POCT/Point of Care Tests: D-Dimer und Troponin

EUnetHTA-Report

Endbericht

eunethta

Ludwig Boltzmann Institut
Health Technology Assessment

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Inhalt

1 Hintergrund

1.1 Technische Charackteristika

Die Biomarker Troponin (Tn) und D-Dimer können mittels Testung im Zentrallabor (engl. Central laboratory = CL) oder mittels Point of Care Tests (POCTs) gemessen werden. POCTs bieten eine schnelle Rückmeldung der Testergebnisse und ermöglichen schnellere Entscheidungen über das PatientInnenmanagement. Sowohl die Probenahme als auch die Datenanalyse wird am gleichen Standort durchgeführt, wodurch Transport- und Verarbeitungsverzögerungen reduziert werden.

Biomarker Tests: Tn & D-Dimer

POCT ermöglicht schnelle Diagnostik

Tn-POCT und D-Dimer POCT können zur Unterstützung der Diagnose von PatientInnen mit Symptomen verwendet werden, die auf ein akutes Koronarsyndrom (ACS) bzw. eine venöse Thromboembolie (VTE) hinweisen. Theoretische Vorteile von POCT sind schnellere Bearbeitungszeiten (engl. Turnaroundtime = TAT), kürzere Verweildauer und weniger unnötige Krankenhausaufenthalte bzw. weitere Tests. Spezifisch für die einzelnen Biomarker-Schnelltests werden folgende Szenarien diskutiert:

Tn-POCT: akutes Koronarsyndrom

D-Dimer POCT: venöse Thromboembolie

- **Tn-POCT** soll insbesondere dort einen besonderen Stellenwert haben, wo Troponin-Tests in einem Zentrallabor nicht vor Ort oder nicht 24 Stunden am Tag verfügbar sind, da der Zeitfaktor für die Diagnose des akuten Koronarsyndroms entscheidend ist.
- **D-Dimer POCT** soll beispielsweise bei der Hausärztin/dem Hausarzt zum Einsatz kommen, um vorwiegend unnötige Krankenhauseinweisungen/weitere Testungen zu reduzieren.

Die untersuchten POC-Diagnostika können sowohl in der Notfallmedizin (z. B. Notfallambulanz im Krankenhaus) als auch in ambulanter Versorgung (z. B. durch AllgemeinmedizinerInnen und FachärztInnen) eingesetzt werden. Tn-POCT kann zudem in anderen präklinischen notfallmedizinischen Settings wie z. B. im Krankenwagen verwendet werden.

Settings: Notfallmedizin (z. B. Notfallambulanz, Krankentransport) Ambulante Versorgung (z. B. niedergelassener Bereich)

Für Tn-POCT wurden 15 Geräte für diesen EUnetHTA-Bericht identifiziert. Davon messen 14 Geräte Troponin quantitativ und ein weiteres Gerät qualitativ. Für D-Dimer POCT wurden elf Geräte identifiziert, von denen acht D-Dimer quantitativ messen. In Anbetracht der Eigenschaften der identifizierten Geräte ist zu konstatieren, dass diese zwischen den Geräten sowohl in Bezug auf analytische Charakteristika (z. B. Unterschiede in Probengröße) als auch auf weitere technologische Merkmale (z. B. ob sie mit einem anderen Gerät verbunden werden können, auf dem die Diagnosedaten gespeichert werden können) heterogen sind.

26 POCT Produkte identifiziert: 15 Tn-POCTs 11 D-Dimer POCTs

Für D-Dimer Tests unterscheiden sich die von der Food and Drug Administration (FDA) zugelassenen handelsüblichen Geräte in Bezug auf Referenzwerte und klinische Cut-offs stark. Ähnlich dazu sind Troponin-Testverfahren – unabhängig davon, ob sie in einem CL oder am „Point of Care" getestet werden – weder standardisiert noch harmonisiert. Das heißt: Assays verwenden oft leicht unterschiedliche Ansätze, wie Troponin im Blut erfasst wird.

