies. Two primary studies were additionally included that specifically considered deep vein thrombosis, which had not been adequately addressed in the reviews. The included systematic reviews reached a moderate to high quality according to the AMSTAR-2 assessment. Regarding the risk of bias of the primary studies (assessed with the ROBINS-I tool), one study was considered to have a moderate risk of bias for the patient management outcomes while the risk of bias of the other study was rated as severe.

10 Leitlinien

Ten guidelines met our inclusion criteria and included some form of recommendation or mention of D-dimer POCT. Regarding quality (AGREE-II), five guidelines were fully recommendable, and the remaining guidelines were recommendable with modifications.

Wirksamkeit und Sicherheit:

Clinical effectiveness and safety: Evidence was identified in ambulatory (primary and community) care and emergency care. Three systematic reviews reported on evidence in ambulatory care (primary and community care), whilst two reviews restricted their review to the emergency department or hospital emergency care settings. One further review did not specify the setting and only mentioned the outpatient setting (without further description). Two primary studies were further identified that focused on primary care.

In **ambulatory care settings (primary and community care**), the evidence identified suggests that, when used among patients with a low probability of venous thromboembolism, the combination of D-dimer POCT (especially the quantitative test) with a clinical decision rule (e.g. when general practitioners use a D-dimer POCT in combination with the Wells clinical decision rule) leads to a more accurate diagnosis of venous thromboembolism than without POCT.

im Anwendungssetting: Primärversorgung

(quantitative) D-dimer POCT in Kombination mit klinischer Entscheidungsregel: hoher NPV

The negative predictive value of the combined D-dimer POCT and clinical decision rule can be high (>95%), meaning that some patients may avoid referrals to imaging. However, efficient use of a D-dimer POCT combined with a clinical decision rule requires training, expertise and practice. No direct comparative evidence elaborates on the effect of D-dimer POCT on mortality/morbidity, quality of life, or patient management in ambulatory care settings. The two additional primary studies updating the evidence from the systematic reviews reported on data with regard to turnaround time (1 study: <5 min-34 min) and referral rates (one study: no statistically significant difference between intervention and usual care), confirming the available body of evidence within the reviews. Compared to the current situation, there is a lack of reliable, good-quality evidence proving superiority (primary and community care settings with no immediate CL testing).

die Anwendung von Entscheidungsregeln bedarf aber Training und Expertise

keine Evidenz zu Mortalität, Morbidität, QoL
keine belastbare Evidenz für Überlegenheit zu Standarddiagnostik (ohne POCT)

Concerning the potential effect of implementing D-dimer POCT in **emergency care**, one systematic review reported evidence on the effect of implementing D-dimer POCT on patient management, although this was a purely narrative review with only moderate quality at most. Based on observational studies, this review found a reduction in turnaround time, number of hospital admissions and length of stay. The diagnostic test accuracy for D-dimer POCT was not reported. However, the evidence is insufficient to show a beneficial effect on patient management, and no evidence was found to evaluate the effect on mortality/morbidity and quality of life in the emergency department. Consequently, there is a lack of reliable, good-quality evidence to show non-inferiority (in emergency care with the availability of CL) compared to CL testing.

im Anwendungssetting: Notfallabteilung (mit Möglichkeit für zeitnahe Labor-Testung)

keine belastbare Evidenz für Nicht-Unterlegenheit gegenüber Labor-Testung

With regard to safety, none of the identified reviews highlighted side effects/negative effects. However, data on diagnostic accuracy can indirectly indicate whether the harms of false positives and false negatives can be expected. The reviews confirm that D-dimer testing is very sensitive, with a high negative predictive value but not very specific. The sensitivity of the D-dimer test is improved when it is combined with a pre-test clinical probability score, and reviews concur that D-dimer POCT should not be used without this. The specificity of D-dimer decreases steadily with age, so age-adjusted cut-offs are needed among the elderly.

Nebenwirkungen und negative Effekte von falsch-positiven und falsch-negativen Diagnosen durch D-Dimer POCT

nur mit klinischer Entscheidungsregel

Guideline synopsis: Ten guidelines met our inclusion criteria and included some form of recommendation or mentioning of D-dimer POCT. The guideline recommendations are consistent in terms of the use of D-dimer tests more broadly. Eight out of ten guidelines conclude that POCT can be used to exclude suspected pulmonary embolism or deep vein thrombosis. Only one guideline does not make a recommendation due to lack of or weak evidence and one guideline makes an indirect recommendation saying that there is no need for an ultrasound if D-dimer level can be measured with POCT.

10 Leitlinien

konsistente Empfehlungen zum Ausschluss von pulmonaler Embolie (trotz schwacher Evidenz)

unterschiedliche Expertenaussagen: Mangel an Expertise für D-Dimer POCT in Primärversorgung vs. ausreichend Expertice

Expert consultation (Austria): Some experts believed that D-dimer POCT could only have a limited role outside the hospital setting because of the shortage in the training and expertise required to correctly interpret the results alongside the pre-test probability. In addition, a prerequisite for the use of the test is familiarity with and routine use of clinical decision rules, which may not be the case in ambulatory care settings in Austria, unlike other healthcare systems with a strong primary care sector. However, one of the consulted experts believes that Austrian family doctors do have (must have) the needed expertise to use D-dimer POCT.

keine laufenden Studien

Upcoming evidence: For D-dimer POCT, no ongoing NRCTs or RCTs were identified.

Discussion and conclusion

Zielsetzung des Assessments: klinischer Nutzen in 2 Anwendungsbereichen

Notfallambulanz und Primärversorgung

The aim of this report was to evaluate the clinical utility/effectiveness and safety of Tn-POCT and D-dimer POCT in symptomatic patients presenting to ambulatory (primary or community care) or emergency care with symptoms that could be related to acute coronary syndrome and suspected deep vein thrombosis or pulmonary embolism, respectively. For both Tn-POCT and D-dimer POCT, there is insufficient evidence to show non-inferiority compared to CL testing and superiority compared to the current situation (with no immediate CL testing) in the ambulatory (primary and community care) settings.

insuffiziente Evidenz, Ergebnisse sind Anwender-abhängig und nicht leicht aus anderen Gesundheitssystemen übertragbar

In addition, it should also be mentioned that any benefits found from implementing Tn-POCT and D-dimer POCT are strongly dependent on the setting and health care system. For this reason, evalu ation studies in the field of health service research might be better suited to fully determine the clinical benefit in specific settings than traditional RCTs.

2 Update 2024

2.1 Objectives and Scope of Update

In contrast to the 2019 report [1, 2], the scope of this assessment is limited to primary and community care settings.

2024 Update-Bericht: Fokus nur auf Primärversorgung

The AIHTA assessment 2024 addresses the research question whether using the point of care tests (POCT) for D-dimer and troponin (Tn) in symptomatic patients presenting at ambulatory (primary or community care) is more effective and/or safer than current diagnostic practice. Subsequently, the following research questions can be formulated:

Forschungsfrage: Vergleich von D-Dimer und Troponin POCT mit der aktuellen Praxis

- Are the point of care tests (POCT) D-dimer and troponin (Tn) in symptomatic populations presenting in primary care settings as effective and/or as safe or more effective and/or safer concerning patient management (e.g., number of hospital referral rate, number of hospital admissions), mortality, morbidity and patient quality of life (QoL) than current diagnostic practice?

bezügl. Endpunkte im Patient*innen-Management

2.2 Methodology

2.2.1 Inclusion criteria

The inclusion criteria of the previous systematic review from 2019 have been slightly adapted regarding the setting and outcomes. Details are summarized in Table 2-1.

Einschlusskriterien

Table 2-1: Inclusion criteria (PICO) for (high-sensitivity) Tn-POCT

Population	Adult patients (≥18 years) with signs and/ or symptoms such as chest pain or breathlessness that are potentially indicative of acute myocardial infarction (MI), presenting in primary care (general practice, internal medicine or pulmonology in private practice) and has not been ruled out. Specific high-risk groups of patients will be excluded. MeSH-terms: acute coronary syndrome, myocardial infarction, unstable angina pectoris, cardiac troponin. ICD-10: I20-I24
Intervention	Quantitative point of care tests (POCT) (high-sensitivity, hs) cardiac troponin (Tn) products that are available on the market such as: ■ PATHFAST (LSI Medicine Corporation, Tokyo, Japan); ■ TriageTrue (QuidelOrtho, San Diego, United States); ■ Atellica VTLi (Siemens Healthineers, Erlangen, Germany) with the intention to rule-out the acute disease. If hs-cT POCTs are not investigated, quantitative non-hs Tn POCTs are also considered.
Comparison	All comparators will be included. For the impact of POCT on patient management, usual care (incl. central laboratory methods) will be used. In diagnostic performance testing, reference standard tests are likely to include echocardiography, angiography and laboratory testing (as opposed to the near-patient testing devices).
Outcomes	Critical endpoints for safety: ■ Major adverse cardiac events (MACE)* ■ AEs, SAEs Critical endpoints for clinical utility: ■ Hospital and ED referrals and visits; ■ Hospital admissions; ■ Health related QoL; ■ Patient / Staff satisfaction (e.g., user-friendliness) Diagnostic accuracy: ■ Sensitivity, specificity, positive and negative predictive value *MACE is defined as a combined endpoint of ACS, percutaneous coronary intervention, coronary artery by-pass grafting, coronary angiography revealing procedurally correctable stenosis managed conservatively and all-cause mortality
Study design	An iterative step-wise approach will be conducted: ■ At the first stage, systematic reviews and meta-analyses as well as HTA-reports and evidence-based guidelines (Level of Evidence/LoE and Grade of Recommendation/GoR) will be searched. ■ In a second stage, primary studies (controlled trials ≥ 10 participants) may be included to update the results of available systematic reviews or expand the scope of available systematic reviews. ■ Inclusion period: June 1, 2019 – March 1, 2024

Table 2-2: Inclusion criteria (PICO) for D-dimer POCT

Population	Adult patients (≥18 years) with low pre-test probability of deep vein thrombosis (DVT) or pulmonary embolism (PE), with symptoms such as leg swelling, chest pain or trouble breathing that are potentially indicative of DVT or PE, presenting in primary care (general practice, internal medicine or pulmonology in private practice) and has not been ruled out. Specific high-risk groups of patients (e.g. those with a previous VTE or those with cancer) will be excluded. MeSH-terms: pulmonary embolism, venous thrombosis, thromboembolism, "fibrin fibrinogen degradation products" Pulmonary embolism ICD 10: 0882, I269, I260; Deep vein thrombosis ICD 10: I801, I828, I829, O223, I822, I820, I802, I81, O082, I823, O871; Thrombophlebitis ICD 10: I809, I821, I808, I803.
Intervention	Quantitative D-dimer POCTs included the following products: ■ Exdia TRF Plus (Precision Biosensor Inc.) ■ AFIAS-1® (Boditech Med Inc) ■ Standard F200® (SD Biosensor) ■ LumiraDx™ (LumiraDx Ltd.) ■ Hipro AFS/1® (Hipro Biotechnology) ■ Nano-checker 710 (Nano-Ditech Corporation) ■ iChroma-II (Boditech Med Inc) with the intention to rule out the presence of venous thromboembolism, in conjunction with the use of a clinical prediction rule (e.g., such as Wells or Geneva). Studies investigating both, quantitative and qualitative D-dimer POCTs are considered also.
Comparison	All comparators will be included. For the impact of POCT on patient management, usual care (incl. central laboratory methods) will be used. In diagnostic performance testing, reference standard tests are likely to include computerized tomography pulmonary angiography (CTPA), ultrasound, venography/ angiography and laboratory testing (as opposed to the near-patient testing devices).
Outcomes	Critical endpoints for safety: ■ AEs, SAEs Critical endpoints for clinical utility: ■ Hospital or ED referral rate; ■ Hospital admissions; ■ Morbidity and mortality (all-cause and VTE-related mortality); ■ Health-related QoL; ■ Patient / Staff satisfaction (e.g., user-friendliness) Diagnostic accuracy ■ Sensitivity, specificity, positive and negative predictive value
Study design	An iterative step-wise approach will be conducted: ■ At the first stage, systematic reviews and meta-analyses, as well as HTA reports and evidence-based guidelines (Level of Evidence/LoE and Grade of Recommendation/GoR), will be searched. ■ In the second stage, primary studies (controlled trials ≥ 10 participants) may be included in order to update the results of available systematic reviews or expand the scope of available systematic reviews. ■ Inclusion period: June 1, 2019 – March 1, 2024

2.2.2 Literature search and Study selection

systematische Literatursuche in 4 Datenbanken

A systematic literature search was performed first in February 2024, using

- the Cochrane Library,
- Medline via Ovid,
- Embase and
- International Network of Agencies for Health Technology Assessment Database (INAHTA)

2-stufige Suche:

1. SRs und HTAs
2. Primärstudien

for new systematic reviews (SRs) and HTA reports. The search for SRs and HTAs was limited to studies published in German or English from June 2019 to February 2024. Searching and study selection were conducted separately for each POCT: 44 references on Troponin and 38 for D-dimer were identified.

As none of the SRs or HTAs were found relevant to our update, a second systematic literature search was performed in March 2024 for primary studies separately for each POCT for the period June 2019 to March 2024, using three databases (Medline, Embase, and the Cochrane Central Register of Controlled Trials). Details on the search strategy can be found in the Appendix I: Literature search

Suche nach Leitlinien und laufenden Studien

A targeted hand search in the Trip and Guidelines International Network (GIN) databases complemented the systematic search. No guidelines that were updated or with literature search since June 2019, relevant to our scope, were found.

A hand search was conducted for ongoing studies in the ClinicalTrials.gov registry in February 2024. Two ongoing RCTs were found for Tn-POCTs and two ongoing observational studies for D-dimer POCTs (see details in Table A - 6 and Table A - 7; Appendix IV.)

Two independent researchers (MH, CW) for each POCT undertook study selection in accordance with the PRISMA statement [6].

Abstrakt-Screening: 709 Publikationen zu Tn-POCT und 489 zu D-Dimer POCT

For Tn-POCT, after the removal of duplicates, the abstracts of 709 records were screened independently by two researchers (MH, CW) and 34 full texts were evaluated for inclusion eligibility. In case of discrepancies, mutual discussion or consultation with a third reviewer was used to resolve the issue. In the end, three studies in four publications were included.

For D-dimer POCT, after the removal of duplicates, the abstracts of 489 records were screened independently by two researchers (MH, CW) and 28 full texts were evaluated for inclusion eligibility. In case of discrepancies, mutual discussion or consultation with a third reviewer was used to resolve the issue. In the end, three studies in three publications were included.

The flow diagrams depicting the selection process of primary studies can be found below (see Figure 2-1 and Figure 2-2).

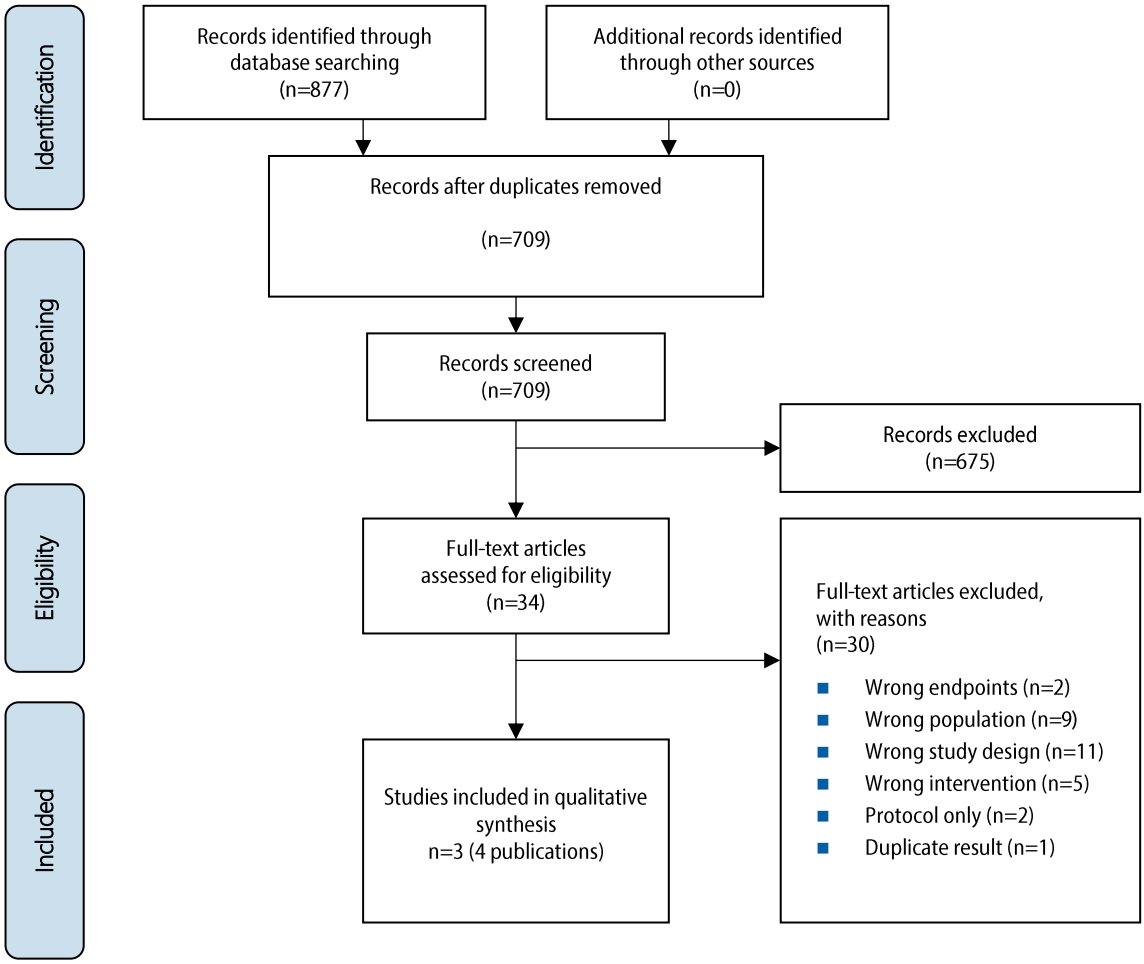

Figure 2-1: PRISMA Flow Diagram Tn-POCTs

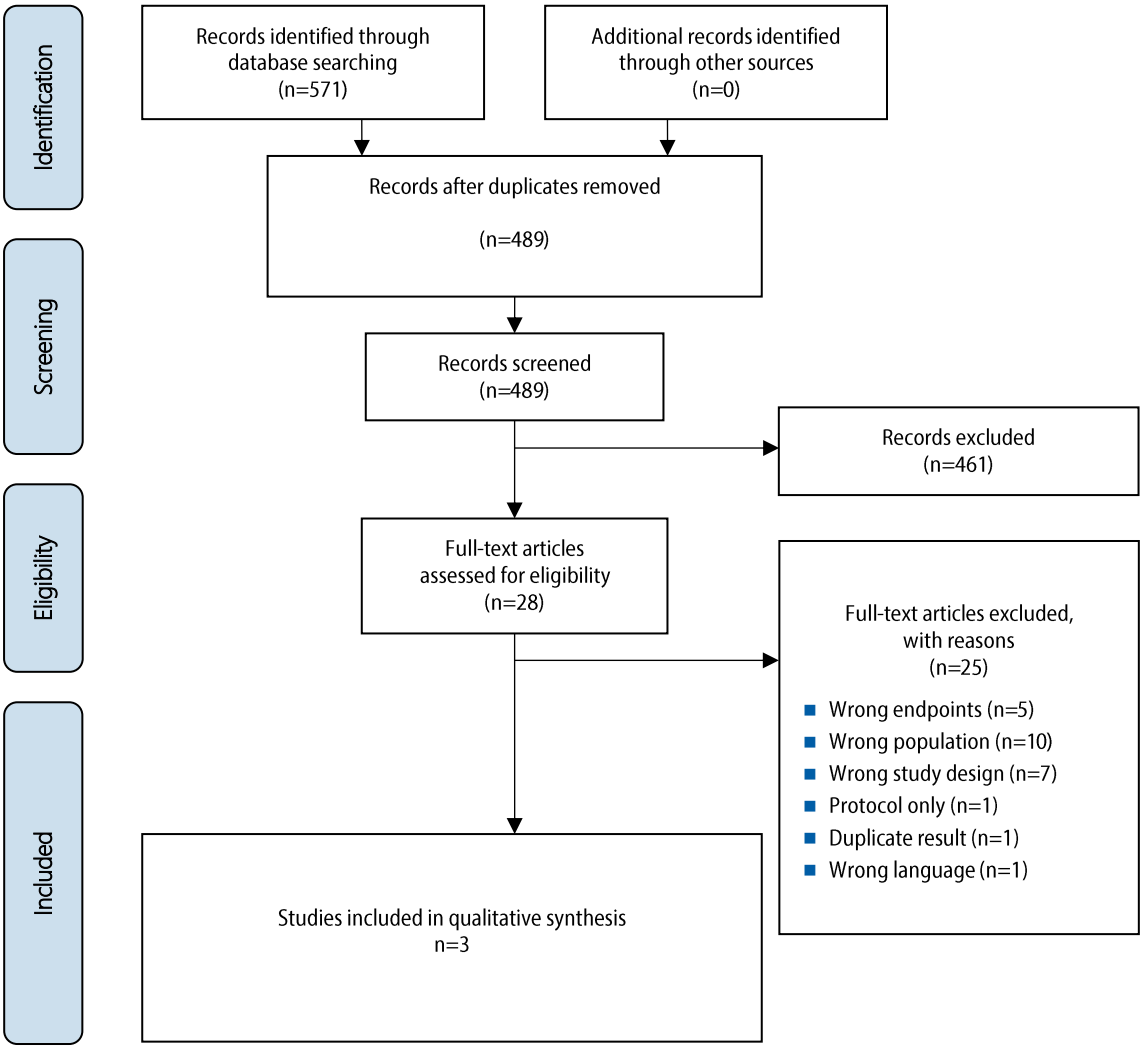

Figure 2-2: PRISMA Flow Diagram D-dimer-POCTs

2.2.3 Data extraction

Datenextraktion und Datenkontrolle

One researcher (MH) systematically extracted all relevant data into extraction tables, which were reviewed for accuracy by a second researcher (JE). In case of discrepancies, mutual discussion or consultation with a third reviewer resolved the issue.