Heterogenität der technischen Charakteristika

Für diesen Bericht dient die übliche Versorgung („usual care") als Komparator. Je nach Setting kann dieser einen Versorgungspfad mit oder ohne Möglichkeit einer prompten Zentrallabortestung darstellen.

Komparator: übliche Versorgung

1.2 Gesundheitsproblem und aktuelle Nutzung

1.2.1 Tn-POCT: Akutes Koronarsyndrom

akutes Koronarsyndrom Myokardinfarkt/ Ischämie

Das akute Koronarsyndrom (engl. acute coronary syndrome = ACS) ist ein Gesundheitszustand, welcher mit verschiedenen Symptomen (v. a. Brustschmerz) einhergeht und im Wesentlichen von einem verminderten Blutfluss in den Koronararterien (Myokardischämie) verursacht wird. Der Begriff ACS wird für PatientInnen 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.

Risikofaktoren, die die Wahrscheinlichkeit einer ACS-Entwicklung erhöhen könnten, sind hohes Lebensalter, männliches Geschlecht, eine positive Familienanamnese der koronaren Herzkrankheit, das Vorliegen einer peripheren arteriellen Verschlusskrankheit, Diabetes mellitus, Hyperlipidämie, Hypertonie, Niereninsuffizienz, frühere Myokardinfarkte (MI) und vorherige Revaskularisierung.

ischämische Erkrankungen häufige Todesursache

Ischämische Herzerkrankungen gehören nach wie vor zu den häufigsten Todesursachen weltweit. In Europa sterben jährlich etwa 1.800.000 Menschen an ischämischen Herzerkrankungen. Das sind 20 Prozent aller Todesfälle, wenngleich Unterschiede zwischen den Ländern zu verzeichnen sind.

Brustschmerzen: rasche Diagnostik notwendig

Es ist wichtig, die Ursache der Brustschmerzen schnell zu erkennen, um umgehend mit einer geeigneten Therapie beginnen zu können, da sich bei einer frühzeitigen Intervention bessere Ergebnisse erzielen lassen: Das vorrangige Ziel einer frühen Evaluierung/Erstbewertung ist es, die Diagnose von ACS zu bestätigen („rule-in“) oder ACS als Ursache der Symptome auszuschließen („rule-out“).

Die Zielpopulation für die Anwendung von Tn-POCT sind erwachsene PatientInnen mit Anzeichen und Symptomen von ACS. Bei allen PatientInnen mit Verdacht auf kardiale Ischämie sollten im Rahmen der Erstuntersuchung kardiale Biomarker getestet werden. Herzspezifisches Troponin ist der am weitesten verbreitete diagnostische Biomarker für den Myokardinfarkt (MI).

Standardversorgung bei ACS:

sofortige Linderung der Ischämie/Prävention eines Myokardinfarkts

Die Standardversorgung von PatientInnen, die mit ACS behandelt werden, einschließlich solcher mit wiederkehrenden Symptomen, ischämischen EKG-Veränderungen oder positiven kardialen Troponinen, ist die Aufnahme ins Krankenhaus. Der Schwerpunkt in den ersten 12 Stunden liegt auf der sofortigen Linderung der Ischämie und der Prävention des Myokardinfarkts und schließlich des Todes. Die PatientInnen werden einer kontinuierlichen EKG-Rhythmusüberwachung und Beobachtung bei rezidivierender Ischämie unterzogen. PatientInnen mit Verdacht auf ACS in der Ambulanz werden im präklinischen Umfeld beurteilt und vor Aufnahme ins Krankenhaus behandelt, was unter anderem die Verabreichung einer dualen Thrombozytentherapie beinhaltet.