2.2.4 Quality assessment of the studies

Bewertung der Studienqualität für RCTs anhand des Cochrane RoB 2.0 Tools und für NRCTs anhand des ROBINS-I Tools

Risk of bias was assessed using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions [7]. The quality of RCT was assessed with the Cochrane Risk of Bias 2 (RoB 2) tool for randomized controlled trials (RCTs) [8] by one reviewer (MH) and double-checked by a second reviewer (JE). The quality of prospective observational studies was assessed using the ROBINS-I tool for non-randomised controlled trials (NRCTs) [9, 10] by one reviewer (MH) and also double-checked by a second reviewer (JE).

2.2.5 Synthesis and presentation of findings

narrative Präsentation der Ergebnisse

A qualitative synthesis of the evidence was performed. The results were presented in plain text format.

3 Results

keine neuen SRs und Leitlinien gefunden

This updated literature search found no SRs and no clinical or diagnostic guidelines related to high-sensitivity (hs) POC Tn testing in primary care settings in low-risk adult patients with suspected non-ST-elevation acute coronary syndrome (NSTE-ASC). Only three studies were identified investigating Tn-POCTs; however, all of them had non-high-sensitivity POC Tn tests.

inkludierte Primärstudien:
3 zu Tn-POCT
3 zu D-Dimer POCT

Also, no new SRs and clinical or diagnostic guidelines were found related to quantitative POC D-Dimer tests in primary care settings in adult patients with a low pre-test probability of deep venous thrombosis (DVT) or pulmonary embolism (PE). Only three studies were identified investigating D-Dimer POCTs, two assessing quantitative POC D-Dimer tests, and one using qualitative and quantitative POC D-Dimer tests.

3.1 Study Characteristics

3.1.1 Tn-POCT

3 Studien – keine zu hochsensitiven Tn-POCT:
1 RCT und 2 prospektive Kohortenstudien

Three studies (one RCT and two prospective observational studies) investigating Tn POCTs were included, all three using non-high sensitivity POC Tn tests.

1 RCT (ARTICA):
prähospitale- vs. Notaufnahme-Ausschlussstrategie
2 Kohortenstudien:
30-Tage Nachbeobachtung

One is a multicentre randomised, open-label controlled trial (RCT) (ARTICA, NCT05466591) conducted in the Netherlands (with published results in two articles, at 30-day and 1-year follow-up) [11, 12]. The aim was to assess healthcare costs and safety (as the incidence of major adverse cardiac events - MACE) of a pre-hospital rule-out strategy using a POC Tn measurement in low-risk suspected non-ST-segment elevation acute coronary syndrome (NSTE-ASC) patients. This trial has a high risk of bias. The other two studies are prospective observational studies conducted in rural New Zealand, with 30-day follow-up, and have critical [13] and serious risk of bias [14]. Detailed risk of bias assessment can be found in Table A - 3 and Table A - 4, Appendix III.

RCT: Patient*innen mit niedrigem Risiko für NSTE-ACS

866 Patient*innen

In the ARTICA RCT [11, 12], the study population consisted of low-risk patients suspected of having a NSTE-ACS who have had an onset of symptoms ≥2 h before ambulance arrival at home. Low risk was defined as a HEAR score (HEART score without the Tn component) of ≤3. It includes the history, ECG, age and risk factors components. The ambulance paramedics performed screening of patients, the informed consent procedure, randomisation, and the POC Tn measurement. Eligible patients (n=866) were randomised 1:1 to the *pre-hospital or emergency department (ED) rule-out strategy.*

prähospitale Ausschlussstrategie:
Tn-POCT mit Cobas h232, nicht-hochsensitiver Test

In the *pre-hospital rule-out strategy*, patients underwent *one POC Tn T measurement* on-site, measured using the **Cobas h232** (**Roche Diagnostics**), **non-high-sensitivity assay**. If POC Tn T was low (<40 ng/L), the patient was transferred to the general practitioner (GP) (the normal procedure for not transporting patients). Patients with elevated POC Tn T were transported to the ED.

According to standard practice, patients were transported to the ED without POC Tn measurement in the *ED rule-out strategy*. At the EDs in the Netherlands, the European Society of Cardiology 0h/1h algorithm (with hs Tn (T or I) laboratory tests) is standard practice.

Notaufnahme-Ausschlussstrategie: kein POCT

The **primary outcome** was healthcare costs at 30 days and one year. **Secondary outcomes** were safety, QoL, and cost-effectiveness. Safety was assessed by the incidence of MACE at 30 days and 1 year, which was defined as one or more of the following events: ACS, unplanned revascularization, and all-cause death. Incidence of MACE at one year was compared between groups in the total population and in the ruled-out ACS population (all patients for whom an ACS was ruled out, either in the pre-hospital setting or in the ED). Quality of life was assessed at 30 days and one year and measured with a validated health-related QoL instrument, the EuroQol-5D -5L (EQ -5D -5L).

primärer Endpunkt (bei 30 Tagen und 1 Jahr): Gesundheitskosten;

sekundäre Endpunkte (bei 30 Tagen und 1 Jahr): Sicherheit: Inzidenz von MACE
QoL: EQ-5D-5L

The sample size calculation was based on the primary outcome – 30-day healthcare costs (total of 866 patients). Analysis of the total population (434 pre-hospital rule-out strategy vs 429 ED rule-out strategy) and analysis of the ruled-out ACS population (419 vs 417) was performed. MACE was a secondary outcome measure, so the trial was not formally powered to conclude that the pre-hospital rule-out strategy is non-inferior for safety.

Gesamtpopulation: 434 vs. 429
ACS-ausgeschlossene Population: 419 vs. 417

The first prospective observational study published by Norman et al. [13] was a small pilot study aimed at assessing the real-life feasibility and acceptability of implementing rural accelerated diagnostic chest pain pathway (RACPP) to identify low-risk patients who do not require urgent transfer to a hospital for further cardiac work-up, as well as to make a preliminary assessment of the effectiveness and safety of implementing this RACPP in the New Zealand rural general (family) practice. RACPP was modified from a validated metropolitan emergency department (ED) chest pain accelerated diagnostic pathway (ADP), which incorporated the Emergency Department Assessment of Chest Pain Score (EDACS), ECG and POC-Tn measurements at presentation and 2 hours at the rural general practice. The **non-high-sensitivity POCT** used in the study was the **Abbott i-STAT c-TnI** assay.

kleine Beobachtungsstudie: Bewertung eines diagnostischen Pfades für Brustschmerzen in ländlichen Gebieten (RACPP) zur Identifizierung von Niedrigrisiko-Patient*innen ohne Notwendigkeit für Hospitalisierung

The study population consisted of adult patients presented acutely to rural general practice with suspected ischaemic chest pain for whom the doctor intended transfer to hospital for serial troponin measurement, in whom RACPP was implemented to distinguish low-risk patients and non-low-risk patients. Non-low risk patients were referred to hospital for assessment and serial troponin testing. Median time from index chest pain onset to presentation to rural practice was 15 hours (IQR: 3.1–40.2 hours).

Studienpopulation: akute Brustschmerzen, Verdacht auf ischämische Schmerzen

Outcomes were divided into **implementation outcomes** (adherence to the pathway, patient acceptability and satisfaction with care, and participating sites' acceptability) and **intervention outcomes** (proportion of patients identified as low-risk by the pathway and managed in the community without transfer to hospital, with no 30-day MACE; MACE within 30 days of presentation in non-low-risk patients; ACS (AMI or unstable angina) within 30 days of presentation in non-low-risk patients; non-emergency coronary revascularisation within 30 days of presentation in non-low-risk patients, and agreement between POC and laboratory-measured cardiac troponin concentrations). MACE was defined as death that was not known to be from non-cardiac causes, emergency coronary revascularisation procedure, cardiac arrest, AMI, ventricular arrhythmia, cardiogenic shock and high-degree atrioventricular block needing intervention.

Endpunkte zur Implementierung: Adhärenz, Akzeptanz und Zufriedenheit

Endpunkte zur Intervention: Anteil der Niedrigrisiko-Patient*innen ohne Krankenhausverlegung, 30-Tage-MACE, bei nicht-Niedrigrisiko-Patient*innen: 30-Tage-MACE, ACS, etc.

A sample size of **200 patients** was estimated to provide at least 70 low-risk patients by the rural accelerated chest pain pathway.

größere Beobachtungsstudie: Bewertung der Sicherheit und Effektivität des RACPP in größerer Kohorte

The second prospective observational study published by Miller et al. [14] was following the above-mentioned pilot study, with the aim to evaluate the safety and effectiveness of the RACPP in a larger cohort of patients, at multiple rural hospital and primary care sites across New Zealand. These 29 study sites consisted of rural hospitals (75.9%, staffed by generalist doctors with broad scopes of practice who often work in both hospital and primary care settings), rural and urban general practices (20.2%), and urgent care clinics (4%).

Studienpopulation: Erwachsene mit Brustschmerzen, Verdacht auf ischämische Ursache oder AMI
POCT: 2 nicht-hochsensitive Tests

The study population consisted of adult patients who had chest pain that the treating clinician considered could be due to cardiac ischaemia or AMI that began or worsened within the last 72 hours and would have ordinarily required transfer for an urgent hospital-based assessment if presenting to a primary care setting (general practice or urgent care). In these patients the RACPP was implemented to distinguish low-risk patients and non-low-risk patients. **Two non-high-sensitivity POC-cTn assays** were used: **Abbott iSTAT cTnI (iSTAT)** and **Radiometer AQT-90 FLEX cTnT (AQT90)**, *at presentation and 2 hours* at the practice. Non-low risk patients were referred to hospital for assessment and serial troponin testing. Median time from index chest pain onset to assessment was 4 hours and 36 minutes (IQR: 2–14 h and 30 min).

primärer Endpunkt: 30-Tage-MACE bei Niedrigrisiko-Patient*innen

Primary outcome was presence of 30-day MACEs in low-risk patients. MACE was defined as death, cardiac arrest, emergency revascularization procedure, cardiogenic shock, ventricular arrhythmia, ventricular fibrillation, high-degree atrio-ventricular block needing intervention, or acute myocardial infarction.

sekundäre Endpunkte: Anteil der Niedrigrisiko-Patient*innen ohne Krankenhausverlegung oder mit früher Entlassung
30-Tage-MACE bei nicht-Niedrigrisiko-Patient*innen

Secondary outcomes were percentage of patients classified as low-risk that avoided transfer or were eligible for early discharge and percentage of patients in the group identified as not low-risk who developed a 30-day MACE.

The total sample size was 1000 patients estimated to ensure inclusion of at least 410 patients at low-risk of developing MACE.

Details of studies characteristics can be found in Table A - 1, Appendix II.

3.1.2 D-Dimer POCT

3 prospektive Beobachtungsstudien:
2 mit quantitativen POCTs,
1 mit qualitativen und quantitativen POCTs

Three prospective cohort studies investigating D-Dimer POCTs were included: two assessed quantitative POC D-Dimer tests, and one used qualitative and quantitative POC D-Dimer tests. All three studies were conducted in the Netherlands, in general practice. One study has a serious risk of bias [15], and the other two have a critical risk of bias [16, 17].

Detailed risk of bias assessment can be found in Table A - 5, Appendix III.

In one comparative diagnostic test accuracy study, Heerink et al. 2023 [15] evaluated the clinical performance (diagnostic accuracy) of five novel POC D-Dimer devices with a capillary finger stick feature for predicting Venous thromboembolism (VTE) in general practice: **AFIAS-1®**, **Exdia TRF Plus**, **Hipro AFS/1®**, **LumiraDx™** and **Standard F200®**. In primary care patients with a low suspicion of a VTE (clinical decision rule (CDR) score of ≤3 for a suspicion of DVT and ≤4 for PE), who consented to draw additional venous blood samples, perform a capillary POC D-dimer test, and approach their general practitioner afterwards for clinical outcomes, venous plasma samples from 511 participants (including plasma samples and clinical outcome data from 237 patients enrolled in EVA-1 study [16, 18] were processed on all POC devices and a laboratory-based assay (STA-Liatest®D-Di PLUS assay). Results were compared with clinical outcomes to generate performance characteristics. Capillary and venous blood results were used for a matrix comparison.

1 Beobachtungsstudie
Ziel: Bewertung der klinischen Performanz von 5 D-Dimer POCTs

Studienpopulation: Patient*innen mit niedrigem VTE-Verdacht, Verfahren: venöse Blutproben, kapillare D-Dimer POCTs, Bewertung durch Allgemeinarzt

Primary outcomes include clinical performance (from the venous sample): sensitivity, specificity, false-negative rate (FN rate), positive and negative predictive values (PPV/NPV), likelihood ratio of a negative test result (LR-), accuracy and efficacy presented as VTE performance parameters for a fixed (500 ng/mL) and age-dependent D-dimer cutoff value, as well as equivalence between capillary and venous blood sample (matrix comparison). Patients were followed up for three months. For clinical performance analyses, the sample size was at least 220 plasma samples, and for matrix comparisons (capillary vs venous blood sample), at least 40 samples per device.

primäre Endpunkte: Sensitivität, Spezifität, FN-Rate, PPV, NPV, LR, diagnostische Genauigkeit

Heerink et al. 2020 [16] evaluated the analytical performance of five quantitative POC D-dimer tests with a laboratory D-dimer test as the reference standard, in 242 patients suspected of having VTE in general practice. User-friendliness was assessed in a hands-on session, in which eleven GP assistants filled out questionnaires based on the System Usability Scale (SUS) after their first-time use of the test systems. Five novel quantitative POC D-dimer tests include **Nano-Checker 710 Ddimer®**, **AFIAS-1®**, **iChroma-II®**, **Standard F200®**, and **Hipro AFS/1®**.

1 Beobachtungsstudie
Ziel: Bewertung der analytischen Performanz von 5 quantitativen D-Dimer POCTs
Benutzerfreundlichkeit: Bewertung mit System Usability Scale (SUS)

Van Maanen et al. 2020 [17] aimed to determine the real-life impact of two clinical prediction rules (CPRs), Wells for PE and Oudega rule for DVT, for suspected VTE in 1477 patients in primary care. In low-risk patients, with a score of ≤3 points on the DVT CPR, or ≤4 points on the PE CPR, a qualitative or a quantitative D-dimer POC test was performed. Patients were followed-up for three months. **Primary outcomes** were the diagnostic failure rate, defined as the 3-month incidence of VTE in the non-referred group, and the efficiency, defined as the proportion of non-referred patients in the total study population. Secondary outcomes were determinants for and consequences of incorrect application of the CPRs. During the inclusion period, the qualitative D-dimer POCT (**Clearview Simplify**) was withdrawn from the market, because of too many false-negative results likely due to periprocedural quality-related faults when performing the test (i.e., incorrect withdrawal of capillary blood or not keeping test cold enough until use). In 357 patients (209 suspected DVT and 148 suspected PE), a quantitative D-dimer test was performed.

1 Beobachtungsstudie
Ziel: Bewertung von CPRs (Wells- und Oudega-Regeln) bei VTE-Verdacht in der Primärversorgung

Studienpopulation: Patient*innen mit niedrigem VTE-Verdacht, qualitativer oder quantitativer D-Dimer POCT, 3-monatige Nachbeobachtung
Primäre Endpunkte: FN, Sekundäre Endpunkte: Faktoren und Folgen inkorrekter CPR-Anwendung

Details of studies characteristics can be found in Table A - 2, Appendix II.

3.2 Outcomes

3.2.1 Tn-POCT

MACE in RCT: Vergleich prähospitale und Notaufnahme-Ausschlussstrategie. 30-Tage MACE: 3,9% vs. 3,7% 1-Jahres MACE: 5,1% vs. 4,2%

ausgeschlossene ACS-Patient*innen: 30-Tage MACE: 0,5% vs. 1,0% 1-Jahres MACE: 1,7% vs. 1,4%

MACE in 2 Beobachtungsstudien:

30-Tage bei niedrigem Risiko: keine MACE bei nicht-Niedrigrisiko: 13% und 23% MACE

The most important clinical outcomes, morbidity and mortality, such as ACS, unplanned revascularization, and all-cause death, were assessed as a combined safety outcome – MACE (major adverse cardiac events). MACE is defined as one or more of the following events: ACS, unplanned revascularization, and all-cause death.

MACE at 30-day and 1-year

In the ARTICA RCT [12], in the total study population, 30-day MACE was comparable between groups (3.9% (17/434) in the pre-hospital strategy vs. 3.7% (16/429) in ED strategy; p=0.89). Specifically, incidence of ACS was 3.9% in the pre-hospital strategy vs. 3.5% in the ED strategy (risk difference 0.4%, p=0.74); incidence of unplanned revascularisation was 2.8% vs. 3.0% (risk difference -0.3%, p=0.82) and all cause death 0.0% vs. 0.2% (risk difference -0.2%, p=0.31).

In the total study population, the 1-year MACE rate was comparable between groups: 5.1% (22/434) in the pre-hospital strategy vs. 4.2% (18/429) in the ED strategy (risk difference 0.9%, p=0.54) [11]. Specifically, incidence of ACS was 4.6% in the pre-hospital strategy vs. 3.5% in the ED strategy (risk difference 1.1%, p=0.41); incidence of unplanned revascularisation was 3.5% vs. 3.0% (risk difference 0.4%, p=0.72) and all cause death 0.5% vs. 0.7% (risk difference -0.2%, p=0.64).

In 836 patients (96.9% of the study total population), ACS was ruled out, either in the pre-hospital setting or at the ED. In this ruled-out ACS population, MACE was very low at 30-days: 0.5% (2/419) vs. 1.0% (4/417), with a risk difference of −0.5% (95% CI −1.6%–0.7%; p=0.41). Specifically, the incidence of ACS was 0.5% in the pre-hospital strategy vs. 0.7% in the ED strategy (risk difference -0.2%, p=0.65); incidence of unplanned revascularisation was 0.5% vs. 0.7% (risk difference -0.2%, p=0.65) and all-cause death 0.0% vs. 0.2% (risk difference -0.2%, p=0.32).

The 1-year incidence of MACE was 1.7% after ruled-out ACS in the pre-hospital rule-out strategy and 1.4% after ruled-out ACS in the ED rule-out strategy, with a non-significant risk difference of 0.2% (95% CI −1.4% to 1.9%, p=0.79). Specifically, the incidence of ACS was 1.2% in the pre-hospital strategy vs. 0.7% in the ED strategy (risk difference 0.5%, p=0.48); incidence of unplanned revascularisation was 1.2% vs. 0.7% (risk difference 0.5%, p=0.48) and all-cause death 0.5% vs. 0.7% (risk difference -0.2%, p=0.65).