1.2.2 D-Dimer POCT: Venöse Thromboembolien

venöse Thromboembolie umfasst Lungenembolie und tiefe Venenthrombose

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.

häufig unspezifische Anzeichen

Klinische Anzeichen und Symptome von VTE sind unspezifisch und oft asymptomatisch. Folgende Symptome können jedoch auf eine TVT hinweisen: Beinschmerzen und/oder Schwellungen, Rötungen und Wärme im Bein. Häufige Symptome der LE sind, unter anderem, Dyspnoe, Brustschmerzen, Präsynkope oder Synkope, Fieber, Husten oder einseitige Beinschmerzen. VTE kann in der akuten Phase tödlich sein oder zu chronischen Krankheiten und Behinderungen führen, was die langfristige Lebensqualität und Funktionsfähigkeit der PatientInnen beeinträchtigt.

dritthäufigste Herz-Kreislauf-Erkrankung

VTE ist die dritthäufigste Herz-Kreislauf-Erkrankung. Die jährliche Gesamtinzidenz beträgt 100-200 pro 100.000 Einwohner in Europa. PatientInnen, die älter als 40 Jahre sind, sind einem erhöhten Risiko ausgesetzt, und das Risiko verdoppelt sich mit jedem Folge-Jahrzehnt.

Diagnosealgorithmus: Einschätzung Prätestwahrscheinlichkeit, D-Dimer Test, etwaige weitere Untersuchungen

Der Diagnosealgorithmus für DVT und LE beginnt mit der ersten Bewertung der Prätestwahrscheinlichkeit. Die Messung des D-Dimers ist der zweite Schritt; dies wird in der Regel mit einem klinischen Vorhersagewert kombiniert. Bei positivem D-Dimer Test folgen weitere Untersuchungen, wie z. B. Ultraschall zur Diagnose einer TVT, Beatmungs-Perfusions-Scan und Computertomographie-Lungenangiographie zur Diagnose von PE.

Die Zielpopulation für die Verwendung von D-Dimer POCT sind erwachsene PatientInnen mit geringem bis mittlerem Risiko der TVT oder PE. Die Standard-Diagnostik für die TVT umfasst die Bildgebung: Vor dem Hintergrund der Kosten für bildgebende Verfahren und zunehmender Anzahl negativer Tests ist eine genaue Überlegung des diagnostischen Pfads wesentlich: Bei einigen PatientInnen besteht beispielsweise keine Notwendigkeit einer diagnostischen Bildgebung, um die Krankheit auszuschließen. Die diagnostische Aufarbeitung stützt sich dann auf die Wahrscheinlichkeitsbewertung vor dem Test, ergänzt durch die Ergebnisse des D-Dimer Tests.

Behandlung: Antikoagulation

Die gängige Standardbehandlung von VTE ist die Antikoagulation. Diese Medikamente „verdünnen“ das Blut und verhindern eine weitere Gerinnung.

2 Forschungsfragen

Forschungsfragen:

Leitlinienempfehlungen

Evidenz zum klinischen Nutzen von

Tn-POCT
D-Dimer POCT

Im Zuge dieses Projekts wurden vier Forschungsfragen gewählt:

- Was empfehlen evidenzbasierte Leitlinien, wie D-Dimer POCT und Tn-POCT eingesetzt werden sollen (Stellenwert in diagnostischem Pfad, Schwellenwerte in unterschiedlichen PatientInnenpopulationen: Notfallmedizin, niedergelassener Bereich)?
- Welchen klinischen Nutzen im Management von symptomatischen PatientInnen (Erwachsene) hat der D-Dimer POCT?
- Welchen klinischen Nutzen im Management von symptomatischen PatientInnen (Erwachsene) hat der Tn-POCT?
- Kann ein etwaiger theoretischer Nutzen von POCT (D-Dimer und Tn) im österreichischen Kontext realisiert werden?