In both observational prospective studies [13, 14], no MACE was found within 30 days of the presentation among low-risk patients. In the pilot study [13], 13.0% (9/69, 95% CI 6.5%–23.8%) of patients with a 30-day MACE were in the non-low-risk group. In the larger study [14], 23% (138/599) of patients with a 30-day MACE were reported in the non-low-risk group.

Hospital and emergency department (ED) referrals and visits

In the ARTICA RCT [11, 12], ED visits results were derived from the cost data tables and were statistically significantly lower in the pre-hospital rule-out strategy compared to the ED rule-out strategy, both at 30-day (one ED visit: 13.6% vs 95.8%, p<0.001 and two or more ED visits: 1.2% vs 4.2%, p=0.006) and 1-year follow-up (one ED visit: 17.5% vs 83.9%, p<0.001 and two or more ED visits: 5.8% vs 16.1%, p<0.001).

ED-Besuche im RCT:
30-Tage:
91,5% der Patient*innen in der prähospitalen Ausschlussstrategie nicht in die ED überwiesen

At the 30-day follow-up, only 8.5 % of the patients in the pre-hospital rule-out strategy were directly referred to the ED; the same is true at the 1-year follow-up, in comparison with the ED rule-out strategy, where 100% of the patients were transported to the ED.

1-Jahr:
8,5% prähospitale vs. 100% Notaufnahme-Strategie in die ED überwiesen

At one year, in the pre-hospital rule-out strategy, 37/434 patients (8.5%) were transported to the ED because of elevated POC troponin T (n = 18), failed POC troponin T test (n = 12), or GP decision ($n = 7$).

In the large observational study, with a 30-day follow-up [14], the majority of low-risk patients, 435/474 (91.8%), were discharged home, avoiding transfer or hospital admission. Only 8.2% of low-risk patients were transferred to metropolitan hospitals with specialist care and central laboratory services.

Beobachtungsstudie:
91,8% der niedrig-Risiko Patient*innen ohne Krankenhausaufnahme entlassen

Hospital admissions

In the ARTICA RCT [11, 12], the number of hospitalisations at 30-day (7.4% vs 9.8%, p=0.21) and 1-year follow-up (13.4% vs 13,5%, p=0.95) was not statistically significantly different between pre-hospital rule-out strategy and the ED rule-out strategy.

Krankenhausaufenthalte im RCT: kein signifikanter Unterschied bei 30-Tage und 1-Jahr

Observational studies did not plan to measure or analyse this outcome.

Health related quality of life (QoL)

Only one study, the ARTICA RCT, measured QoL at 30 days and 1 year [11, 12], which was not statistically significantly different between the pre-hospital rule-out strategy and the ED rule-out strategy: mean difference -0.009 (95% CI -0.048 to 0.030, p=0.65) and 0.008 (95% CI -0.033 to 0.050, p=0.69), respectively.

QoL im RCT:
kein signifikanter Unterschied

Patient/Staff satisfaction

Only one small pilot observational study [13] measured and analysed patient satisfaction with care, with a 75% response rate. Satisfaction with care was very high and similar in low-risk and non-low-risk patients, 94% vs. 95.5%, respectively.

Zufriedenheit mit der Versorgung: sehr hoch

Other safety outcomes: Adverse events (AEs) and serious adverse events (SAEs)

No evidence is available on other safety outcomes: AEs and SAEs.

Diagnostic accuracy: Sensitivity, specificity, negative predictive value and positive predictive value

diagnostische Genauigkeit für MACE im RCT: ähnlich in prähospitaler und Notaufnahme-Ausschlussstrategie

In the RCT [11], the sensitivity, specificity, negative predictive value and positive predictive value of the pre-hospital rule-out strategy for detecting a 1-year MACE in low-risk patients were 68.2% (95% CI 47.5% to 84.9%), 100%, 98.3% (95% CI 96.8% to 99.3%) and 100%, and almost identical to the ED rule-out strategy: 66.7% (95% CI 43.7% to 85.2%), 100%, 98.63% (95% CI 97.1% to 99.4%) and 100%.

Beobachtungsstudien: Sensitivität 100%, Spezifität 50,7% und 63,8%, NPV, 100%, PPV 23% und 12,5% für 30-Tage MACE bei niedrigem Risiko

In two observational studies [13, 14] diagnostic accuracy of the pathway (RACPP) for detecting a 30-day MACE in low-risk patients was similar.

More specifically, the sensitivity was the same in both studies: 100.0% (95% CI 70.1% to 100%) [13] and 100% (95% CI 97.3 to 100%) [14] as well as negative predictive value: 100% (95% CI 96.7 to 100%) [13] and 100% (95% CI 99.2 to 100%) [14]. Specificity was 63.8% (95% CI 56.4 to 70.6%) [13] and 50.7% (95% CI 47.5 to 53.9%) [14] and positive predictive value was 12.5% (95% CI 6.7 to 22.1%) and 23.0% (95% CI 19.8 to 26.6%), respectively.

The table below summarizes the safety, clinical utility, and diagnostic accuracy results from three primary studies. Details of the studies' results are in Table A - 1, Appendix II.

Table 3-1: Summary of safety, clinical utility and diagnostic accuracy results: Troponin-POCT (three primary studies)

Safety, clinical utility and diagnostic accuracy of Tn-POCT: evidence from 1 RCT and 2 prospective observational studies					
Evidence base	**Study design**	**Included pts**	**Setting**	**Risk of Bias**	**Summary of the results**
Effect on MACE					
3 studies (4 publications) [11-14]	1 RCT [11, 12]	434 vs. 429 total pop.; 419 vs. 417 rule-out pop.	Primary care	High	**Pre-hospital rule-out strategy vs. ED rule-out strategy** **30-day MACE:** ***Total population***: 3.9% (17/434) vs. 3.7% (16/429); risk difference 0.2% (95% CI −2.4% to 2.7%, p=0.89), n.s. ***Rule-out ACS population***: 0.5% (2/419) vs. 1.0% (4/417), risk difference −0.5% (95% CI −1.6%–0.7%; p=0.41), n.s. **1-year MACE:** ***Total population***: 5.1% (22/434) vs. 4.2% (18/429); risk difference 0.9% (95% CI −1.9% to 3.7%, p=0.54), n.s. ***Rule-out ACS population***: 1.7% (7/419) vs. 1.4% (6/417), risk difference 0.2% (95% CI −1.4% to 1.9%; p=0.79), n.s.
	2 NRCTs [13, 14]	111 low- risk vs. 69 non-low risk pts; 474 low-risk vs. 599 non-low risk pts	Primary care	Serious to critical	**Low-risk vs. non-low-risk pts** **30-day MACE:** 0% (0/111 pts) (95% CI 0.0% to 3.3%) vs. 13.0% (9/69 pts) (95% CI 6.5%–23.8%) [13] 0% (0/474 pts) (95% CI 0–0.3%) vs. 23% (138/599 pts) [14]
Effect on hospital and ED referrals and visits					
2 studies (3 publications) [11, 12, 14]	1 RCT [11, 12]	434 vs 429	Primary care	High	**Pre-hospital rule-out strategy vs. ED rule-out strategy** **At 30 days** 1 ED visit: 59 (13.6%) vs. 411 (95.8%), p<0.001, s.s. ≥ 2 ED visits: 5 (1.2%) vs. 18 (4.2%), p=0.006, s.s. **At 1 year** 1 ED visit: 76 (17.5%) vs. 360 (83.9%), p<0.001, s.s. ≥ 2 ED visits: 25 (5.8%) vs. 69 (16.1%), p<0.001, s.s. **At 30 days and 1 year** ED referrals: 8.5% vs 100%
	1 NRCT [14]	435/474 low risk pts	Primary care	Serious	435/474 (91.8%; 95% CI 88.8-93.9%) of low-risk pts discharged home: 293/330 (88.8%;95% CI 84.9–91.9%) from rural hospitals, 101/102 (99%; 95% CI 94.7-99.8%) from general practice and urgent care clinics (97.6%; 95% CI 87.7-99.9%); 8.2% referrals to metropolitan hospital
Effect on hospital admissions					
1 study (2 publications) [11, 12]	RCT	434 vs 429	Primary care	High	Pre-hospital rule-out strategy vs. ED rule-out strategy **At 30 days** 32 (7.4%) vs 42 (9.8%), p=0.21, n.s. **At 1 year**

					58 (13.4%) vs 58 (13.5%), p=0.95, n.s.
Effect on QoL					
1 study [11]	RCT	376 vs. 362	Primary care	High	**Pre-hospital rule-out strategy vs. ED rule-out strategy** Mean difference in EQ -5D -5L utility score at 1 year: 0.008 (95% CI –0.033 to 0.050, p=0.69), n.s.
Effect on patient/staff satisfaction					
1 study [13]	NRCT	111 of 148 pts responded	Primary care	Critical	**Low-risk vs. non-low-risk pts:** 94% vs. 95.5% satisfied with care
Effect on other AEs and SAEs					
No evidence available					
Diagnostic accuracy outcomes					
3 studies [11, 13, 14]	1 RCT [11]	434 vs. 429	Primary care	High	***Pre-hospital rule-out strategy for MACE at 1 year.*** SEN: 68.2% (95% CI 47.5% to 84.9%) SPEC: 100% PPV: 100% NPV: 98.3% (95% CI 96.8% to 99.3%) ***ED rule-out strategy for MACE at 1 year.*** SEN: 66.7% (95% CI 43.7% to 85.2%) SPEC: 100% PPV: 100% NPV: 98.63% (95% CI 97.1% to 99.4%)
	2 NRCTs	111 and 474 low-risk pts	Primary care	Serious to critical	***For MACE at 30-day in low-risk pts:*** SEN: 100.0% (95% CI 70.1% to 100%) [13] SPEC: 63.8% (95% CI 56.4–70.6%) PPV: 12.5% (95% CI 6.7–22.1%) NPV: 100% (95% CI 96.7–100%); SEN: 100% (95% CI 97.3–100%) [14] SPEC: 50.7% (95% CI 47.5–53.9%) PPV: 23.0% (95% CI 19.8–26.6%) NPV: 100% (95% CI 99.2–100%)

Abbreviations: *ED – emergency department; MACE – major adverse cardiac events; NPV – negative predictive value; NRCT – nonrandomised controlled trial; pts – patients; n.s. – not statistically significant; QoL – quality of life; pop – population; PPV – positive predictive value; RCT – randomised controlled trial; SEN – sensitivity; SPEC – specificity; s.s. – statistically significant*

3.2.2 D-dimer POCT

Only one study measured hospital or ED referral rate and morbidity [17], one [16] measured staff satisfaction and one study diagnostic accuracy [15]. No studies measured hospital admissions, QoL and safety outcomes (AEs and SAEs).

nur 1/3 Studien zu klinischem Nutzen

Hospital or ED referral rate

Hospital or ED referral rate was expressed through the efficiency outcome defined as the proportion of non-referred patients in the total study population and measured in one study [17]. Overall efficiency of both CPRs combined in the total study population was 53% (95% CI 50.4 to 55.5), with hospital or ED referral rate of 47% when CPRs were correctly applied (n=787), the efficiency increased to 58.1% (95% CI 55.2 to 61.0) with decreased hospital or ED referral rate of 41.9%. As the CPRs were incorrectly applied in 339 patients, this resulted in a decreased efficiency of 35.7% (95% CI 30.6 to 41.1) with increased hospital or ED referral rate of 64.3%.

„Effizienz" (Rate der nicht in die Notfallaufnahme überwiesenen Pts.): 58,1% bei korrekter Anwendung der CPRs (47% überwiesen) und 35,7% (64,3% überwiesen)

Hospital admissions

No evidence available.

Morbidity and mortality

VTE was confirmed in 267 (18.1%) of the included 1477 patients. Failure rate, defined as the 3-month incidence of VTE in the non-referred group, was measured in one study [17]. The overall failure rate of both CPRs combined in the total study population (n=1477) was 1.8% (95% CI 1.02 to 3.06). When CPRs were correctly applied (n=787), the failure rate decreased to 1.51% (95% CI 0.77 to 2.86). As the CPRs were incorrectly applied in 339 patients, this resulted in an increased failure rate of 3.31% (95% CI 1.07 to 8.76).

diagnostische Fehlerrate: 1,8% (3-Monats-Inzidenz von VTE in der nicht-überwiesenen Gruppe); resp. 1,5% bei korrekter Anwendung der CPRs, aber 3,3% bei inkorrekter Anwendung der CPRs

QoL

No evidence is available.

Patient/Staff satisfaction

One study measured staff satisfaction as user-friendliness of D-dimer POCTs [16]. A group of eleven GP assistants, unfamiliar with the devices but familiar with CRP POC testing, directly carried out one D-dimer test on all five POC D-dimer test systems in a random order and completed a SUS questionnaire accordingly, along with a few additional questions about sample management and readability of displays and results.

Benutzerfreundlichkeit: hohe Variabilität in den System Usability Scale-Ergebnissen zwischen einzelnen Produkten

System Usability Scale (SUS) score is calculated using a set of 10 questions, with range from 0 to 100. Median SUS score of the five systems varied from 37.5 to 75.0. SUS score for user-friendliness was highest for Hipro AFS/1®: 75.0 (IQR 47.5 to 97.5) and Nano-Checker 710 Ddimer®: 70.0 (IQR 55.0 to 85.0), followed by AFIAS-1®: 65.0 (IQR 40.0 to 90.0) and Standard F200®: 57.5 (IQR 35.0 to 85.0). The lowest was for iChroma-II®: 37.5 (IQR 30.0 to 60.0).

Safety: AEs and SAEs

No evidence is available.

Diagnostic accuracy: Sensitivity, specificity, positive and negative predictive value

diagnostische Genauigkeit
hohe Sensitivität:
die meisten Geräte über 90%;
mäßige bis gute Spezifität:
Werte variieren zwischen 65% und 78%;

FN: durchwegs niedrig;
PPV: generell niedrig;
NPV: sehr hoch, nahezu 100% bei den meisten Geräten

One study [15] measured different diagnostic accuracy outcomes. Venous plasma samples from 511 participants (320 DVT suspicions and 191 PE suspicions), of whom 57 had VTE, were used for diagnostic accuracy analyses. Capillary whole blood samples ranging from 47 to 69 subjects for each type of POC D-dimer device were used for matrix comparison.

Based on venous plasma samples, sensitivity of five D-dimer POC tests ranged from 93% to 100%, specificity from 65% to 78%, PPV from 22.4% to 34.2% and NPV from 98.6 to 100%. Results were comparable to a standard laboratory-based assay (STA R Max: sensitivity 94.7% (95% CI 84.5 to 98.6), specificity 68.1% (95% CI 63.5 to72.3), PPV 27.1% (95 % CI 21.2 to 34.0), NPV 99.0% (95% CI 97.0 to 99.8).

Results for each test are as follows: for Exdia TRF Plus: sensitivity 94.7% (95% CI 84.5 to 98.6), specificity 67.4% (95 % CI 62.8 to- 71.7), PPV 26.7% (95 % CI 20.9 to 33.5), NPV 99.0% (95% CI 97.0 to 99.7); for AFIAS-1® device: sensitivity 91.2% (95% CI 80 to 96.7), specificity 78.0% (95 % CI 73.8 to 81.6), PPV 34.2% (95 % CI 26.8 to 42.4), NPV 98.6% (95% CI 96.6 to99.5); for Standard F200: sensitivity 96.5% (95% CI 86.8 to 99.4), specificity 69.6% (95% CI 65.1 to 73.8), PPV 28.5% (95% CI 22.4 to 35.5), NPV 99.4% (95% CI 97.5 to 99.9); for LumiraDx™ device: sensitivity 100.0% (95 % CI 92.1 to 100), PPV 22.4% (95% CI 17.6 to 28.2), NPV 100.0% (95 % CI 98.5 to 100.0) and for Hipro AFS/1: sensitivity 93.0% (95% CI 82.2 to 97.7), specificity 65.0% (95 % CI 60.4 to 69.3), PPV 25.0% (95% CI 19.4 to 31.5), NPV 98.7% (95% CI 96.4 to 99.6).

Ergebnisse für Korrelation zwischen Kapillarblut und Venenplasma

A poor capillary-plasma correlation was observed in some of these quantitative POC tests, with correlation coefficients ranging from 0.11 (95% CI - 0.15 to 0.36) to 0.94 (95% CI 0.90 to 0.97). Results for capillary whole blood versus venous plasma comparison for D-dimer POCTs are as follows: for Exdia TRF Plus: correlation 0.71 (95% CI 0.54 to 0.83); concordance 90.1%/93.5%; for AFIAS-1: correlation 0.94 (95% CI 0.90 to 0.97); concordance 89.8%/100%; for Standard F200: correlation 0.69 (95% CI 0.54 to 0.80); concordance 87.1%/84.2%; for LumiraDx: correlation 0.88 (95% CI 0.80 to 0.93); concordance 93.6%/91.0% and for Hipro AFS/1: correlation 0.11 (95% CI -0.15 to 0.36); concordance 71.4%/72.9%.

The summary of results on outcomes related to the clinical utility, safety and diagnostic accuracy, from three primary studies, can be found in Table 3-2 below. Details of study results can be found in Table A - 2, Appendix II.

Table 3-2: Summary of clinical utility, safety and diagnostic accuracy results: D-dimer-POCT (three observational studies)

Clinical utility, safety and diagnostic accuracy of D-dimer-POCT: evidence from 3 prospective observational studies					
Evidence base	**Study design**	**Included pts**	**Setting**	**Risk of Bias**	**Summary of the results**
Effect on hospital and ED referrals and visits					
1 study [17]	NRCT	1477 total pop; 787 CPR correctly applied pts vs. 339 CPR incorrectly applied pts	Primary care	Critical	Overall efficacy (proportion of non-referred patient) in the total study population: 53% (95% CI 50.4 to 55.5); referral rate of 47% CPRs correctly applied: efficiency 58.1% (95% CI 55.2 to 61.0); referral rate of 41.9% CPRs incorrectly applied: efficiency 35.7% (95% CI 30.6 to 41.1); referral rate of 64.3%
Effect on hospital admissions					
No evidence available					
Effect on morbidity and mortality					
1 study [17]	NRCT	1477 total pop; 787 CPR correctly applied pts vs. 339 CPR incorrectly applied pts	Primary care	Critical	VTE confirmed in 267/1477 (18.1%) Overall failure rate (3-month incidence of VTE in non-referred group) in the total study population: 1.8% (95% CI 1.02 to 3.06) CPRs correctly applied: failure rate 1.51% (95% CI 0.77 to 2.86) CPRs incorrectly applied: failure rate 3.31% (95% CI 1.07 to 8.76)
Effect on QoL					
No evidence available					
Outcome: Patient / Staff satisfaction					
1 study [16]	NRCT	11 GP assistants	Primary care	Critical	System Usability Scale (SUS) score for user-friendliness: ***Hipro AFS/1®***: 75.0 (IQR 47.5 to 97.5) ***Nano-Checker 710 Ddimer®***: 70.0 (IQR 55.0 to 85.0) ***AFIAS-1®***: 65.0 (IQR 40.0 to 90.0) ***Standard F200®***: 57.5 (IQR 35.0 to 85.0) ***iChroma-II®***: 37.5 (IQR 30.0 to 60.0).
Effect on safety outcomes: AEs and SAEs					
No evidence available					
Diagnostic accuracy outcomes: Sensitivity, specificity, positive and negative predictive value					
1 study [15]	NRCT	511 pts (320 DVT suspicions and 191 PE suspicions)	Primary care	Serious	***Exdia TRF Plus***: SEN 94.7% (95% CI 84.5 to 98.6), SPEC 67.4% (95% CI 62.8 to 71.7), PPV 26.7% (95% CI 20.9 to 33.5), NPV 99.0% (95% CI 97.0 to 99.7); ***AFIAS-1® device***: SEN 91.2% (95% CI 80 to 96.7), SPEC 78.0% (95% CI 73.8 to 81.6), PPV 34.2% (95% CI 26.8 to 42.4), NPV 98.6% (95% CI 96.6 to 99.5); ***Standard F200***: SEN 96.5% (95% CI 86.8 to 99.4), SPEC 69.6% (95% CI 65.1 to 73.8), PPV 28.5% (95% CI 22.4 to 35.5), NPV 99.4% (95% CI 97.5 to 99.9); ***LumiraDx™ device***: SEN 100.0% (95% CI 92.1 to 100), PPV 22.4% (95% CI 17.6 to 28-2), NPV 100.0% (95% CI 98.5 to 100.0) ***Hipro AFS/1***: SEN 93.0% (95% CI 82.2 to 97.7), SPEC 65.0% (95 % CI 60.4 to 69.3), PPV 25.0% (95% CI 19.4 to 31.5), NPV 98.7% (95% CI 96.4 to 99.6). ***Standard laboratory assay STA R Max***: SEN 94.7% (95% CI 84.5 to 98.6), SPEC 68.1% (95% CI 63.5 to 72.3), PPV 27.1% (95% CI 21.2 to 34.0), NPV 99.0% (95% CI 97.0 to 99.8)

Abbreviations: *DVT - deep venous thrombosis; GP – general practitioner; IQR – interquartile rate; NPV – negative predictive value; NRCT – non randomised controlled trial; PE- pulmonary embolism; pop – population; PPV – positive predictive value; pts – patients; SEN – sensitivity; SPEC – specificity; SUS score - System Usability Scale .*

4 Discussion

4.1 Summary of Findings

Tn-POCT

Update 2024 von Bericht 2019: keine neuen SRs oder Leitlinien zu hochsensitiven Tn-POCT in der Primärversorgung bei niedrigem NSTE-ACS-Risiko

In this update of the EUnetHTA report 2029 [1, 2], no new systematic reviews and clinical or diagnostic guidelines were identified related to the diagnostic accuracy and clinical utility of high-sensitivity POC Tn tests in the primary care setting in low-risk patients with suspected non-ST-segment elevation acute coronary syndrome (NSTE-ASC).

eingeschlossene Studien: 3 Studien (n=2.116): 1 RCT, 2 prospektive Beobachtungsstudien, alle mit nicht-hochsentitivem Tn-POCT

Also, only three studies with a total study population of 2116 patients were included in this updated report, one RCT (ARTICA) [11, 12] and two observational prospective studies [13, 14], with high [11, 12], critical [13] or serious [14] risk of bias, respectively. However, none of the identified studies investigated high-sensitivity Tn POCT. When measured and analysed, MACE incidence at 30-day and 1-year follow-ups, as well as hospital admissions, were similar, ED referrals were reduced, and ED visits were statistically significantly lower between groups. QoL and patient satisfaction with care were measured only in one study each [11, 13]; results were similar between groups.

Ergebnisse RCT: MACE-Inzidenz 30-Tage und 1-Jahr, Lebensqualität und Zufriedenheit: ähnliche Ergebnisse zwischen die Gruppen; Krankenhausbesuche: signifikant reduzierte unnötige ED-Besuche, keine signifikanten Unterschiede bei Krankenhausaufenthalten; Genauigkeit: vergleichbar mit ED-Strategie, hohes NPV bei 1-Jahr MACE

In the ARTICA RCT [11, 12], MACE incidence was analysed as secondary safety outcome. 30-day and 1-year MACE incidence was low and comparable between pre-hospital rule-out strategy and the ED rule-out strategy, especially when ACS was ruled out at initial presentation, irrespective of whether this was performed at home or in-hospital. In a pilot observational study [13] and one large observational study [14], conducted in a real-world setting, with critical and serious risk of bias respectively, no MACE was found within 30 days of the presentation among low-risk patients.

Only one study, the ARTICA RCT [11, 12], measured QoL with no statistically significant difference between the pre-hospital rule-out strategy and the ED rule-out strategy.

In the RCT [11, 12], the pre-hospital rule-out strategy significantly reduced the number of unnecessary ED visits. No statistically significant difference was seen in number of hospitalisations. In the larger observational study [14], almost all low-risk patients were discharged home, avoiding transfers or hospital admissions. Only one small pilot observational study [13] measured and analysed patient satisfaction with care; which was found to be very high and similar in low-risk and non-low-risk patients.

Beobachtungsstudien: keine 30-Tage MACE bei Niedrigrisiko-Patient*innen; Zufriedenheit: sehr hoch

In the RCT [11], the diagnostic accuracy of the pre-hospital rule-out strategy, with single time-point POCT Tn measurement, for detecting MACE at 1-year in low-risk patients in primary care setting, was comparable and almost identical to that of the ED rule-out strategy. The negative predictive value of a rural accelerated diagnostic chest pain pathway, with two time-points POCT Tn measurements for MACE at 30 days, was high (100%) in both observational studies [13, 14].

D-dimer POCT

In the literature search for this update, no new systematic reviews and clinical or diagnostic guidelines were found investigating quantitative POC D-dimer tests in primary care settings in adult patients with a low pre-test probability of deep venous thrombosis (DVT) or pulmonary embolism (PE).

Update 2024 von Bericht 2019: keine neuen SRs oder Leitlinien zu quantitativen D-Dimer POCT in der Primärversorgung bei Patient*innen mit niedriger Vortestwahrscheinlichkeit für DVT oder PE

Only three new prospective cohort studies [15-17] investigating D-dimer POCTs were identified, one with a serious risk of bias [15] and two with a critical risk of bias [16, 17]. Two studies assessed quantitative POC D-dimer tests [15, 16], and in one study, qualitative and quantitative POC D-dimer tests were used [17]. All three studies were conducted in the Netherlands, in general practice; two studies [15, 17] had a 3-month follow-up. Only one study measured hospital or ED referral rate and morbidity [17], one [16] measured staff satisfaction and one study diagnostic accuracy [15]. No studies measured hospital admissions, QoL and safety outcomes (AEs and SAEs).

One study [17] measured failure rate (3-month incidence of VTE in the non-referred group) and efficiency (the proportion of non-referred patients in the total study population) of two clinical prediction rules (CPRs), followed by D-dimer POC testing. If the Oudega and Wells rule were correctly used, the proportion of non-referred patients was high and the 3-month incidence of VTE in the non-referred group was acceptably low for patients suspected of DVT and PE. But, in one fifth of patients (21%), the CPRs were incorrectly applied resulting in a higher failure rate and a considerably higher referral rate.

One study [16] measured staff satisfaction as user-friendliness of five novel quantitative POC D-dimer tests. Considerable variation in overall user-friendliness was found between investigated D-dimer POCTs, but most devices were judged easy to use.

One study [15] measured diagnostic accuracy of five quantitative D-dimer POC tests. Each showed comparable diagnostic accuracy to laboratory-based D-dimer testing, to safely exclude low-risk patients with suspected VTE in clinical practice (high sensitivity and high NPV with low false negative rate). However, a poor capillary-plasma correlation was observed in some of these quantitative POC tests, with correlation coefficients ranging from 0.11 (95% CI - 0.15 to 0.36) to 0.94 (95% CI 0.90 to 0.97).

3 prospektive Kohortenstudien (n=1.988 Patient*innen und 11 Arzt-Assistent*innen):
Studie 1: niedrige Fehlerrate nur bei korrekter Anwendung der CPRs, aber 21% inkorrekte Anwendung der CPR
Studie 2: erhebliche Unterschiede in der Benutzerfreundlichkeit
Studie 3: vergleichbar mit Labortests, hohe Sensitivität und NPV, niedrige Fehlerrate; schlechte Korrelation (bei einigen Tests) zwischen Kapillarblut und Plasma

4.2 Interpretation

Tn-POCT

Despite equivalent or positive results related to the safety and effectiveness of the pre-hospital rule-out strategy, with a single time-point POCT Tn measurement and a clinical diagnostic pathway (RACPP) in primary care and rural settings (with two time-points POCT Tn measurements), caution is warranted in the interpretation of these results. The results are based on three studies with high, critical or serious risk of bias only. The primary care settings (in the Netherlands and New Zealand) and reported outcomes were heterogeneous, as well as the follow-up time of patients and pre-hospital rule-out strategies (some not validated in primary care). All POCTs were non-high sensitivity assays (so-called contemporary POCTs), and the two observational studies required two blood tests two hours apart, which could put a strain on the time of primary care providers.

nur 3 Studien mit hohem Verzerrungsrisiko mit Vorsicht zu interpretieren:

heterogene Settings, Nachbeobachtungszeiträume, Anzahl der POCT-Anwendungen, keine hs-Tn POCTs verwendet
zweit-zeitige POCTs

nur 1 Studie mit Langzeit-Ergebnissen

Only one study with a high risk of bias (the ARTICA RCT), which was not formally designed and powered to estimate the safety of pre-hospital rule-out, provided a long-term follow-up of one year. Despite the long-term follow-up, caution is warranted in the interpretation of the outcome 'MACE'. The two observational studies had a short follow-up duration of 30 days only.

verfügbare hs-cTn POCTs: keine Bewertung der diagnostischen Genauigkeit und klinischem Nutzen in der Primärversorgung;

validiert für Vollblut und Plasma, nur ein POCT auch für Kapillarblut;

None of the currently available high-sensitivity (hs) POCTs was assessed for diagnostic accuracy and clinical utility (effectiveness and safety) in primary care settings. Three hs cTnI POCTs are currently on the market worldwide:

- Atellica VTLi (Siemens Healthineers, Erlangen, Germany) – CE-mark 2021,
- PATHFAST (LSI Medicine Corporation, Tokyo, Japan) - CE-mark, and
- TriageTrue (QuidelOrtho, San Diego, United States) – CE-mark 2018.

These assays were validated for use in whole blood and plasma, only one of them for use in capillary blood: the Atellica VTLi is a portable immunoassay analyser with battery capacity for up to 60 tests providing high-sensitivity-Tn in eight minutes. In addition to whole blood and plasma the VTLi has also been validated for use in capillary blood. PATHFAST is a larger benchtop immunoassay analyser and does require a higher degree of operator skill; it provides results within 17 minutes. The TriageTrue is an immunoassay analysed on the QuidelOrtho Triage MeterPro device: it is portable and can run approximately 100 tests on batteries. It provides hs troponin I results in <20 minutes.

mehrere weitere hs-Tn POCT-Systeme in Entwicklung

RCTs zur Bestätigung der klinischen Nützlichkeit in der Primärversorgung sind notwendig

There are several other hs-cTn POCT systems currently under development [19-24]. Further studies confirming the clinical utility of hs-cTn POCT in primary care setting are therefore warranted, preferably through RCTs.

2 laufenden RCTs:

POB HELP RCT: Vergleich eines klinischen Entscheidungspfads für akute Brustschmerzen mit hs-cTnI POCT aus Kapillarblut vs. Standardversorgung, Setting: Allgemeinmedizin

Einschluss: Verdacht auf ACS, Ausschluss bei Brustschmerzen <1 Stunde

Endpunkte: Krankenhausüberweisung diagnostische Genauigkeit, MACE Kosteneffektivität, Adhärenz, diagnostische Genauigkeit des HEART Scores

Two RCTs, registered in ClinicalTrial.gov (Table A - 6, Appendix IV), are currently ongoing, both in the Netherlands, with estimated high number of patients, ranged from 852 to 1500, in pre-hospital setting (primary care and in emergency medical transport).

- **POB HELP** (NCT05827237, 'Rule Out of ACS in Primary Care Using a Decision Rule for Chest Pain Including Hs-troponin I POCT'), a clustered diagnostic RCT, will compare clinical decision rule for acute chest pain, consisting of the Marburg Heart Score (five questions) combined with a hs troponin I POCT (**Siemens Atellica VTLi** immunoassay analyser) with standard care, in adults with acute chest pain seen by a GP. The Atellica VTLi hs-cTnI analyser provides hs-cTnI measurements within eight minutes in capillary blood, obtained by a fingerstick, highly suitable for pre-hospital setting. The inclusion is based on clinical suspicion of ACS by general practitioners, as in daily clinical practice, which may lead to inclusion bias. Patients with an onset of chest pain for <1 hour are excluded, because hs-cTnI measurement within this time window may be false negative due to time-dependent troponin release. Primary endpoints are hospital referral rate for acute chest pain within 24 hours and six weeks after inclusion, as well as diagnostic accuracy of the clinical decision rule within six weeks and six months after inclusion (i.e., sensitivity, negative predictive value) for acute coronary syndrome (ACS) and major adverse cardiac events (MACE). Secondary endpoints are the cost-effectiveness of the clinical decision rule, adherence to the recommendations of the clinical decision rule by GPs, the patients' reassurance, the diagnostic accuracy of the GPs' gut feeling and the diagnostic accuracy of the HEART (history, ECG, age, risk factors and troponin) score for all patients with an ECG available. It is expected that results of this study will be generalisable to other countries with similar primary care

system, with the GPs as a gatekeeper, like in Canada, Scandinavian countries and the UK [25, 26].

The estimated study completion date is September 2024, with 946 enrolled patients.

- **URGENT 2.0** (NCT04904107, 'A Multicentre Randomized Controlled Trial to Improve the accUracy of Referrals to the emerGency departmEnt of patieNts With chesT Pain by Using the modified HEART Score in Emergency Medical Transport') will compare the modified HEART score (including fingerstick POC hs cTnI analysis) with standard care, in adults with chest pain or other complaints suspect of ACS for at least two hours, where the general practice or emergency medical personnel are in need of further diagnostics or risk stratification to come to a decision of referral. Primary endpoints are the incidence of non-cardiac chest pain (NCCP) patients admitted at the cardiac ED (at 30 days) and the incidence of MACE at 30 days, six months and one year [27].

  The estimated study completion date is June 2024, with 852 enrolled patients.

URGENT 2.0:
Vergleich des modifizierten HEART-Scores (inkl. POC hs-cTnI) mit Standardversorgung
Einschluss: Patient*innen mit Brustschmerzen oder ACS-Verdacht seit min. 2 Stunden
Endpunkte: Inzidenz von NCCP-Patient*innen in der kardiologischen Notaufnahme (30 Tage) und MACE (30T, 6M, 1J)

- No **clinical or diagnostic guidelines** were found related to diagnostic accuracy and clinical utility of hs POC troponin tests in primary care setting, in low-risk patients with suspected non-ST-segment elevation acute coronary syndrome (NSTE-ASC).

Leitlinien zu hs POCTs zu diagnostischer Genauigkeit und klinischem Nutzen in der Primärversorgung bei niedrigem NSTE-ASC-Risiko

- NICE's 2020 diagnostic guidance [28] states that further research is recommended into the diagnostic performance of the Tri-ageTrue High Sensitivity Troponin I test when used at the point of care in emergency departments.

NICE 2020: weitere Forschung zu TriageTrue hs-Troponin I in Notaufnahmen empfohlen

- The recommendations from the European Society of Cardiology (ESC) guidelines for the management of ACS, published in 2023 [29], are for use of laboratory-based assays only. It is clearly pointed out that the vast majority of cTn assays that run on automated platforms in the central laboratory are sensitive (i.e. allow for the detection of cTn in ~20–50% of healthy individuals) or high-sensitivity (i.e. allow for the detection of cTn in ~50–95% of healthy individuals) assays. High-sensitivity assays are recommended over lower-sensitivity assays, as they provide higher diagnostic accuracy at an identical low cost. Therefore, hs-cTn assays are now considered the reference analytical standard against which diagnostic strategies must be compared [30]. The majority of currently used POCTs cannot be considered hs assays and automated assays have been more thoroughly evaluated than POCTs, so they are currently not preferred [29]. As this is a rapidly developing field, it will be important to re-evaluate this preference when more extensively validated hs POCTs are clinically available. In the near future, clear recommendations for the use of hs POCTs in primary care are needed from high-quality diagnostic/clinical guidelines.

ESC-Leitlinien 2023: nur laborbasierte Tests empfohlen, hs-cTn-Assays bevorzugt

Faktoren für die Umsetzung einer prähospitalen Ausschlussstrategie: gut organisiertes Gesundheitssystem, Verfügbarkeit von hs POCTs, Zugang zur Primärversorgung, und Ausbildung der Anwender

Anforderungen an POCT cTn-Assays: gleiche Performanz wie zentrale Labor-Assays, Nachweis von Benutzerfreundlichkeit, Wirksamkeit und Kosten-Effektivität

Further **considerations for implementation** of hs POC troponin testing within a pre-hospital rule-out strategy of NSTE-ACS in low-risk patients, as stand-alone tool or in combination with a clinical decision rule, with single time-point measurement, depend on a well-functioning healthcare system, availability of hs POCTs, the accessibility of primary care and the level of education and training related to this strategy. The local healthcare infrastructure should be taken into account when extrapolating the results of these studies to other countries. Reducing hospital admissions and transfers to EDs will have obvious added value for patients (reducing travel and time away from home or work, increasing patient satisfaction) and to the healthcare system as well (fewer ambulance transfers and hospital admissions). It may lead to a substantial reduction of costs, as was shown in previous studies [11, 31]. POCT cTn assays need similar analytical and clinical performance as central laboratory hs-cTn assays. Utility of POCT requires valid data demonstrating user-friendliness, increased effectiveness and improved cost-effectiveness compared to central laboratory hs-cTn assays. Large numbers of educational and practical measures are necessary before a new routine involving POCT may be established. Future studies are needed to provide the necessary data and further investigate the benefits and utilities of hs-cTn POCT assays.

D-dimer POCT

neue quantitative POC D-Dimer-Geräte ermöglichen Kapillarblutentnahme durch Fingerstick wenig Studien zum klinischen Nutzen in der Primärversorgung

Recently, several quantitative POC D-dimer devices have been introduced on the market (e.g., Exdia TRF Plus (Precision Biosensor Inc.), AFIAS-1® (Boditech Med Inc), Standard F200® (SD Biosensor), LumiraDx™ (LumiraDx Ltd.) and Hipro AFS/1® (Hipro Biotechnology)). The latest generation of tests also enables small volumes of whole blood to be collected by a capillary finger stick. A capillary finger stick is most commonly preferred in primary care settings, by GPs, where venipuncture and plasma preparation are not widely performed or is very difficult to perform, for example in rural general practice and nursing homes [16, 32, 33].

nur diagnostische Genauigkeit und analytische Performanz, Benutzerfreundlichkeit hohe Verzerrungsrisiken mit Vorsicht zu interpretieren: heterogene Ergebnisse

So far, only a few studies are available on the clinical utility of quantitative POC D-dimer devices. One study analysed the analytical performance of five quantitative tests and staff satisfaction through user-friendliness. In another study, which analysed two clinical utility outcomes, a qualitative D-dimer test was performed in most patients (a quantitative D-dimer test was performed only in 24% of patients). As these studies have serious or critical risk of bias, caution is warranted in the interpretation of these results. Even though the setting in which these studies were performed was the same - general practices in the Netherlands, reported outcomes were heterogeneous and very limited to the clinical utility of these tests. Additionally, the two have only a short follow-up of 30 days.

venöses Plasma: vergleichbare D-Dimer-Werte wie Labor Kapillarblut: schlechte Korrelation bei einigen POCT

A diagnostic accuracy study presented that each of the five included quantitative POCTs was able to generate D-dimer values from venous plasma samples (obtained by standard venipuncture technique) comparable to laboratory-based D-dimer testing and to safely exclude a subset of low-risk patients with suspected VTE in general practice. In general practice the priority is not to miss a VTE, which is reflected in the sensitivity and NPV percentages, that were much higher for all five devices than the specificity and PPV percentages. However, the poor capillary-plasma correlation was observed in some of these quantitative POCTs, suggesting that the capillary whole blood finger sticks feature of certain devices needs to be further improved.

As pointed out in the latest version of the Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy from 2023, the paired measures of sensitivity and specificity and positive and negative predictive values reflect proportions of patients undergoing testing who were correctly classified, but they do so in separate ways. The clinical utility of a test will always depend on both sensitivity and specificity and will also be influenced by the proportion of the target condition among those tested. It is therefore crucially important always

to report sensitivity and specificity in pairs: a high sensitivity may be achievable for many continuous tests, but if it comes at the cost of an extremely low specificity, the test may not be helpful – most of those with the target condition are classed as positives, but also many of those without the condition. Sensitivity and specificity are often preferred in the interpretation and communication of test results; the main emphasis in a meta-analysis of test accuracy research is on a meta-analysis of sensitivity and specificity [34].

As staff satisfaction (through user-friendliness outcome) was measured in a very small group of GP assistants, generalisability of this results to GPs is still limited.