3 Methodisches Vorgehen

3.1 Leitliniensynopse

Leitliniensynopse: Systematische Suche, manuelle Suche

Für die Leitliniensynopse wurde zunächst eine systematische Literatursuche nach relevanten evidenzbasierten Leitlinien in Leitliniendatenbanken („Guideline International Network (GIN), Trip Database) durchgeführt. Ergänzend dazu wurden ausgewählte Websites internationaler Institutionen (z. B. National Institute for Health and Care Excellence) zur Identifikation relevanter Leitlinien manuell durchsucht.

Leitlinienauswahl, Qualitätsbewertung

Die Leitlinienauswahl erfolgte durch zwei unabhängige WissenschafterInnen. Die Qualität der eingeschlossenen Leiltinien wurde mittels AGREE-II (Appraisal of Guidelines for Research & Evaluation) durch eine Person bewertet und durch eine andere Person kontrolliert.

Fokus auf Empfehlungen, wie/ob der Einsatz von POCTs empfohlen/diskutiert wird

Hinsichtlich der relevanten, zu extrahierenden, Daten der Leitlinien wurden Empfehlungen zur Anwendung der POCTs nach Stellenwert in diagnostischem Pfad, Schwellenwert und Aussagekraft der Testergebnisse in unterschiedlichen PatientInnenpopulationen (Notfallmedizin, Allgemeinmedizin) gewählt. Relevante Daten wurden von einer Person extrahiert und von einer zweiten verifiziert.

3.2 Overview of Reviews

systematische Suchen in 4 Datenbanken

Es wurden zwei systematische Übersichtsarbeiten von systematischen Übersichtsarbeiten (Overview of Reviews) zum patientInnenrelevanten Nutzen von POC-Diagnostika D-Dimer und Troponin erstellt. Dabei wurden zwei systematische Literatursuchen in folgenden Datenbanken durchgeführt:

- Cochrane (CENTRAL)
- Centre for Research and Dissemination (CRD)
- Embase
- Ovid MEDLINE

Update Suche nach Primärstudien

Zusätzlich wurde jeweils eine Update-Suche der Evidenz für beide Biomarker POCTs auf Basis der bereits vorhandenen Suchstrategien, die von den identifizierten systematischen Übersichtsarbeiten zum Einsatz kamen, durchgeführt.

Studienselektion & Qualitätsbewertung

Zwei unabhängige WissenschafterInnen führten die Studienselektion und die Qualitätsbewertung der Studien durch. Zur Qualitätsbeurteilung der Studien kamen entsprechende Instrumente für systematische Übersichtsarbeiten (AMSTAR-2) und für nicht randomisierte Kontrollstudien (ROBINS-I) zum Einsatz. Die Datenextraktion wurde von einer Person durchgeführt und von einer zweiten Person verifiziert.

3.3 ExpertInneninvolvierung

ExpertInnen-Befragung für österr. Kontext

Zur Beantwortung der Frage hinsichtlich des österreichischen Kontexts wurden VetreterInnen der Notfallmedizin, der Allgemeinmedizin und der Fachmedizin (Kardiologie, etc.) gesucht und hinsichtlich der beiden Diagnostika befragt. Die Gespräche wurden protokolliert, gegenübergestellt und narrativ beschrieben.

4 Ergebnisse

Verfügbare Produkte

26 verfügbare Produkte: Heterogenität (quantitativ, qualitativ) und Ungewissheit, welche in Ö zum Einsatz kommen

Es wurden im Zuge der manuellen Suche nach relevanten Produkten 26 POC-Diagnostika identifiziert. Davon messen 15 Geräte Troponin und elf Produkte D-Dimer. Die meisten Produkte messen die Biomarker quantitativ (Tn: 14/15; D-Dimer: 8/11). Es zeigte sich zudem, dass Heterogenität hinsichtlich der analytischen Performanz und technologischen Charakteristika besteht. Es herrscht Unsicherheit darüber, welche Diagnostika in Österreich zum Einsatz kommen.