Generalisierbarkeit der Benutzerfreundlichkeit fraglich

In one study measured morbidity through failure rate (defined as the 3-month incidence of VTE in the non-referred group) and hospital/ED referral rate through efficiency outcome (defined as the proportion of non-referred patients in the total study population), the clinical predication rule (CPR) was incorrectly applied in 21% of patients, which resulted in higher failure rate and increased hospital/referral rate. In only one fourth of patients a quantitative D-dimer test was performed. Around 60% of all patients, in whom a VTE diagnosis was missed, had false-negative results on a qualitative POC D-dimer test (which was later withdrawn from the market during the inclusion period of this report): such false-negative results likely resulted in more missed VTE diagnoses and therefore an underestimation of the safety of the CPRs in combination with POC D-dimer test.

inkorrekte Anwendung der CPR führt zu höherer Fehlerrate und niedrigerer Wirksamkeit, falsch-negative Ergebnisse führen zur Unterschätzung der Sicherheit der CPRs in Kombination mit dem D-Dimer- POCT

No new **clinical or diagnostic guidelines** were found related to diagnostic accuracy and clinical utility of these tests in primary care setting.

keine neuen Leitlinien zu D-Dimer-POCTs in Primärversorgung

- The latest International Council for Standardisation in Haematology (ICSH) guidance for International Normalised Ration (INR) and D-dimer testing using POCT in primary care recommended that POC D-dimer assays should only be used in patients with a low to moderate clinical probability for VTE, stressing the need to combine them with a validated clinical prediction model. The use of qualitative POC assays should be restricted to strictly controlled settings where regular quality control is implemented and where regulatory requirements permit their use [35].

ICSH 2023:
D-Dimer POCTs nur bei niedriger bis mittlerer VTE-Wahrscheinlichkeit in Kombination mit Vorhersagemodell, qualitative POCTs nur in streng kontrollierten Umgebungen

- According to the latest NICE guideline recommendations [36], when offering D-dimer testing for suspected DVT or PE, a POCT should be considered if laboratory facilities are not immediately available. If using a POC D-dimer test, a fully quantitative test is recommended. When using a POC or laboratory D-dimer test, an age-adjusted D-dimer test threshold for people aged over 50 should be considered.

NICE 2020:
POCT nur bei fehlenden Laboreinrichtungen, vollständig quantitative Tests bevorzugt

- In the latest German consensus guideline „S2k-Leitlinie Diagnostik und Therapie der Venenthrombose und Lungenembolie“ (2023) from the „Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften e. V. (AWMF), there are no specific recommendations regarding POC D-dimer tests in primary care setting [37, 38]. Authors only stated that a quantitative D-dimer determination carried out in a central or coagulation laboratory is preferred over near-patient immediate diagnostics (POCT). If laboratory diagnostics are not promptly available, quantitative POCT tests can alternatively be used, which are considered almost equivalent today and are more accurate than semi-quantitative or qualitative tests [38].

AWMF S2k 2023:
Labordiagnostik mit quantitativen Tests bevorzugt, POCT nur wenn zeitnahes Labor nicht verfügbar

Clear recommendations for the use of quantitative D-dimer POCTs in primary care are still needed from high-quality diagnostic/clinical guidelines.

Scoping Review (2022) definiert notwendige Endpunkte für POCT-Evidenz

A scoping review published in 2022 [39] addresses considerations for implementing POCT (including D-dimer POCT) in outpatient care in Germany. Six endpoints should be addressed in the evaluation of POCTs targeted for outpatient care: diagnostic performance, clinical performance, time and costs, impact on clinical routines/processes, perspectives of medical professionals and patients, and broader aspects.

Further studies, preferably through RCTs, are still warranted to confirm the clinical utility of D-dimer POCTs in the primary care setting.

2 laufende Studien mit LumiraDx in Primärversorgung

We found only two observational studies currently ongoing, both registered in ClinicalTrial.gov (Table A - 7, Appendix IV).

DESTINY: Beobachtungsstudie

Studie sollte 3/2023 abgeschlossen sein, aber keine publizierten Ergebnisse

- **DESTINY** (NCT05109260), an observational feasibility study aiming to assess the precision and accuracy of the **LumiraDx** Point of Care (POC) D-Dimer test when used in 244 primary care UK patients presenting with symptoms of VTE, which mainly comprises DVT or PE. Two POC immunoassay devices are compared with laboratory tests: one measuring D-dimer levels in capillary blood (LumiraDx POC D-dimer test), and the other in venous blood (Roche Cobas H 232 POC D-dimer test). The study will compare the data from these D-dimer POCTs and those gained using laboratory D-dimer tests [40].

  The estimated study completion date was March 2023 (no publication available), with 244 enrolled patients.

EMBOL1: Beobachtungsstudie

Studie sollte 9/2022 abgeschlossen sein, aber keine publizierten Ergebnisse

- **EMBOL1** (NCT04737954) an observational study conducted in patients in Germany and the UK. The accuracy of the **LumiraDx** POC D-Dimer test was assessed using capillary whole blood, venous blood, and plasma samples, by comparison to the D-Dimer results obtained from the same individuals as analysed by trained laboratory professionals using a reference device. Also, the assessment of accuracy of using the D-Dimer cut-off set by the LumiraDx D-Dimer test in excluding patients with symptoms of VTE (DVT and PE) when used in combination with the pre-probability test (Wells Score) over 10 months will be performed [41].

  The estimated study completion date was September 2022 (no publication available), with 1000 enrolled patients.

4.3 Limitations

4.3.1 Limitations of the Evidence

Tn-POCT

keine einzige Studie zu hs-Tn POCT identifiziert

No studies with a low risk of bias were found to assess the effectiveness and safety of high-sensitivity Tn-POCTs, whether used alone or in combination with a clinical decision rule. Only three studies were identified and included in this update report, each with a high, serious, or critical risk of bias. All utilized POCTs that were not high-sensitivity assays.

in kleinen Studien werden Effekte überschätzt große Studien müssen ausreichend „power" für einzelne Endpunkte haben

One of the included studies, an RCT was not formally designed and powered to estimate the safety (MACE outcome) of pre-hospital rule-out. Another study, a small pilot observational study was not confirmatory, but aimed to pilot real-life feasibility and acceptability, and to preliminary assess effectiveness and safety of a diagnostic pathway (RACPP) in rural primary care settings. Small studies are not intended to make a precise estimate of effectiveness and safety. Estimated effect size is very likely overestimated in such studies. The sensitivity for MACE was 100% in the non-low-risk group, but the

95% CI was large, ranging from 70% to 100%. Also, small sample size limits generalisability of the findings.

Generalisability is also limited due to possible differences in the sociodemographic profiles and underlying risk of ischaemic heart disease among patient populations in rural general practices. Two time-points POCT Tn measurements could provide a time burden on primary care providers. The authors did not use appropriate statistical methods to control for the confounding factors. Clinical decision rules used in the studies are not validated in primary care, and rural setting, but only in the ED. Median time from index chest pain onset to presentation to rural practice was very different: 15 hours (IQR: 3.1-40.2 hours) and 4 hours and 36 minutes (IQR: 2-14 hours and 30 minutes), in the small pilot study and the larger observational study, respectively.

Generalisierbarkeit ist stark limitiert
weitere Einschränkungen: 2-zeitige POCTs bedürfen Zeit, die es ev. in der Praxis nicht gibt
keine Kontrolle von Confoundern

Only one study, the RCT, measured QoL, in which EQ -5D -5L questionnaires were not completed by all patients. Only one small pilot observational study measured and analysed satisfaction with care in rural general practice. There is no data indicating that the patient satisfaction questionnaire was validated. Additionally, the small number of respondents and possible high recall bias (the research nurse performed telephone follow-up at 30 days to complete this survey) may affect the reliability of the results. In each observational study, there was a protocol deviation. In the pilot study, 18.8% of patients classified as non-low risk were not transferred for hospital assessment. In the larger observational study, about 11% of patients were excluded due to protocol deviation, either because only one troponin was drawn or there was inadequate time between samples. The potential for underestimating the risk due to incomplete testing could lead to unrecognized adverse outcomes, which might not have been captured due to the limitations in follow-up and data collection. The reasons for such deviations are not known.

klinische Entscheidungsregeln müssen auch in Primärversorgung validiert werden
Validierung von Erhebungsinstrument zur Zufriedenheit
Protokollverletzungen führen zur Unterschätzung des Risikos

D-Dimer POCT

Several serious and critical limitations were found in the three included observational studies. In all, there is no information on explicit methods used to adjust for potential confounding factors. Additionally, there is no data on the long-term clinical outcomes available.

keine Informationen zu Methoden, Confounder zu berücksichtigen, keine längeren Nachbeobachtungen

In one diagnostic accuracy study [15], additional 237 patients from another separate observational study were included [18]. A small number of patients suspected of having DVT had a risk score of ≥4. According to guidelines, these patients would not require a D-dimer test but would be eligible for direct ultrasound or imaging; study authors decided to include these patients nonetheless, as they aimed to include a population representative of everyday practice. Direct clinical validation based on capillary whole blood finger stick samples, similar to the evaluation based on the plasma samples distributed to all devices, was not conducted because it was not feasible to achieve these numbers for capillary finger stick testing within a prospective design.

Einschlusskriterien nicht Leitlinien-konform

Related to user-friendliness outcome measured in a study, only a limited group of GP assistants, unfamiliar with the devices but familiar with CRP POC testing, were given a short instruction by a laboratory technician and all assistants were given a written instruction chart. They then directly carried out one D-dimer test on all five POC D-dimer test systems in a random order and completed a System Usability Scale (SUS) questionnaire accordingly, along with a few additional questions about sample management and readability of displays and results. The SUS questionnaire for this outcome was not completed by the laboratory technicians who performed all D-dimer tests in patients; instead, it was completed by GP assistants. These GP assistants used blood samples obtained from venipunctures, so aspects related to sample collection through finger-prick methods were not taken into account. As tests were performed by experienced laboratory technicians, potential issues encountered by non-laboratory users may influence test results.

Fragebogen zur Benutzerfreundlichkeit von Assistent*innen ausgefüllt

zu Samples aus venösem und nicht zu kapillärem Blut

inkorrekte Verwendung der klinischen Entscheidungsregeln bei 1/5 der Patient*innen

hohe Fehlerrate

Detection Bias wahrscheinlich

Widerruf eines qualitativen POCT wegen hoher Rate an falsch-negativen Ergebnissen

In study which measured two clinical utility outcomes, CPR was incorrectly applied in 21% of patients, which resulted in higher failure rate, defined as the 3-month incidence of VTE in the non-referred group, and lower efficiency with increased hospital or ED referral rate. The reference standard between referred and non-referred patients was different. For patients referred to secondary care, the reference standard consisted of further diagnostic procedures; in the non-referred patients, it consisted of a 3-month follow-up period. Differential verification might result in bias towards overestimating the safety (detection bias). A quantitative D-dimer test was performed in only 24% of patients. During the inclusion period for this report, the qualitative POCT for D-dimer (Clearview Simplify) used in the study was withdrawn from the market, because of too many false-negative results probably due to periprocedural quality-related faults when performing the test, false-negative results likely resulted in more missed VTE diagnoses and therefore an underestimation of the safety of the CPRs. Around 60% of all patients, in whom a VTE diagnosis was missed, had false-negative results on this qualitative POC D-dimer test.

4.3.2 Limitations of the Report

Limitation des Berichts: nur Studien 2019 bis 2024 berücksichtigt

aber keine Veränderung der Schlussfolgerung

There are also limitations of this report: Only studies published between 2019 and 2024 (5 years) were considered for this update report. Due to the narrower scope (use of POCT in primary care only), the full body of evidence (including studies from the 2019 report) was not used to draw conclusions.

However, as this report and the earlier EUnetHTA report also arrived at the same conclusion, the full body of evidence (considering earlier studies) would not have changed anything in our results.

5 Conclusion

Tn-POCT

Evidence on the clinical utility of high-sensitivity POC Tn tests in primary care settings is still limited. No new systematic reviews, clinical or diagnostic guidelines related to diagnostic accuracy and clinical utility of hs-Tn POCTs in primary care settings for low-risk patients suspected of non-ST-segment elevation acute coronary syndrome (NSTE-ASC) were found. Additionally, no studies with a low risk of bias were found to assess the effectiveness and safety of hs-Tn POCTs in combination with a clinical decision rule.

Tn POCT:
limitierte Evidenz,
keine Studien zu hochsensitiven Tn POCT,
keine Studien mit geringem Verzerrungsrisiko

Further larger studies, confirming the clinical utility of single time-point fingerstick measurement of hs-Tn POCTs, in primary care setting are therefore warranted, preferably through RCTs with longer follow-up. Two such RCTs in pre-hospital setting are currently ongoing, both will have results in the coming months of 2024.

große valide Studien zu einzeitiger Anwendung von hs Tn POCT an Kapillarblut sind notwendig,
2 laufende RCTs, die 2024 abgeschlossen werden

Implementation of the pre-hospital rule-out strategy of NSTE-ACS in low-risk patients with the use of hs-Tn POC testing, in combination with a clinical decision rule, with single time-point measurement, depends not only on the availability of hs-Tn POCTs but also on the training of GPs. In any case, should the local healthcare infrastructure be taken into account when extrapolating the results of studies to other countries. A single time-point fingerstick measurement of hs-Tn POCT in a primary care setting could reduce the number of unnecessary emergency department visits and their overcrowding. Additionally, reducing hospital admissions and transfers to EDs offers clear added value for both patients. However, the evidence to support this strategy is not available yet.

bei Implementierung muss nicht nur die Verfügbarkeit von hs Tn POCT bestehen, sondern auch Training der Ärzt*innen berücksichtigt werden
derzeit: insuffiziente Evidenz für Tn POCT

D-dimer POCT

Evidence on the clinical utility of quantitative POC D-dimer tests in primary care settings is still limited. No new systematic reviews, clinical or diagnostic guidelines were found of these tests in primary care settings, investigated in low-risk suspected VTE patients. In total, only three observational studies with serious or critical risk of bias were found to assess diagnostic accuracy or clinical utility of POC D-dimer tests in combination with a clinical decision rule (the Oudega for DVT and the Wells rule for PE). No studies with a low risk of bias were found to assess the effectiveness and safety of quantitative D-Dimer POCTs.

D-Dimer POCT
limitierte Evidenz:
Studien zum klinischen Nutzen von D-Dimer POCT in Kombination mit klinischer Entscheidungsregel fehlen, nur diagnostische Genauigkeit gemessen

keine Studien mit geringem Verzerrungsrisiko

Since the two studies which measured only a few clinical utility outcomes have critical risk of bias, they are too problematic to provide valid evidence. Based on evidence from only one study POC D-dimer testing with five quantitative POCTs can adequately rule out VTE in adult patients who present to primary care with symptoms suggestive of DVT and PE and who have a low pretest probability. These tests have a high sensitivity and a high negative predictive value with low false negative rate. Consequently, the diagnostic accuracy of these tests, using plasma samples, is comparable to that of a laboratory-based D-dimer test. As the poor capillary-plasma correlation was observed in some of these quantitative POC tests, the capillary whole blood finger sticks feature of certain devices need to be further improved. Capillary measurement is important in settings where a venipuncture is not widely performed or is very difficult to perform, like in rural general practices and nursing homes.

diagnostische Genauigkeit allerdings nur gleichwertig (mit Labor) an Plasma nicht an Kapillarblut

The evidence is insufficient to suggest that implementing D-dimer POCT in combination with a clinical decision rule in primary care is superior in comparison to usual care. Larger studies, preferably RCTs, are still needed to confirm the clinical utility of D-dimer POCTs in primary care settings.

derzeit: insuffiziente Evidenz für D-Dimer POCT

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Appendix

Appendix I: Literature search

Primary studies

POCT Troponin

Cochrane (March 2024)	
Search Name: POCT_Troponin (Update 2024)	
Last Saved: 18/03/2024 19:23:50	
Comment: MH/CW	
ID	Search
#1	MeSH descriptor: [Point-of-Care Systems] explode all trees
#2	MeSH descriptor: [Point-of-Care Testing] explode all trees
#3	("point of care") (Word variations have been searched)
#4	(POCT):ti,ab,kw
#5	(POC):ti,ab,kw
#6	("near patient" NEXT test*) (Word variations have been searched)
#7	#1 OR #2 OR #3 OR #4 OR #5 OR #6
#8	MeSH descriptor: [Troponin] explode all trees
#9	(troponin*) (Word variations have been searched)
#10	(Tn):ti,ab,kw
#11	(cTn?):ti,ab,kw
#12	(path*fast*) (Word variations have been searched)
#13	(triage*true*) (Word variations have been searched)
#14	(Atellica*) (Word variations have been searched)
#15	#8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14
#16	#7 AND #15
#17	((troponin* OR tn OR cTn?) NEAR (test* OR path*fast* OR triage*true* OR Atellica* OR "point of care" OR POCT OR POC))) (Word variations have been searched)
#18	#16 OR #17
#19	#16 OR #17 in Trials
#20	#16 OR #17 with Publication Year from 2019 to 2024, in Trials
#21	English:la
#22	German:la
#23	#21 OR #22
#24	#20 AND #23
#25	(conference proceeding):pt
#26	(abstract):so
#27	(clinicaltrials OR trialsearch OR ANZCTR OR ensaiosclinicos OR Actrn OR chictr OR cris OR ctri OR registroclinico OR clinicaltrialsregister OR DRKS OR IRCT OR Isrctn OR rctportal OR JapicCTI OR JMACCT OR jRCT OR JPRN OR Nct OR UMIN OR trialregister OR PACTR OR R.B.R.OR REPEC OR SLCTR OR Tcr):so
#28	#25 OR #26 OR #27
#29	#24 NOT #28
	64 Hits

Embase (March 2024)

Session Results		
No.	Query Results	Results
#30	#28 NOT #29	239
#29	#28 AND 'Conference Abstract'/it	80
#28	#27 AND ([english]/lim OR [german]/lim)	319
#27	#26 AND [28-05-2019]/sd NOT [19-03-2024]/sd	325
#26	#22 OR #24 OR #25	735
#25	#21 AND ('controlled clinical trial'/de OR	316
	'observational study'/de)	
#24	#21 AND #23	477
#23	'crossover procedure':de OR 'double-blind	3,298,754
	procedure':de OR 'randomized controlled trial':de	
	OR 'single-blind procedure':de OR	
	random*:de,ab,ti OR factorial*:de,ab,ti OR	
	crossover*:de,ab,ti OR ((cross NEXT/1	
	over*):de,ab,ti) OR placebo*:de,ab,ti OR ((doubl*	
	NEAR/1 blind*):de,ab,ti) OR ((singl* NEAR/1	
	blind*):de,ab,ti) OR assign*:de,ab,ti OR	
	allocat*:de,ab,ti OR volunteer*:de,ab,ti	
#22	#21 AND ([controlled clinical trial]/lim OR	183
	[randomized controlled trial]/lim)	
#21	#19 OR #20	4,745
#20	(troponin* OR tn OR ctn$) NEAR/4 (test* OR	3,589
	path$fast* OR triage$true* OR atellica* OR poct	
	OR poc OR 'point of care')	
#19	#11 AND #18	1,675
#18	#12 OR #13 OR #14 OR #15 OR #16 OR #17	64,300
#17	'near patient* test*'	599
#16	.'poc':ti,ab	10,679
#15	'poct':ti,ab	3,966
#14	'point of care'	58,802
#13	'point of care testing'/exp	23,213
#12	'point of care system'/exp	4,271
#11	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 #9 OR #10	127,411
#10	atellica*	742
#9	'atellica'/exp	110
#8	triage$true*	5
#7	path$fast*	256
#6	'pathfast'/exp	32
#5	ctn$:ti,ab	17,471
#4	tn:ti,ab	27,069
#3	troponin*	96,171
#2	'troponin'/exp	90,045
#1	'troponin test kit'/exp	221
Date	18 Mar 2024	

Medline (March 2024)

Database: Ovid MEDLINE(R) ALL <1946 to March 15, 2024>

Search Strategy:

1	exp Point-of-Care Systems/ (20725)
2	exp Point-of-Care Testing/ (4524)
3	point* of care.mp. (43838)
4	POCT.ti,ab. (3137)
5	POC.ti,ab. (8175)
6	near patient* test*.mp. (358)
7	1 or 2 or 3 or 4 or 5 or 6 (48423)
8	exp Troponin/ (20988)
9	troponin*.mp. (37832)
10	Tn.ti,ab. (19246)
11	cTn?.ti,ab. (10767)
12	path?fast*.mp. (57)
13	Triage?True*.mp. (1)
14	Atellica*.mp. (124)
15	8 or 9 or 10 or 11 or 12 or 13 or 14 (59344)
16	7 and 15 (718)
17	((troponin* or tn or cTn?) adj5 (test* or path?fast* or Triage?True* or Atellica* or POCT or POC or point* of care)).mp. (2255)
18	16 or 17 (2634)
19	limit 18 to (controlled clinical trial or observational study or randomized controlled trial) (195)
20	((randomized controlled trial or controlled clinical trial).pt. or randomi#ed.ab. or placebo.ab. or drug therapy.fs. or randomly.ab. or trial.ab. or groups.ab.) not (exp animals/ not humans.sh.) (5186455)
21	18 and 20 (484)
22	Epidemiologic studies/ or exp case control studies/ or exp cohort studies/ or Case control.tw. or (cohort adj (study or studies)).tw. or Cohort analy$.tw. or (Follow up adj (study or studies)).tw. or (observational adj (study or studies)).tw. or Longitudinal.tw. or Retrospective.tw. or Cross sectional.tw. or Cross-sectional studies/ (3958449)
23	18 and 22 (808)
24	exp cohort studies/ or exp epidemiologic studies/ or exp clinical trial/ or exp evaluation studies as topic/ or exp statistics as topic/ (6751226)
25	((control and (group* or study)) or (time and factors) or program or survey* or ci or cohort or comparative stud* or evaluation studies or follow-up*).mp. (8876226)
26	24 or 25 (11663399)
27	(animals/ not humans/) or comment/ or editorial/ or exp review/ or meta analysis/ or consensus/ or exp guideline/ (9888593)
28	hi.fs. or case report.mp. (733476)
29	27 or 28 (10526967)
30	26 not 29 (9133705)
31	18 and 30 (1439)
32	19 or 21 or 23 or 31 (1610)
33	limit 32 to ed=20190527-20240318 (491)
34	limit 32 to dt=20190527-20240318 (513)
35	33 or 34 (585)
36	limit 35 to (english or german) (575)
37	remove duplicates from 36 (574)
Date	18.03.2024

POCT D-dimer

Cochrane (March 2024)

Search Name:POCT_D-Dimer (Update 2024)

Last Saved: 22/03/2024 19:06:46

Comment: MH/CW

ID	Search
#1	MeSH descriptor: [Point-of-Care Systems] explode all trees
#2	MeSH descriptor: [Point-of-Care Testing] explode all trees
#3	("point of care") (Word variations have been searched)
#4	(POCT):ti,ab,kw
#5	(POC):ti,ab,kw
#6	("near patient" NEXT test*) (Word variations have been searched)
#7	#1 OR #2 OR #3 OR #4 OR #5 OR #6
#8	(D-dimer*) (Word variations have been searched)
#9	(dimer*) (Word variations have been searched)
#10	MeSH descriptor: [Fibrin Fibrinogen Degradation Products] explode all trees
#11	(AFIAS*) (Word variations have been searched)
#12	(Exdia*) (Word variations have been searched)
#13	(Standard NEXT F*200*) (Word variations have been searched)
#14	(Standard NEXT F-200*) (Word variations have been searched)
#15	(Lumira*) (Word variations have been searched)
#16	(Hipro*) (Word variations have been searched)
#17	(Nano*checker*) (Word variations have been searched)
#18	(Nano-checker*) (Word variations have been searched)
#19	(i*Chroma*) (Word variations have been searched)
#20	(i-Chroma*) (Word variations have been searched)
#21	##8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20
#22	#7 AND #21
#23	(dimer* NEAR (test* OR "point of care" OR POCT OR POC OR Exdia* OR Standard NEXT F*200* OR Lumira* OR Hipro* OR i*Chroma* OR i-Chroma*)) (Word variations have been searched)
#24	#22 OR #23
#25	#22 OR #23 in Trials
#26	#22 OR #23 with Publication Year from 2019 to 2024, in Trials
#27	English:la
#28	German:la
#29	#27 OR #28
#30	#26 AND #29
#31	(conference proceeding):pt
#32	(abstract):so
#33	(clinicaltrials OR trialsearch OR ANZCTR OR ensaiosclinicos OR Actrn OR chictr OR cris OR ctri OR registroclinico OR clinicaltrialsregister OR DRKS OR IRCT OR Isrctn OR rctportal OR JapicCTI OR JMACCT OR jRCT OR JPRN OR Nct OR UMIN OR trialregister OR PACTR OR R.B.R.OR REPEC OR SLCTR OR Tcr):so
#34	#31 OR #32 OR #33
#35	#30 NOT #34
	20 Hits

Embase (March 2024)

Session Results		
No.	Query Results	Results
#43	#43. #41 NOT #42	130
#42	#42. #41 AND 'Conference Abstract'/it 4	48
#41	#41. #40 AND ([english]/lim OR [german]/lim)	178
#40	#40. #39 AND [31-05-2019]/sd NOT [23-03-2024]/sd	183
#39	#39. #35 OR #37 OR #38 511	511
#38	#38. #34 AND ('controlled clinical trial'/de OR 'observational study'/de)	240
#37	#37. #34 AND #36	301
#36	#36. 'crossover procedure':de OR 'double-blind procedure':de OR 'randomized controlled trial':de OR 'single-blind procedure':de OR random*:de,ab,ti OR factorial*:de,ab,ti OR crossover*:de,ab,ti OR ((cross NEXT/1 over*):de,ab,ti) OR placebo*:de,ab,ti OR ((doubl* NEAR/1 blind*):de,ab,ti) OR ((singl* NEAR/1 blind*):de,ab,ti) OR assign*:de,ab,ti OR allocat*:de,ab,ti OR volunteer*:de,ab,ti	3,303,573
#35	#34 AND ([controlled clinical trial]/lim OR [randomized controlled trial]/lim)	131
#34	#32 OR #33	3,890
#33	dimer* NEAR/4 (test* OR poct OR poc OR 'point of care' OR afias* OR exdia* OR 'standard f*200*' OR lumira* OR hipro* OR nano*checker* OR 'nano-checker*' OR 'i chroma*' OR ichroma*)	3,271
#32	#7 AND #31	781
#31	#9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30	209,718
#30	'ichroma*'	103
#29	'i chroma*'	244
#28	'i chroma'/exp	13
#27	'nano-checker*'	1
#26	nano*checker*	4
#25	hipro*	124
#24	lumira*	1,328
#23	'lumiradx'/exp	16
#22	'standard f-200*'	
#21	'standard f*200*'	10
#20	exdia*	11
#19	afias*	80
#18	#18. 'fibrin degradation product'/exp	4,787
#17	dimer*	205,293
#16	'd-dimer*'	48,971
#15	'd dimer blood level'/exp	32
#14	'd dimer assay'/exp	23
#13	'd dimer test'/exp	53
#12	'd dimer'/exp	43,672
#11	'd dimer blood level'/exp 32	32
#10	'd dimer assay'/exp 23	23
#9	'd dimer'/exp	43,672
#8	'crossover procedure':de OR 'double-blind procedure':de OR 'randomized controlled trial':de OR 'single-blind procedure':de OR random*:de,ab,ti OR factorial*:de,ab,ti OR crossover*:de,ab,ti OR ((cross NEXT/1 over*):de,ab,ti) OR placebo*:de,ab,ti OR ((doubl* NEAR/1 blind*):de,ab,ti) OR ((singl* NEAR/1 blind*):de,ab,ti) OR assign*:de,ab,ti OR allocat*:de,ab,ti OR volunteer*:de,ab,ti	3,303,573
#7	.#1 OR #2 OR #3 OR #4 OR #5 OR #6	64,467
#6	'near patient* test*' 599	599
#5	'poc':ti,ab	10,704
#4	'poct':ti,ab	3,977
#3	'point of care'	58,956
#2	'point of care testing'/exp	23,265
#1	'point of care system'/exp	4,284
Date	22 Mar 2024	

Medline (March 2024)

Database: Ovid MEDLINE(R) ALL <1946 to March 21, 2024>

Search Strategy:

1	exp Point-of-Care Systems/ (20742)
2	exp Point-of-Care Testing/ (4531)
3	point* of care.mp. (43882)
4	POCT.ti,ab. (3145)
5	POC.ti,ab. (8183)
6	near patient* test*.mp. (358)
7	1 or 2 or 3 or 4 or 5 or 6 (48473)
8	D-dimer*.mp. (18310)
9	dimer*.mp. (165871)
10	exp Fibrin Fibrinogen Degradation Products/ (10174)
11	AFIAS*.mp. (25)
12	Exdia*.mp. (5)
13	Standard F?200*.mp. (4)
14	Standard F-200*.mp. (0)
15	Lumira*.mp. (295)
16	Hipro*.mp. (38)
17	Nano?Checker*.mp. (3)
18	Nano-Checker*.mp. (1)
19	i?Chroma*.mp. (43)
20	Chroma*.mp. (185)
21	8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 (170262)
22	27 and 21 (322)
23	((D-Dimer* or dimer*) adj5 (test* or POCT or POC or point* of care or AFIAS* or Exdia* or Standard F?200* or Standard F-200* or Lumira* or Hipro* or Nano?Checker* or Nano-Checker* or i?Chroma$4 or i-Chroma$4)).mp. (2295)
24	22 or 23 (2525)
25	limit 24 to (controlled clinical trial or observational study or randomized controlled trial) (90)
26	((randomized controlled trial or controlled clinical trial).pt. or randomi#ed.ab. or placebo.ab. or drug therapy.fs. or randomly.ab. or trial.ab. or groups.ab.) not (exp animals/ not humans.sh.) (5189852)
27	24 and 26 (455)
28	Epidemiologic studies/ or exp case control studies/ or exp cohort studies/ or Case control.tw. or (cohort adj (study or studies)).tw. or Cohort analy$.tw. or (Follow up adj (study or studies)).tw. or (observational adj (study or studies)).tw. or Longitudinal.tw. or Retrospective.tw. or Cross sectional.tw. or Cross-sectional studies/ (3961730)
29	24 and 28 (753)
30	exp cohort studies/ or exp epidemiologic studies/ or exp clinical trial/ or exp evaluation studies as topic/ or exp statistics as topic/ (6754649)
31	((control and (group* or study)) or (time and factors) or program or survey* or ci or cohort or comparative stud* or evaluation studies or follow-up*).mp. (8881504)
32	30 or 31 (11669925)
33	(animals/ not humans/) or comment/ or editorial/ or exp review/ or meta analysis/ or consensus/ or exp guideline/ (9893203)
34	hi.fs. or case report.mp. (733955)
35	33 or 34 (10531995)
36	32 not 35 (9139133)
37	24 and 36 (1171)
38	25 or 27 or 29 or 37 (1423)
39	limit 38 to ed=20190531-20240322 (331)
40	limit 38 to dt=20190531-20240322 (392)
41	39 or 40 (435)
42	limit 41 to (english or german) (425)
43	remove duplicates from 42 (421)
Date	22.03.2024

Appendix II: Study characteristics and results from three primary studies

Table A - 1: Study characteristics and results from three primary studies on Tn-POCTs

Study name/Study ID / Author, year, reference number	ARTICA, NCT05466591, Aarts et al. 2024 [11]	Norman et al. 2022 [13]	Miller et al. 2022 [14]
Study design, study phase	RCT, multicentre, open-label	Prospective observational (pilot) study	Prospective observational study
Centres (single centre or multicentre), country, setting	Multicentre, Netherlands, ambulatory (primary care, 112 ambulances with paramedics at home)	Multicentre, New Zealand, 12 rural (family) practices	29 study sites: Rural hospitals (75.9%, staffed by generalist doctors with broad scopes of practice who often work in both hospital and primary care settings), rural and urban general practices (20.2%), and urgent care clinics (4%)
Sponsor/ lead institution	The Netherlands Organisation for Health Research and Development (ZonMw); 2018 grant number 852001942	Heart Foundation of New Zealand (1708) and the Waikato Medical Research Foundation (275). Abbott Point of Care, New Zealand provided i-STAT analysers to each of the participating practices, consumables and training for the point-of-care cardiac troponin I testing.	Heart Foundation of New Zealand (1770). Further study funding was provided by an investigator grant from Abbott Diagnostics Point of-Care. The funding bodies had no role in the design of the study, analysis of data, or writing of this report.
Patient population (number of included patients) / Baseline characteristics	**Low-risk** chest pain **patients (*HEAR score ≤3**) with **suspected NSTE-ACS**, **onset of symptoms at least 2h before** ambulance presentation were **randomised 1:1 to pre-hospital rule-out with POC troponin measurement (n=434) or the ED rule-out strategy (n=429);** **866 randomised/863 followed-up** (3 patients withdrew after randomisation) Mean age: 54±13 years (53.7±13.1 vs 53.2±12.5; 56.9% vs 57.8% female; median HEAR score of 3 (IQR 2–3) vs 3 (IQR 2–3) **Sample size calculation on primary outcome (cost): n=866** Analysis of the total population (434 pre-hospital rule-out strategy vs 429 ED rule-out strategy) and	Patients aged ≥18 years, presented acutely to rural general practice with suspected ischaemic chest pain for whom the doctor intended transfer to hospital for serial troponin measurement 186 patients identified using the clinical pathway/**180 followed-up and analysed** (6 patients excluded) 111 (**61.7%**) **low-risk** vs. 69 (38.3%) non-low-risk patients Mean age: low-risk patients 52 (11.8) vs non-low-risk patients 69 (10.9); non-low-risk patients more likely to be male, and to have cardiovascular risk factors or a history of ischaemic heart disease **Sample size calculation: n=200** ***Low-risk patients***: No red flags (history of ongoing pain or haemodynamically unstable or history suggestive of crescendo angina).	1205 enrolled; 132 (11%) excluded, majority due to protocol breaches. 1073 patients included in the primary analysis: 474 (44.0%) low-risk patients vs. 599 (56%) non-low-risk patients. Mean age: 63 years (SD: 15 years): in low risk: 55 (13) vs. non-low-risk 70 (12); 515/1072, 48.0%: female: in low-risk 60% vs non-low risk 39%; EDACS 14; 10 in low-risk vs 19 in non-low risk Estimated total **sample size** of 1000 patients to ensure inclusion of at least 410 patients at low-risk of developing MACE ***Low-risk patients***: No red flags (history of ongoing pain or haemodynamically unstable or history suggestive of crescendo angina). Absence of possible new ischaemic changes on ECG: ST-segment depression (≥0.5 mm) in two contiguous leads (including reciprocal changes), abnormal T-wave inversion

	analysis of the ruled-out ACS population (419 vs 417) performed.	Absence of possible new ischaemic changes on ECG: ST-segment depression (≥0.5 mm) in two contiguous leads (including reciprocal changes), abnormal T-wave inversion (≥2 mm), Q-waves (>30 ms and ≥0.1 mV depth) in two contiguous leads, or new bundle-branch block on an ECG at 0 and 2 hours. EDACS <16. POC-cTn: Abbott i-STAT cTnI <40 ng/L (decision limit) at 0 and 2 hours. No further chest pain or ECG changes and remained clinically stable. Eligible for discharge from the rural general practice to home, with follow-up outpatient exercise tolerance testing where indicated. ***Non-low-risk patients***: Did not fulfil the criteria for the low-risk pathway and referred to hospital for assessment and serial troponin testing. Median time from index chest pain onset to presentation to rural practice was 15 hours (IQR: 3.1–40.2 hours)	(≥2 mm), Q-waves (>30 ms and ≥0.1 mV depth) in two contiguous leads, or new bundle-branch block on an ECG at 0 and 2 hours. EDACS <16 POC-cTn: Serial point-of-care troponin concentrations below the lower rule out threshold at 0 and 2 h. ***Non-low-risk patients***: Did not fulfil the criteria for the low-risk pathway and referred to hospital for assessment and serial troponin testing Median time from pain onset to assessment: 4 h and 36 min (interquartile range: 2–14 h and 30 min)
Inclusion criteria	Age ≥18 years, suspected NSTE-ACS, symptom duration of at least two hours, modified HEAR(T) score ≤3, provided written informed consent	Patients aged ≥18 years who presented acutely to rural general practice with suspected cardiac ischaemia (primarily chest pain) who would ordinarily be referred by the doctor and transferred to hospital for serial troponin measurement	Patients aged ≥18 years who had chest pain that the treating clinician considered could be due to cardiac ischaemia or AMI that began or worsened within the last 72 h and would have ordinarily required transfer for an urgent hospital-based assessment if presenting to a primary care setting (GP or urgent care)
Exclusion criteria	ST -segment elevation, suspected non-cardiac cause of the symptoms requiring ED visit, comatose state (defined as a GCS score <8), known cognitive impairment, pregnancy, cardiogenic shock (= systolic blood pressure <90mmHg, heart rate >100bpm and peripheral oxygen saturation <90%), syncope, signs of heart failure, heart rhythm disorders and second-degree or third-degree atrioventricular block, known end-stage renal disease (dialysis and/or MDRD <30mL/min), suspected aortic dissection or pulmonary embolism, confirmed AMI, PCI or CABG <30 days prior to inclusion, communication issues with the patient and/or	ST-segment elevation myocardial infarction; proven or suspected non-coronary pathology as the cause of chest pain (eg, pancreatitis or pulmonary embolism); requiring transfer to hospital regardless of a POC-cTn below the prespecified threshold, due to other medical conditions, or the need for other investigations or were systemically unwell; chest pain symptoms greater than 72 hours; representation with chest pain symptoms during the evaluation period; or an anticipated problem with follow-up (eg., resident outside NZ)	Presented with STEMI, a proven or suspected non-coronary artery pathology cause of the chest pain, required transfer to a metropolitan hospital regardless of the result of the RACPP due to other medical conditions, or had an anticipated problem with follow-up (e.g. overseas tourist leaving within 30 days).

	language barrier, decision of a present general practitioner to evaluate the patient at the ED, decision of the consultant cardiologist to evaluate the patient at the emergency department, any significant medical or mental condition, which in the investigator's opinion may interfere with optimal participation in the study		
Intervention (strategy and type of POCT)	**Pre-hospital rule-out strategy**: **low-risk patients** underwent on-site **single POC troponin T measurement**; Cobas h232 (Roche diagnostics, Basel, Switzerland), the detection limits are 40–2000 ng/L. Concentrations of 40–2000 ng/L on this assay are comparable to high-sensitivity troponin T concentrations in the laboratory. The 99th percentile of normal on the laboratory high-sensitivity troponin T assay is 14 ng/L, which is below the detection limit of the Cobas h232. If POC troponin T was low (<40 ng/L), the care for the patient was transferred to the GP, as normal procedure in patients who are not transported. If POC troponin T was elevated (≥40 ng/L), the patient was mandatory transported to the ED. ***Non-high sensitivity POC Troponin tests***	**Rural accelerated diagnostic chest pain pathway (RACPP)** specifically adapted for management of suspected cardiac chest pain in rural general practice: **Emergency Department Assessment of Chest Pain Score** (**EDACS**), **ECG** and **two POC-cTn Measurements** - at presentation and 2 hours at the practice Abbott i-STAT c-TnI assay has a limit of detection (LoD) of 20 ng/L, limit of quantitation of 40 ng/L and 99th percentile at 80 ng/L POC contemporary troponin Assay i-STAT (Abbot) cTnI <40 ng/L (decision limit): validated for use with both contemporary and high-sensitivity assays ***Non-high sensitivity POC Troponin tests***	**RACPP: EDACS**, **ECG** and **two POC-cTn Measurements** - at presentation and 2 hours at the practice Two POC-cTn assays were used: (1) Abbott iSTAT cTnI (iSTAT) (IL, USA): The upper reference limit (URL) based at 99th percentile 0.08 µg/L, limit of blank=0.02 µg/L. The coefficient of variation (CV) at the 99th percentile was 16.5%. (2) Radiometer AQT-90 FLEX cTnT (AQT90) (Brønshøj, Denmark): URL=0.17 µg/L (17 ng/L), limit of detection=0.008 µg/L. The CV at the 99th percentile was 5.2%. For the iSTAT: patients were considered low-risk if the troponin concentration was below a decision-making threshold of 0.04 µg/L (lower rule out threshold). Compared with the 99th percentile, this lower threshold improves the clinical sensitivity of the iSTAT cTnI, and was used in the pilot study and is consistent with guidelines. Patients were considered high-risk if they had (i) any troponin concentration above the URL (0.08 µg/L) or (ii) a troponin concentration ≥0.04 µg/L but ,0.08 µg/L with a difference between the first and second concentrations of ≥0.02 µg/L. For the AQT90: there was a single decision-making threshold at 18 ng/L. ***Non-high sensitivity POC Troponin tests***
Comparator(s) (strategy and tests)	**ED rule-out strategy**: **low-risk patients** were transferred directly to the ED for evaluation without POC troponin measurement and evaluated according to standard practice: high-sensitivity troponin (T or I) was measured at the ED according to the prevailing guidelines; additional diagnostic tests were at the discretion of the cardiologist.	**Standard care for non-low-risk patients**: referral to hospital for assessment and serial troponin testing	**Standard care for non-low-risk patients**: Patients that presented to primary care settings were transferred to their usual referral centre and those that presented to rural hospitals were admitted to that facility
Primary Outcome(s)	Healthcare costs	*Implementation outcomes*	Presence of 30-day MACEs in low-risk patients