4.1 Tn-POCT

Verfügbare Evidenz

2 SRs moderat bis hohe Qualität

Für die Bewertung des klinischen Nutzens der Implementierung von Tn-POCT wurden zwei systematische Übersichtsarbeiten mit moderat bis hoher Qualität eingeschlossen; wovon eine ein HTA-Bericht der Canadian Agency for Drugs and Technologies in Health (CADTH) mit ähnlicher Fragestellung war. Es konnten keine weiteren Primärstudien im Zuge der Update-Suche identifiziert werden.

42 Primärstudien davon 7 RCTs

Die beiden systematischen Übersichtsarbeiten enthielten 42 Primärstudien. Der CADTH-Bericht identifizierte 41 Primärstudien. Von diesen untersuchten neun Studien die diagnostische Genauigkeit von Tn-POCT und 30 Studien den klinischen Nutzen. Weitere zwei Studien wurden vom CADTH-Bericht eingeschlossen, die sowohl die diagnostische Testgenauigkeit als auch den klinischen Nutzen untersuchten. Die andere eingeschlossene systematische Übersichtsarbeit identifizierte zwei Studien im Setting der Primärversorgung, wovon eine dieser Studien auch im CADTH-Bericht eingeschlossen wurde. Die Gesamtzahl der PatientInnen wurde im CADTH-Bericht nicht berichtet und in der anderen systematischen Übersichtsarbeit betrug diese 545 PatientInnen.

8 Leitlinien: 3 LL nachdrücklich zu empfehlen, 3 LL unter Vorbehalt zu empfehlen, 2 LL nicht zu empfehlen/unsicher

Darüber hinaus erfüllten acht Leitlinien unsere Einschlusskriterien und wurden im Zuge der Leitliniensynopse eingeschlossen. In Bezug auf die Qualität (AGREE-II) waren jeweils drei Leitlinien nachdrücklich zu empfehlen, bzw. unter Vorbehalt zu empfehlen. Die beiden verbleibenden Leitlinien sind nicht zu empfehlen bzw. als unsicher anzusehen.

Overview of Reviews

Overview of Reviews: 1 CADTH-Bericht, 11 Studien zu DTA (POCT vs CL): Niedrigere SEN/npW Höhere SPEZ/ppW

1 weiterer SR: 2 Studien zu DTA (nicht komparative Daten)

Die Ergebnisse in Bezug auf die diagnostische Testgenauigkeit zeigen, dass erhebliche Inkonsistenzen hinsichtlich Aussagen zur diagnostischen Genauigkeit bestehen. Diese sind vor allem in den elf, vom CADTH-Bericht eingeschlossenen, Studien ersichtlich. Des Weiteren gab es bedeutende Einschränkungen bei der Studienqualität der Primärstudien (z. B. ausschließlich nichtvergleichende Studien in der anderen systematischen Übersichtsarbeit). Die im CADTH-Bericht gefundene Evidenz zeigt, dass Tn-POCT im Vergleich zu CL-Tests tendenziell eine geringere Sensitivität, einen niedrigeren negativen prädiktiven Wert (npW), eine höhere Spezifität und einen höheren positiven prädiktiven Wert (ppW) aufweist.

Klinischer Nutzen: 32 Primärstudien

Die beiden inkludierten systematischen Übersichtsarbeiten umfassten 32 Studien, die den klinischen Nutzen von Tn-POCT untersuchten. Davon waren sieben Studien randomisierte Kontrollstudien (RCTs). Im Allgemeinen ist die identifizierte Evidenz unzureichend, um eine Nicht-Unterlegenheit der Implementierung von Tn-POCT gegenüber CL-Tests nachweisen zu können, wenn CL-Tests vor Ort oder rechtzeitig verfügbar sind (z. B. in der Notfallambulanz). Die Evidenz ist ebenfalls unzureichend, um eine deutliche Überlegenheit gegenüber der Standardversorgung in Settings ohne oder mit verzögerter CL-Testung (z. B. bestimmte ambulante Einrichtungen, präklinische Notfallmedizin) zu zeigen.