		Adherence to the pathway. Patient acceptability and satisfaction with care. Participating sites' acceptability. *Intervention outcomes* Proportion of patients identified as low-risk by the pathway, and managed in the community, without transfer to hospital, with no 30-day MACE. ***MACE** was **defined** as death that was not known to be from non-cardiac causes, emergency coronary revascularisation procedure, cardiac arrest (International Classification of Diseases, 10th Version codes I460, I461, I469), and AMI (I210, I211, I212, I213, I214, I219, I220, I221, I228, I229), ventricular arrhythmia (I472), cardiogenic shock (R570) and high-degree atrioventricular block needing intervention (I4442).* MACE within 30 days of presentation in non-low-risk patients. ACS (AMI or unstable angina) within 30 days of presentation in non-low-risk patients. Non-emergency coronary revascularisation within 30 days of presentation in non-low-risk patients. Agreement between POC and laboratory measured cardiac troponin concentrations.	MACE was defined as 'death, cardiac arrest, emergency revascularization procedure, cardiogenic shock, ventricular arrhythmia, ventricular fibrillation, high-degree atrio-ventricular block needing intervention, or acute myocardial infarction'
Patient-relevant secondary or tertiary outcome(s)	Safety by the incidence of major adverse cardiac events - ***MACE*** (one or more of the following events: ACS, unplanned revascularization or all-cause death) compared between groups in the total population and in the ruled-out ACS population (all patients for whom an ACS was ruled out, either in the pre-hospital setting or in the ED); QoL (EuroQol-5D -5L (EQ-5D-5L)); Cost-effectiveness	See above	Percentage of patients classified as low-risk that avoided transfer or were eligible for early discharge Percentage of patients in the group identified as not low-risk who developed a 30-day MACE

Follow-up (weeks, months)	30-day and 1-year	30-day	30-day
Results			
Diagnostic accuracy outcomes			
Sensitivity, specificity, PPV, NPV	***Pre-hospital rule-out strategy for MACE at 1 year***: SEN: 68.2% (95% CI 47.5% to 84.9%) SPEC: 100% PPV: 100% NPV: 98.3% (95% CI 96.8% to 99.3%) ***ED rule-out strategy for MACE at 1 year***: SEN: 66.7% (95% CI 43.7% to 85.2%) SPEC: 100% PPV: 100% NPV: 98.63% (95% CI 97.1% to 99.4%)	For MACE at 30-day in low-risk patients: SEN: 100.0% (95% CI 70.1% to 100%) NPV: 100% (95% CI 96.7 to 100%) SPEC: 63.8% (95% CI 56.4 to 70.6%) PPV: 12.5% (95% CI 6.7 to 22.1%)	For MACE at 30-day in low-risk patients: SEN: 100% (95% CI 97.3 to 100%) NPV: 100% (95% CI 99.2 to 100%) SPEC: 50.7% (95% CI 47.5 to 53.9%) PPV: 23.0% (95% CI 19.8 to 26.6%) PLR: 2.0 (95% CI 1.9 to 2.2) NLR: 0 (not able to estimate a CI)
Clinical utility/Effectiveness and Safety outcomes			
MACE**	**30-day MACE, pre-hospital rule-out strategy vs ED rule-out strategy** ***Total population***: 3.9% (17/434) vs. 3.7% (16/429); risk difference 0.2% (95% CI −2.4% to 2.7%, p= 0.89) In the pre-hospital rule-out strategy group: 17 (3.9%) patients had an ACS, of which 4 (0.9%) had an ST-segment elevation myocardial infarction (STEMI), 12 (2.8%) received unplanned revascularization and no patients died. 15/17 (88%) were directly transferred to the ED because they did not have low POC troponin. In ED rule-out strategy 3 (0.7%) patients had an ACS, 3 (0.7%) patients received unplanned revascularization and 1 (0.2%) patient died after an ACS was ruled-out at the ED. ***Rule-out ACS population***: 0.5% (2/419) vs. 1.0% (4/417), risk difference −0.5% (95% CI −1.6% to 0.7%; p=0.41) in favour of the pre-hospital strategy In the pre-hospital rule-out strategy group: 2 (0.5%) patients had an ACS, 2(0.5%) received unplanned revascularization and no patients died after an ACS was ruled-out in the pre-hospital setting. In the ED rule-out strategy group: 3 (0.7%) patients had an ACS, 3 (0.7%) received unplanned revascularization and 1 (0.2%) patient died after an ACS was ruled-out at the ED.	**30-day MACE** Low-risk patients: 0% (0/111 patients) with 30-day MACE (0%, 95% CI 0.0% to 3.3%) vs 13.0% (9/69 patients) (95% CI 6.5%–23.8%) in non-low risk patients From the 56 non-low risk patients referred to hospital, 9/56 (16.1%) had at least one MACE Overall 30-day MACE rate, for all non-low-risk patients presenting to participating rural general practices with suspected cardiac chest pain: 5.0%	**30-day MACE** Low risk patients: 0/474 (95% CI 0 to 0.3%) Non-low-risk patients: 138 (23.0%) (high-risk: 124/236, 52.5%), intermediate-risk: 14/363, 3.9%) AMI (125/138, 90.6%), and more than a third of such patients received an emergency revascularization procedure (51/138, 37.0%), 3 deaths (3/138, 2.2%)

	1-year MACE, pre-hospital rule-out strategy vs ED rule-out strategy ***Total population***: 5.1% (22/434) vs. 4.2% (18/429); risk difference of 0.9% (95% CI −1.9% to 3.7%, p=0.54) In the pre-hospital rule -out strategy group: 20 patients (4.6%) had an ACS, of which 14 (3.2%) had a non-ST-segment elevation myocardial infarction (NSTEMI), 5 (1.2%) had STEMI, and 1 patient (0.2%) had unstable angina. Unplanned revascularization was performed in 15 patients (3.5%), and 2 patients (0.5%) died. 15/22 (68%) directly transported to the ED because of either an elevated POC troponin T concentration (*n*=14) or a failed test (*n*=1). In the ED rule-out strategy group: 15 patients (3.5%) had an ACS, of which 11 (2.6%) had an NSTEMI and 4 (0.9%) had unstable angina. Unplanned revascularization was performed in 13 patients (3.0%), and 3 patients (0.7%) died. ***Rule-out ACS population***: 1.7% (7/419) vs. 1.4% (6/417), risk difference 0.2% (95% CI −1.4% to 1.9%; p=0.79) In the pre-hospital rule-out strategy group: 5 patients (1.2%) had an ACS, of which 2 (0.5%) had a NSTEMI, 2 (0.5%) had a STEMI and 1 patient (0.2%) had unstable angina. Unplanned revascularization was performed in 5 patients (1.2%), and 2 patients (0.5%) died. In the ED rule-out strategy group: 3 patients (0.7%) had an ACS, all of them (0.7%) had unstable angina. Unplanned revascularization was performed in all 3 (0.7%), and all 3 patients (0.7%) died.	Not planned as outcome	Not planned as outcome
QoL	***At 30 days*** (completed by 331 (76.3%) patients in the pre-hospital rule-out strategy and 311 (72.5%) patients in the ED rule-out strategy) Mean difference in EQ -5D -5L utility score −0.009 (95% CI −0.048 to 0.030, p=0.65) in complete cases analysis and −0.011 (95% CI −0.038 to 0.015, p=0.39) in the multiple imputation analysis	Not planned as outcome	Not planned as outcome

	At 1-year (completed by 376 (86.6%) patients in the pre-hospital rule-out strategy and 362 (84.4%) patients in the ED rule-out strategy) Mean difference in EQ -5D -5L utility score 0.008 (95% CI −0.033 to 0.050, p=0.69) in the complete cases analysis and 0.005 (95% CI −0.022 to 0.031, p=0.73) in the multiple imputations analysis	Not planned as outcome	Not planned as outcome
One additional ambulance transport ***	63 (14.7%) pre-hospital rule-out strategy vs 29 (6.8%) ED rule-out strategy, **p< 0.001**	Not planned as outcome	Not planned as outcome
ED visits***	***At 30 days*** 1 ED visit: 59 (13.6%) in pre-hospital rule-out strategy vs 411 (95.8%) in ED rule-out strategy, **p<0.001** ≥ 2 ED visits: 5 (1.2%) vs 18 (4.2%), **p=0.006**	Not planned as outcome	435/474 (91.8%, 95% CI 88.8 to 93.9%) of low-risk patients discharged without hospital admission: 293/330 (88.8%, 95% CI 84.9 to 91.9%) from rural hospitals, 101/102 (99%, 95% CI 94.7 to 99.8%) from general practice and urgent care clinics (97.6%, 95% CI 87.7 to 99.9%)
	At 1 year One ED visit: 76 (17.5%) in pre-hospital rule-out strategy vs 360 (83.9%) in ED rule-out strategy, **p<0.001** Two or more ED visits: 25 (5.8%) vs 69 (16.1%), **p<0.001**	Not planned as outcome	Not planned as outcome
Hospitalisation and length of hospitalisation***	***At 30 days*** Hospitalisation: 32 (7.4%) vs 42 (9.8%), p=0.21 Length of hospitalisation (days): median (IQR) 0 (0–0) vs 0 (0–0), p=0.24	Not planned as outcome	Not planned as outcome
	At 1 year Hospitalisation: 58 (13.4%) vs 58 (13.5%), p=0.95 Length of hospitalisation (days): median (IQR) 0 (0–0) vs 0 (0–0), p=0.99	Not planned as outcome	Not planned as outcome
Adherence	Not planned as outcome	Adherence to the low-risk pathway: 95.5% (106/111). 5 patients not completing the 2-hour assessment due to a subsequent diagnosis of non-cardiac chest pain (n=4) or refusal to remain in the practice (n=1). 13 (18.8%) non-low-risk patients not transferred for hospital assessment, against pathway guidance.	Not planned as outcome
Satisfaction with care	Not planned as outcome	Response rate: 75% (111 of 148) Low-risk patients, 94% satisfied with care vs 95.5% of non-low-risk patients	Not planned as outcome

		Pathway considered feasible and acceptable by the general practices (it has been maintained as the standard of care in the participating centres)	
Concordance between POCT and duplicate laboratory measured	Not planned as outcome	Good concordance was observed between POCT and duplicate laboratory measured troponin concentrations: 11 discordant sample observed	Not planned as outcome

***Abbreviations**: ASC: acute coronary syndrome; CI: confidence interval; ED: emergency department; EDACS: Emergency Department Assessment of Chest Pain Score; *HEAR score = HEART (History, Electrocardiogram, Age, Risk Factors and Troponin) score without Troponin; LR: likelihood ratio; **MACE: major adverse cardiac events (one or more of the following events: ACS, unplanned revascularization or all-cause death); NPV; negative predictive value; NSTE-ASC: non-ST-segment elevation acute coronary syndrome; ***Outcomes results from cost data tables; POCT: point of care test; PPV: positive predictive value; RACPP: Rural accelerated diagnostic chest pain pathway; QoL: quality of life*

Table A - 2: Study characteristics and results from three primary studies on D-Dimer-POCTs

Study name/Study ID / Author, year, reference number	Heerink et al. 2023 [15] Netherlands Trial Register (NL71809.028.19)	Heerink et al. 2020 [16]	Van Maanen et al. 2020 [17]
Study design, study phase	Prospective observational cohort study	Prospective observational study	Prospective observational cohort study
Centres (single centre or multicentre), country, setting	Multicentre, Netherlands, general practice	Netherlands, general practice	Multicentre, Netherlands, primary care (general practice)
Sponsor/ lead institution	Jeroen Bosch Hospital, AKSA Medical, Mediphos Medical Supplies B.V., LumiraDx Benelux B.V., Axon Lab B.V., and Boditech Med Inc. The funding organisations played no role in the design of study, choice of enrolled patients, review and interpretation of data, preparation of manuscript, or final approval of manuscript.	Jeroen Bosch Hospital, Julius Centre for Health Sciences and General Practice, University Medical Centre Utrecht. Nano-Ditech Corporation (NJ, USA) has financially contributed on this research. There have been no restrictions placed upon publication by the sponsors, and the manufacturer did not make any contribution to the research and/or publication.	The Netherlands Organization for Health Research and Development (ZonMw, grant number: 837003003). ZonMw did not interfere in the design and conduct of the trial, nor had input into data collection, analysis and interpretation, or preparation of the manuscript.
Patient population (number of included patients / Baseline characteristics)	Primary care patients with a low suspicion of a venous thromboembolism (VTE) (clinical decision rule (CDR) score of ≤3 for a suspicion of deep venous thrombosis (DVT) and ≤4 for pulmonary embolism (PE) 511 participants, of whom 57 had VTE, used for clinical performance analyses Clinical outcome data from patients enrolled in the EVA-I study [16, 18] had been collected using the same methodology and were also included: Out of 349 consecutive patients presenting to the participating diagnostic facilities over a period of 22 months, a total of 336 patients with suspected VTE initially provided informed consent for additional blood samples to be drawn, for a capillary finger stick to be performed and for their GP to be consulted for clinical outcome data. Blood samples from 62 subjects were subtracted due to exclusion, while samples from 237 EVA-I patients were added. Finally, venous plasma samples from 511 participants (320 DVT suspicions and 191 PE suspicions) were used for clinical performance analyses in the current study. Capillary whole blood samples ranging from 47 to 69 subjects for each type of POC D-dimer device were used for matrix comparison.	242 patients suspected of having DVT (CDR ≤3) and/or PE (CDR ≤ 4) in general practice, after patients had provided informed consent 258 primary care patients with suspected VTE and **low CDR score** (16 excluded: inclusion criteria not met or informed consent not provided)	1509 patients with suspected DVT and PE included; 32 (2.1%) patients with missing follow-up information. Patients with suspected DVT(n=993) and suspected PE (n=484) included in analysis

	Sample size calculation on primary outcome at least 220 plasma samples for clinical performance analyses; For matrix comparison, at least 40 samples per device to achieve a wide concentration range		
Inclusion criteria	Adult primary care patients with a **low suspicion of a VTE** (CDR score of ≤3 for a suspicion of DVT and ≤4 for PE provided informed consent)	242 **low CDR score** patients suspected of having DVT (CDR ≤3) and/or PE (CDR ≤ 4) in general practice, with provided informed consent	All adult patients in whom the GP suspected a diagnosis of DVT or PE (based on clinical symptoms such as calf pain or swelling for DVT, and dyspnoea, coughing or chest pain for PE)
Exclusion criteria	Indication other than VTE exclusion; aged <18 years; ongoing anticoagulant treatment (vitamin K antagonists, non-vitamin K oral coagulants or low-molecular-weight heparin); pregnancy; life expectancy < 3 months	NR	Institutionalised frail elderly patients; patients aged <18 years, pregnant or postpartum women, current use of oral anticoagulants (vitamin K antagonist, direct oral anticoagulant or low molecular heparin) and symptoms lasting longer than 30 days
Intervention (strategy and type of POCT)	Five novel **quantitative** point-of-care (POC) D-dimer devices **with a capillary finger stick feature** for predicting VTE in general practice: ***Exdia TRF Plus*** (E), Precision Biosensor Inc., Daejeon, Korea, ***AFIAS-1®*** (A), Boditech Med Inc., Gangwon-do, Korea, ***Standard F200®*** (S), SD Biosensor, Seoul, Korea, ***LumiraDx™ D-dimer*** (L), LumiraDx Ltd., London, ***Hipro AFS/1®*** (H), Hipro Biotechnology, Shijiazhuang, China.	Five novel **quantitative** POC D-dimer assays: ***Nano-Checker 710 Ddimer®***, Nano-Ditech Corporation, Cranbury, USA ***AFIAS-1®*** (A), Boditech Med Inc., Gangwon-do, Korea ***iChroma-II®***, Boditech Med Inc, Gangwon-do, Korea ***Standard F200®***, SD Biosensor, Seoul, Korea ***Hipro AFS/1®***, Hipro Biotechnology, Shijiazhuang, China	**Two CPRs** (**Wells for PE and Oudega rule for DVT**) in 1017 patients suspected of DVT and 492 patients suspected of PE in primary care Both CPRs combine seven clinical items into a score ranging from 0 to 8 for DVT and from 0 to 12.5 for PE, which classifies patients in an 'unlikely' or a 'likely' risk category of having VTE. In **low-risk patients**, with a score of ≤3 points on the DVT CPR, or ≤4 points on the PE CPR, **qualitative or quantitative D-dimer** test to be determined. If D-dimer was below the threshold of 500 ng/mL, patients were classified as low risk of having VTE, and therefore, VTE was considered to be safely ruled out without the need for additional investigation. Patients with a score of ≥4 points for DVT, or ≥4.5 points for PE, or with a D-dimer either above 500 ng/mL or a 'positive' result on a qualitative point-of-care test for D-dimer, were classified as 'high risk' of having VTE. In these patients, all following existing guidelines, referral to the hospital for further diagnostic procedures was recommended. Non-referred patients were instructed to schedule a follow-up appointment with their GP in case of worsening or persistent symptoms. During the inclusion period, the **qualitative** point-of-care test for D-dimer (**Clearview Simplify**) was **withdrawn from the market**, because of too many false-negative results likely due to periprocedural quality-related faults when performing the test (ie, incorrect withdrawal of capillary blood or not keeping test cold enough until use).