Notfallambulanz (Krankenhaus)

Notfallambulanz: unzureichende Evidenz für Nicht-Unterlegenheit (POCT vs. CL)

Die im CADTH-Bericht gefundene Evidenz weist darauf hin, dass die Implementierung von Tn-POCT in der Notfallambulanz die TAT (Reduzierung in 2 RCTs), die Entlassungszeit (Reduzierung in 2 RCTs & 1 Beobachtungsstudie) und die Verweildauer (Reduzierung in 3 RCTs und 2 Beobachtungsstudien, Erhöhung in 1 RCT) reduzieren kann. Darüber hinaus hat die Verwendung von Tn-POCT die Mortalität (2 RCTs, 3 Beobachtungsstudien) oder unerwünschte Ereignisse (2 RCTs, 2 Beobachtungsstudien) im Vergleich zu CL-Tests bis zu einem Jahr nicht statistisch verändert. Die Lebensqualität unterschied sich auch nicht statistisch signifikant bis zu einem Follow-up von drei Monaten (1 RCT). Allerdings ist die Evidenz unzureichend, um die Nicht-Unterlegenheit von Tn-POCT im Vergleich zum CL-Test nachzuweisen – vor allem vor dem Hintergrund der schlechteren Sensitivität und des niedrigeren negativen prädiktiven Werts, wie vorstehend dargestellt.

Ambulante Versorgung (insb. AllgemeinmedizinerInnen und FachärztInnen)

ambulante Versorgung: unzureichende Evidenz für Überlegenheit (POCT vs. klinische Einschätzung + ggf. CL zu späterem Zeitpunkt)

Es wurde unzureichende Evidenz für die Überlegenheit der Verwendung eines Pfades mit Tn-POCT im Vergleich zur Standardversorgung (ohne Tn-POCT) auf der Grundlage der gewählten Endpunkte zum klinischen Nutzen gefunden: Die Evidenz aus einer Kohortenstudie, die durch beide der enthaltenen systematischen Übersichtsarbeiten identifiziert wurde, deutet darauf hin, dass die Einführung von Tn-POCT die Überweisungsraten reduzieren kann. Es wurden keine Nachweise dafür gefunden, dass die Umsetzung von Tn-POCT eine positive oder schädliche Auswirkung auf die Mortalität/Morbidität oder die gesundheitsbezogene Lebensqualität hat.

Präklinische Notfallmedizin (insb. Krankenwagen)

unzureichende Evidenz für Überlegenheit (POCT vs. klinische Einschätzung + ggf. CL zu späterem Zeitpunkt)

Derzeit gibt es keine ausreichende Evidenz dafür, dass die Verwendung eines Pfades mit Tn-POCT im Vergleich zur Standardversorgung (ohne Tn-POCT) etwa im Krankenwagen basierend auf ausgewählten klinischen Endpunkten überlegen ist: Der CADTH-Bericht fand jedoch Evidenz (1 RCT), die keinen Unterschied in der Krankenhausaufnahme aufweist, und einer nicht statistisch-signifikanten Verkürzung der Zeit vom ersten medizinischen Kontakt bis zur Entlassung aus der Notfallambulanz oder der Aufnahme ins Krankenhaus. Der CADTH-Bericht identifizierte zudem eine Beobachtungsstudie, die eine durchschnittliche TAT von 83 Minuten (Range: 46-187) berichtete. Hinsichtlich der Mortalität fand der CADTH-Report Evidenz (1 RCT), die keinen Unterschied bei der 30-Tages Mortalität zeigte. Die Berichterstattung der Ergebnisse ist jedoch stark begrenzt: Es fehlten wichtige weitere Informationen (z. B. genaue Überlebensraten oder p-Werte). Es wurden keine Hinweise auf die möglichen Auswirkungen der Einführung von Tn-POCT auf die Lebensqualität gefunden.

Schaden/Nachteile

Sicherheit: keine/unzureichend direkte Evidenz,

Im Hinblick auf die Sicherheit von Tn-POCT hat keine der identifizierten Überprüfungen Nebenwirkungen/Nachteile als solche hervorgehoben. Daten zur diagnostischen Genauigkeit können jedoch indirekt darauf hinweisen, ob Schäden durch falsch positive/falsch negative Befunde zu erwarten sind.

1 Kohortenstudie: Verweis, dass Rückgang der Überweisung durch POCT negative Konsequenzen haben könnte (2/178 pts mit UA/MI wurden entlassen)

Nur eine einzige Studie, die in beiden systematischen Übersichtsarbeiten identifiziert wurde, berichtete direkt über den Schaden von entlassenen PatientInnen mit einem ACS: Die Evidenz bestand aus einer Kohortenstudie (Setting: ambulante Versorgung), die einen Rückgang der Überweisungen berichtete, der jedoch das Risiko erhöhen kann, PatientInnen mit einem akuten Myokardinfarkt oder einer instabilen Angina pectoris zu entlassen. Zwei von 178 PatientInnen in der Tn-POCT-Gruppe erhielten keine Überweisung, obwohl sie diese benötigt hätten (Überweisungsrate: 25 % und 43 % der PatientInnen, die von Ärzten betreut werden, die Tn-POCT verwenden und nicht verwenden). Der p-Wert war jedoch nicht verfügbar.

Leitliniensynopse

8 Leitlinien

Acht Leitlinien erfüllten die Einschlusskriterien und wurden für die Leitliniensynopse eingeschlossen. Sechs Leitlinien umfassten verschiedene Settings (z. B. Notfallambulanz, prähospitale Notfallmedizin, Primärversorgung, etc.), eine Leitlinie fokussierte auf Katastrophenmedizin und eine weitere Leitlinie definierte keine Settings.

unterschiedliche Settings

keine spezifischen Empfehlungen zu optimaler Zeitpunkt/ Schwellenwerte etc.

Keine der enthaltenen Leitlinien gibt eine Empfehlung bezüglich des optimalen Zeitpunkts der Tests sowie der diagnostischen Schwellenwerte und Pfade ab, mit der Begründung, dass sich die POCTs kontinuierlich und schnell verbessern und ihre Leistungsmerkmale sowohl vom Test als auch vom Krankenhaus abhängig sind. Eine Leitlinie besagt ausdrücklich, dass aufgrund fehlender oder schwacher Evidenz keine Empfehlungen zugunsten/gegen die Verwendung von Tn-POCT abgegeben werden können. Fünf weitere Leitlinien erwähnen nur, dass POCT für die Messung von kardialen Troponinen verwendet werden kann. Eine Leitlinie empfiehlt, den qualitativen Troponin-Test nicht routinemäßig in der hausärztlichen Praxis einzusetzen, um einen akuten Myokardinfarkt auszuschließen, und eine weitere Leitlinie empfiehlt nur die Verwendung von sensitiver oder hoch-sensitiver Tests.

konsistente Empfehlung für Tn-POCT bei TAT < 1 Std von 2 LL

Drei Leitlinien betonen, dass die TAT für die Prüfung von Herzmarkern maximal eine Stunde betragen sollte. Zwei Leitlinien kommen zu dem Schluss, dass eine Implementierung dann sinnvoll ist, wenn eine TAT von einer Stunde nicht eingehalten werden kann.

Empfehlung für quantitative Messung von 1 LL

Des Weiteren wurde eine Leitlinienempfehlung hinsichtlich der technischen Charakteristika der Tests abgegeben: Die Leitlinie empfiehlt, dass Troponintests nicht nur qualitative, sondern auch quantitative Informationen liefern sollten.