			In **357 patients (209 suspected DVT and 148 suspected PE**), a **quantitative D-dimer** test was performed.
Comparator(s) (strategy and tests)	Laboratory-based assay (STA-Liatest®D-Di PLUS assay, used in conjunction with the STA R Max® platform (Stago Diagnostica, Asni`ere-sur-Seine, France)	Laboratory-based assay (STA-Liatest®D-Di PLUS assay) on a routine laboratory analyzer (STA-R MaxVR , Stago Diagnostica, Asni_eres-sur-Seine, France)	Reference standard between referred and non-referred patients suspected of venous thromboembolism differed; clinical follow-up in the non-referred patients and further diagnostic procedures in hospital (most often a compression ultrasound of the leg in case of suspected DVT or a CT pulmonary angiography in case of suspected PE) in the referred patients
Primary Outcome(s)	*Clinical performance (venous sample)* Sensitivity, specificity, false-negative rate (FN rate), positive and negative predictive values (PPV/NPV), likelihood ratio of a negative test result (LR-), accuracy and efficacy presented as VTE performance parameters for a fixed (500 ng/mL) and age-dependent D-dimer cutoff value *Equivalence between capillary and venous blood samples (matrix comparison)*	*Analitical performance (venous sample)* 238 samples were included in the data analysis *User-friendliness* of the POC D-dimer test systems using a questionnaire based on the System Usability Scale (SUS) by 11 GP assistances after their first-time use of the test systems	*Diagnostic failure rate*, defined as the 3-month incidence of VTE in the non-referred group *Efficiency*, defined as the proportion of non-referred patients in the total study population
Patient-relevant secondary or tertiary outcome(s)	NA	NA	*Determinants for* and *consequences* of *incorrect* application of the CPRs
Follow-up (weeks, months)	3 months	NR	3 months
Results			
Diagnostic accuracy outcomes			
Sensitivity, Specificity, Positive predictive values (PPV), Negative predictive values (NPV)	***POCTs*** ***Exdia TRF Plus*** Sensitivity 94.7% (95% CI 84.5% to 98.6%) Specificity 67.4% (95 % CI 62.8 % to 71.7%), FN rate 1.0% (0.3% to 3.1%), PPV 26.7% (95% CI 20.9% to 33.5%), NPV 99.0% (95% CI 97.0 to 99.7%) LR- 0.08 (95%CI 0.03-0.24) Accuracy 70.5% (95% CI 66.5% to 74.4%) Efficacy 60.5% (95% CI 56.1% to 64.7%) ***AFIAS-1® device*** Sensitivity 91.2% (95% CI 80% to 96.7%), Specificity 78.0 % (95% CI 73.8% to 81.6%), FN rate 1.4% (95% CI 0.5% to 3.4%), PPV 34.2% (95% CI 26.8% to 42.4%), NPV 98.6% (95% CI 96.6 to 99.5%) LR- 0.11 (95% CI 0.05 to 0.26) Accuracy 79.5% (95 % CI 76.9% to 83.0%)	Not planned as outcome	Not planned as outcome

	Efficacy 70.3% (95% CI 66.1% to 74.1%) ***Standard F200*** Sensitivity 96.5% (95% CI 86.8% to 99.4%), Specificity 69.6% (95% CI 65.1% to 73.8%), FN rate 0.6% (95% CI 0.1% to 2.5%), PPV 28.5% (95% CI 22.4% to 35.5%), NPV 99.4% (95% CI 97.5 to 99.9%) LR- 0.05 (95% CI 0.01 to 0.20) Accuracy 72.6% (95% CI 68.7% to 76.5%) Efficacy 62.2% (95% CI 57.9 % to 66.4%) ***LumiraDx™ device*** Sensitivity 100.0% (95% CI 92.1 % to 100%), FN rate of 0.0% (95% CI 0.0% to 0.0%) PPV 22.4% (95% CI 17.6% to 28-2%) NPV 100.0% (95% CI 98.5 to 100.0%) LR- 0.00 (95 % CI 0.00 to 0.00) Accuracy 61.3% (95% CI 57.1 to 65.5%) Efficacy 50.1% (95% CI 45.7 to 54.5%) ***Hipro AFS/1*** Sensitivity 93.0% (95% CI 82.2% to 97.7%), Specificity 65.0% (95% CI 60.4% to 69.3%), FN rate 1.3% (0.4% to 3.6%), PPV 25.0% (95% CI 19.4% to 31.5%), NPV 98.7% (95% CI 96.4 to 99.6) LR- 0.11 (95% CI 0.04 to 0.28) Accuracy 68.1% (95 % CI 64.1% to 72.1%) Efficacy 58.5% (95% CI 54.1% to 62.8%) ***Standard laboratory assay*** ***STA R Max*** Sensitivity 94.7% (95% CI 84.5% to 98.6%), Specificity 68.1% (95% CI 63.5% to 72.3%), FN rate 1.0% (95% CI 0.2% to 3.0%), PPV 27.1% (95% CI 21.2% to 34.0%), NPV 99.0% (95% CI 97.0 to 99.8%) LR- 0.08 (95% CI 0.03 to 0.23) Accuracy 71.0% (95% CI 67.1% to 75.0%) Efficacy 61.1% (95% CI 56.7% to 65.3%)		
Capillary whole blood vs venous plasma comparison	***Exdia TRF Plus*** Correlation 0.71 (0.54–0.83); Concordance 90.1% / 93.5% ***AFIAS-1*** Correlation 0.94 (0.90–0.97); Concordance 89.8%	Not planned as outcome	Not planned as outcome

	/ 100% ***Standard F200*** Correlation 0.69 (0.54–0.80); Concordance 87.1% / 84.2% ***LumiraDx*** Correlation 0.88 (0.80–0.93); Concordance 93.6% / 91.0% ***Hipro AFS/1*** Correlation 0.11 (-0.15–0.36); Concordance 71.4% / 72.9%		
Clinical utility/Effectiveness and Safety outcomes			
Diagnostic failure rate and Efficiency	NA	NA	Overall **VTE**: 267/1477 (18.1%: 23.2% DVT and 7.9% PE) Overall **failure rate** of both CPRs combined in the total study population: 1.8% (95% CI 1.02 to 3.06) Overall **efficacy** of both CPRs combined in the total study population: 53% (95% CI 50.4 to 55.5) Total study population *CPRs correctly applied (n=787)*: Failure rate: 1.51% (95% CI 0.77 to 2.86) Efficiency: 58.1% (95% CI 55.2 to 61.0) *CPRs incorrectly applied* (n=339 patients) Failure rate: 3.31% (95% CI 1.07 to 8.76) Efficiency: 35.7% (95% CI 30.6 to 41.1) *Among patients with CPR correctly applied, 408 were not referred (efficiency of 51.8%) and 8 of them had a VTE; the failure rate was 1.96% (95% CI 0.91% to 3.98%);* *Among206 (20.7%) patients with CPR incorrectly applied, the failure rate was 7.02% (95% CI 2.27% to 17.83%), and the efficiency in these patients decreased to 27.7%.* *Of the 351 (72.5%) patients suspected of having PE and CPR correctly applied, 253 (72.1%) patients were not referred: 2 were diagnosed with VTE; failure rate 0.79% (95% CI 0.14% to 3.13%)*

			In 133 (27.5%) patients with suspected PE, the CPR was incorrectly used by the GP. Sixty-four (48.1%) of these patients were not referred. None of them had a missed VTE.
Reasons and determinants for incorrect CPR use	Not planned as outcome	Not planned as outcome	Reasons for incorrect CPR in suspected DVT and PE patients: inappropriate D-dimer testing when the score on the CPR was high; including patients: already on anticoagulants, that were pregnant or postpartum and aged <18 years; application of the Oudega rule rather than the Wells rule was the reason in more than a third of patients suspected of PE. In patients aged between 50 and 75 years and in women, CPRs were less frequently applied incorrectly (OR 0.71 (95% CI 0.54 to 0.94) and 0.69 (95% CI 0.54 to 0.89), respectively). Presence of concurrent heart failure increased the likelihood of incorrect application (adjusted OR 3.26 (95% CI 1.47 to 7.21), as well as in patients with a previous VTE 4.45 (95% CI 2.73 to 7.25)).
User-friendliness (SUS score, IQR)	Not planned as outcome	***Nano-Checker 710 Ddimer®:*** 70.0 (55.0-85.0) ***AFIAS-1®:*** 65.0 (40.0-90.0) ***iChroma-II®:*** 37.5 (30.0-60.0) ***Standard F200®:*** 57.5 (35.0-85.0) ***Hipro AFS/1®:*** 75.0 (47.5–97.5)	Not planned as outcome

Abbreviations*: CI: confidence interval; CDR: clinical decision rule; DVT: deep venous thrombosis; FN rate: % false-negative test results; IQR: interquartile range; PE: pulmonary embolism; POCT: point of care test; PPV: positive predictive value; NA: not applicable; NR: not reported; NPV; negative predictive value; LR-: likelihood ratio based on a negative test result; SUS: System Usability Scale; VTE: venous thromboembolism*

Definitions: Accuracy: % correct test results; Efficacy: % negative test results (=% non-referrals); Efficiency, defined as the proportion of non-referred patients in the total study population; Diagnostic failure rate, defined as the 3-month incidence of VTE in the non-referred group

Appendix III: RISK OF BIAS Tables

Table A - 3: Risk of bias assessed with the Cochrane risk of bias 2 (RoB2) tool

Studies	Randomisation process	Deviations from the intended interventions	Missing outcomes	Measurement of the outcome	Selection of reported results	Overall bias
ARTICA RCT, NCT05466591 Camaro et al 2023, Aarts et al 2024 [11, 12]	Low	High [a]	Low	High [b]	Low	**High**

[a] *Open-label, MACE at 30 days and 1 year as a secondary outcome, 1138 patients screened for eligibility do not include patients for whom no CRF was started, and it is unknown how many patients were deemed ineligible without starting the CRF;*

[b] *Unblinded study: open-label; study was neither formally designed nor powered to investigate outcome MACE (pointed as safety of the pre-hospital rule-out strategy); POC troponin assay (Cobas h232, Roche diagnostics, Basel, Switzerland) is less sensitive than high-sensitivity assays in the hospital laboratory (has a lower limit of detection of 40 ng/L, which is above the 99th percentile of normal on the high-sensitivity troponin T assay in the laboratory (14 ng/L), so patients with a low POC troponin concentration could have mildly increased high-sensitivity troponin concentrations. Follow-up was performed by telephone and e-mail, which could result in a certain degree of misclassification because of the recall bias of the patients. EQ -5D -5L questionnaires were not completed by all patients.*

Table A - 4: ROB of observational studies (nRCTs) with the ROBINS-I tool: Tn-POCTs

	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall bias
MACE at 30-day								
Norman et al. 2022 [13]	Serious*	Moderate**	Low	Serious***	Low	Serious*****	Low	**Critical**
Miller et al. 2022 [14]	Moderate[1]	Moderate[2]	Low	Serious[3]	Low	Moderate[4]	Low	**Serious**
PATIENT SATISFACTION								
Norman et al. 2022 [13]	Serious*	Moderate**	Low	Serious***	Serious****	Serious******	Low	**Critical**

***Emergency Department Assessment of Chest Pain Score (EDACS) is not validated in rural setting; Median time from index chest pain onset to presentation to rural practice was 15 hours (IQR: 3.1–40.2 hours); Small sample size (pilot study). Authors did not use appropriate statistical methods to control for the confounding factors.*

***Proportion identified as not needing transport to an urban hospital is dependent on the subjective judgement of the attending physicians that the patients they included in the pathway would normally have needed transportation, the true proportion of patients who can avoid hospital presentation may be misrepresented by this sample as cannot be ruled out that some patients presenting to the practices may have not been recorded in the customised template built into the practice management system and instead were transferred directly to hospital without pathway assessment.*

****13 (18.8%) patients classified as non-low risk who were not transferred for hospital assessment, against pathway guidance.*

***** Missing data for 25%.*

****** Pilot study, not confirmatory study, aims to pilot real-life feasibility and acceptability, and preliminary assessment of effectiveness and safety, not intended to make a precise estimate of effectiveness and safety. Estimated effect size is very likely overestimated in small sample size studies. Small sample size limits generalisability of the findings. Sensitivity for MACE was 100% in the non-low risk group, but the 95% CI was large (70% to 100%).*

******* Small sample size, pilot: 67 low-risk respondents (out of 111 patients) and 44 non-low risk patient respondents (out of 69 patients). Research nurse performed telephone follow-up at 30 days to complete the patient satisfaction survey. No data that this satisfaction questionnaire was validated. Outcome assessors aware of intervention status (assessment of the outcome is subjective), after 30-days possible self-reported data - recall bias*

[1] Rural hospitals, general practice and urgent care clinics; Median time from pain onset to assessment: 4 h and 36 min (interquartile range: 2–14 h and 30 min). Authors did not use appropriate statistical methods to control for the confounding factors.

[2]Final decisions to include patients in the study was left to the judgement of participating clinicians: likely that some patients judged to be high-risk, were referred directly to hospital, or that very low-risk patients were managed using clinical gestalt (number of these patients not enrolled in the study is unknown).

[3] 11% of patients were excluded due to protocol breaches either because only one troponin was drawn or there was an inadequate amount of time between samples (although all MACEs in this group were identified and managed appropriately). While this initially suggests that the deviations did not compromise patient safety, the potential for underestimating the risk due to incomplete testing could lead to unrecognized adverse outcomes, which might not have been captured due to the limitations in follow-up and data collection.

[4] Two POCTs used, which are not high sensitivity Troponin tests; POC-cTn has poor sensitivity for detecting AMI in isolation, its safety when combined with clinical assessment has previously been demonstrated in metropolitan EDs. It is not possible to directly translate this evidence to the NZ rural context because of the low-resource environment (a feature of rural and primary care clinical settings), as well as possible differences in the available troponin assays, the sociodemographic profile and underlying risk of ischaemic heart disease in the patient populations. Point-of-care testing was already being undertaken at the majority of the study sites and the researchers had no direct control of the quality standards being employed. Emergency Department Assessment of Chest Pain Score (EDACS) is not validated in rural setting.

Table A - 5: ROB of observational studies (nRCTs) with the ROBINS-I tool: D-Dimer-POCTs

	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall bias
Diagnostic accuracy								
Heerink et al. 2023 [15]	Moderate*	Moderate**	Low	Low	Low	Serious***	Low	**Serious**
User-friendliness								
Heerink et al. 2020 [16]	Serious[1]	Serious[1]	Serious[1]	Serious[1]	Low	Serious[2]	Low	**Critical**
Diagnostic failure rate and efficiency								
Van Maanen et al. 2020 [17]	Low	Low	Low	Serious[3]	Low	Critical[4]	Low	**Critical**

**Patients from 2 separate observational studies included and there is no information of explicit methods to adjust for potential confounding factors*

***Small number of patients suspected of having DVT had a risk score of ≥4 (according to guidelines, these patients would not require a D-dimer test, but would be eligible for direct ultrasound or imaging; study authors decided to include these patients nonetheless, as they aimed to include a population representative of everyday practice);*

****Direct clinical validation based on capillary whole blood finger stick samples, similar to the evaluation based on the 511 plasma samples distributed to all (5 + 1) devices, was not conducted (it was not feasible to achieve these numbers for capillary finger stick testing within a prospective clinical study), imaging results are not available for low-risk VTE-patients with a negative D-dimer result (as practice guidelines state that low-risk VTE-patients with a negative D-dimer result do not require further diagnostic testing)*

[1]Number of participants was limited (n=11) for assessing user-friendliness outcome and there is no information of explicit methods to adjust for potential confounding factors - group of 11 GP assistants, unfamiliar with the devices but familiar with CRP POC testing, were given a short instruction by a laboratory technician and all assistants were given a written instruction chart. They then directly carried out one D-dimer test on all five POC D-dimer test systems in a random order and completed a SUS questionnaire accordingly, along with a few additional questions about sample management and readability of displays and results.; SUS questionnaire for this outcome were not performed by laboratory technician (D-dimer tests were performed in a laboratory facility for general practice by an experienced laboratory technician).

[2]Participants (11 GP assistants) used blood samples that were available from venipunctures so aspects of sample collection by drawing blood from a finger-prick were not taken into account. As tests were performed by experienced laboratory technicians, problems in non-laboratory users may influence test results.

[3]CPR not correctly applied in 20.7% patients;

[4]Difference of the reference standard between referred and non-referred patients. For patients referred to secondary care, the reference standard consisted of further diagnostic procedures; in the non-referred patients, it consisted of a 3-month follow-up period. Differential verification might result in bias towards overestimating the safety (detection bias); During the inclusion period, the point-of-care test for D-dimer (Clearview Simplify) was withdrawn from the market, because of too many false-negative results likely due to periprocedural quality-related faults when performing the test (i.e., incorrect withdrawal of capillary blood or not keeping test cold enough until use), false-negative results likely resulted in more missed VTE diagnoses and therefore an underestimation of the safety of the CPRs. 8 of all 14 patients in whom a VTE diagnosis was missed in this study had false-negative results on this qualitative Clearview Simplify D-dimer. Out of 1509 patients, in only 357 (24%) patients (209 suspected DVT and 148 suspected PE), a quantitative D-dimer test was performed. 3 of the patients categorised as having a missed diagnosis of DVT were not referred to secondary care at their own request but did contribute to the calculated failure rate in the group in which the CPR was incorrectly applied; Authors did not perform a sample size calculation a priori, given that for diagnostic validation studies, clear methodological recommendations on how to estimate a reliable sample size calculation are only recently proposed (i.e., after the initiation of our study). Dataset did include a total number of 1447 patients suspected of VTE in primary care, with a total number of 268 outcome VTE events (230 DVT; 38 PE), allowing for robust statistical analyses notably for the full population; the stratified sub-analyses for DVT and PE separately though should be interpreted with caution, notably for those suspected of PE; Authors could not report on the long-term clinical outcomes. It could be hypothesised that when the CPRs are incorrectly applied, the time to diagnose VTE potentially increases. It has been speculated that such delay in diagnosis could lead to a higher risk of long-term complications, such as the post-thrombotic syndrome or chronic thromboembolic pulmonary hypertension, although these effects are still largely uncertain.

Appendix IV: Ongoing studies with Tn-POCTs and D-Dimer POCTs in ClinicalTrials.gov

Table A - 6: List of ongoing studies with Tn-POCTs in ClinicalTrials.gov

Study Identifier	Estimated completion date	Study type	Number of participants/Setting/ Country	Intervention	Comparator	Patient population	Primary endpoints
NCT05827237, **POB HELP**, Rule Out of ACS in Primary Care Using a Decision Rule for Chest Pain Including Hs-troponin I POCT [25] *Published Protocol: van den Bulk et al. 2023* [26]	September 2024	Clustered diagnostic open-label **RCT**	1500 estimated, actual 946 / **Primary care** / Netherlands	Dg test: Clinical decision rule for acute chest pain, consisting of the **Marburg Heart Score** (5 questions) **combined with** a **high-sensitive troponin I point of care test (Siemens Atellica VTLi immunoassay analyser)**	Standard care (Patients in whom the general practitioner decides upon referral following local guidelines)	Adults with acute chest pain seen by **general practitioner**	**Hospital referral rate for acute chest pain** (24 h, 6 weeks); **Diagnostic accuracy of the clinical decision rule** (6 weeks, 6 months) (i.e., sensitivity, negative predictive value) **for Acute coronary syndrome (ACS) and Major Adverse Cardiac Events (MACE)** MACE is defined as a combined endpoint of ACS, percutaneous coronary intervention, coronary artery bypass grafting, coronary angiography revealing procedurally correctable stenosis managed conservatively and all-cause mortality.
NCT04904107, **URGENT 2.0** A Multicentre Randomized Controlled Trial to Improve the accUracy of Referrals to the emerGency departmEnt of patieNts With chesT Pain by Using the modified HEART Score in Emergency Medical Transport [27]	June 2024	RCT, double-blind	852 estimated / pre-hospital, in emergency medical transport / Netherlands	Diagnostic Test: **modified HEART score (including POC hs cTnI analysis)** The modified HEART score: acronym for history, ECG, age, risk factors and troponin at arrival. The components can be rated 0,1 or 2 points each and result in a total score between 0 and 10.	Standard care and triage according to the local (EMT) protocol	Age ≥ 18 years. Chest pain or other complaints suspect of ACS for at least 2 hours where the **GP or emergency medical personnel** are in need of further diagnostics or risk stratification to come to a decision of referral	The incidence of non-cardiac chest pain (NCCP) patients admitted at the cardiac ED (percentage, %) [Time Frame: 30 days] The incidence of MACE (percentage, %) [Time Frame: 30 days, 6 months and 1 year]

Abbreviations: *ASC – acute coronary syndrome; ED – emergency department; ECG - electrocardiography; HEART - History, Electrocardiogram, Age, Risk Factors and Troponin; GP - general practitioners; MACE – major adverse cardiac events; POC - point of care; hs cTnI – high-sensitivity cardiac troponin I; EMT – emergency medical transport; RCT – randomised controlled trial*

Table A - 7: List of ongoing studies with D-Dimer-POCTs in ClinicalTrials.gov

Study Identifier	Estimated completion date	Study type	Number of participants/Setting/ Country	Intervention	Comparator	Patient population	Primary endpoints
NCT05109260, Destiny: D-dimer. Investigating D-dimer Levels Using Point-of-Care (POC)Testing at Primary Care. Observational prospective study [40]	September 2022	Observational feasibility study	244/UK primary care patients	2 POC Immunoassay devices: one will measure D-dimer levels in capillary blood, the other will measure venous: **Roche Cobas H 232 POC D-dimer test** **Lumira Dx D-dimer test**	Laboratory test	Subject >18 years of age. Initial assessment of thrombosis. Consent provided. Patient declared healthy and suitable for participation by PI. Suitable venous access.	D-dimer levels across devices and to standalone testing at secondary care facilities
NCT04737954, EMBOL1 A Performance Evaluation of the **LumiraDx Point Of Care D-dimer** Assay, Observational prospective study [41]	June 2022	Observational prospective study	1000 /Germany, UK	**LumiraDx POC D-Dimer** assay	Laboratory test	Subject >18 years of age able to provide written informed consent presenting with symptoms of Venous thromboembolism (VTE), which mainly comprises deep vein thrombosis (DVT) or pulmonary embolism (PE)	Determine the accuracy of the LumiraDx POC D-Dimer assay when compared to a reference method in patients with suspected VTE. [Time Frame: 2 months] Measurement of blood samples from patients with suspected VTE in a reference method and in the LumiraDx method to assess accuracy of the LumiraDx method. Assessment of accuracy of using the D-Dimer cut-off set by the LumiraDx D-Dimer test in excluding patients with symptoms of VTE (DVT and PE) when used in combination with the pre-probability test (Wells Score). [Time Frame: 10 months] Measurement of blood samples from patients with suspected VTE in the LumiraDx D-dimer assay in conjunction with pre-test probability score and final clinical outcome in order to set a clinical cut-off for the LumiraDx D-dimer assay

Abbreviations: *UK - United Kingdom; POC - point of care; VTE – venous thromboembolism; DVT - deep vein thrombosis; PE - pulmonary embolism*

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