Senitivität von Tn-POCT kontroversiell: 2 LL: geringer als CL, 1 LL: in UK lizenzierte Tn-POCTs vergleichbar mit CL (12 stündig)

Die Sensitivität ist Bestandteil der Diskussion in den identifizierten Leitlinien: 2 Leitlinien sagen aus, dass die Sensitivität von Tn-POCT unter der von CL-Tests liegt und daher nicht als sensitiv oder hoch sensitiv angesehen werden kann. Eine andere Leitlinie besagt dagegen, dass Tn-POCT (lizensiert in UK) in seiner Sensitivität den 12-stündigen laborbasierten Standard-Tn-Assays entspricht. Nach Angaben einer weiteren Leitlinie können Tn-POCT-Werte erste diagnostische Informationen liefern, aber der Vorteil einer kürzeren TAT steht einer geringeren Sensitivität, einer geringeren diagnostischen Genauigkeit und einem niedrigeren negativen prädiktiven Wert gegenüber. Darüber hinaus begünstigt die strenge quantitative Assay-Standardisierung, die für die Routinediagnose erforderlich ist, die CL-Tests.

Einschränkung: Publikationsdatum aller LL vor 2016, Aktualität?

Eine wesentliche Einschränkung der identifizierten Leitlinien besteht darin, dass in den letzten drei Jahren (vor 2016) keine Leitlinien veröffentlicht wurden, wodurch ein Mangel rezenter Leitlinien besteht.

ExpertInnenbefragung

Im Hinblick auf die österreichische Situation waren die von uns konsultierten ExpertInnen der Ansicht, dass es ein theoretisches Potenzial von Tn-POCT in Situationen gibt, in denen ein CL-Test nicht verfügbar wäre oder zu lange dauern würde, bis die Ergebnisse vorliegen. Es besteht jedoch Zweifel, ob solche Szenarien in Österreich tatsächlich existieren.

Input von ExpertInnen: theoretischer Vorteil in Settings ohne CL-Tests, Zweifel, ob es diese in Ö gibt

4.2 D-Dimer POCT

Verfügbare Evidenz

Insgesamt wurden sechs systematische Übersichtsarbeiten mit moderat bis hoher Qualität in diesem Bericht eingeschlossen. Im Zuge der Update-Suche wurden zusätzlich zwei Primärstudien eingeschlossen, welche auf die TVT fokussierten und in den systematischen Übersichtsarbeiten unzureichend berücksichtigt wurden.

6 SRs: moderat bis hohe Qualität

Die systematischen Übersichtsarbeiten erzielten eine moderat bis hohe Qualität nach AMSTAR-2. Das Verzerrungspotenzial der eingeschlossenen nicht randomisierten kontrollierten Studien (NRCTs) war moderat bis schwerwiegend nach Robins-I.

2 NRCTs: moderat-schwerwiegendes Verzerrungspotenzial

In den sechs systematischen Übersichtsarbeiten wurden zwischen vier und 52 Studien eingeschlossen (199-55.268 PatientInnen).

4-52 eingeschlossene Studien (199-55.268 pts)

Darüber hinaus erfüllten zehn Leitlinien die Einschlusskriterien. Hinsichtlich der Qualität (AGREE-II) ist zu konstatieren, dass fünf Leitlinien nachdrücklich, und die verbleibenden fünf Leitlinien nur unter Vorbehalt zu empfehlen sind.

10 Leitlinien: 5 LL nachdrücklich zu empfehlen & 5 LL empfehlenswert unter Vorbehalt

Overview of Reviews

Im Zuge dieser Übersichtsarbeit wurde relevante Evidenz in der ambulanten Versorgung (3 systematische Übersichtsarbeiten), der Notfallambulanz im Krankenhaus (2 systematische Übersichtsarbeiten) gefunden. Eine weitere identifizierte systematische Übersichtsarbeit berichtete nicht von den jeweiligen Settings der gefundenen Evidenz. Die zwei identifizierten Primärstudien fokussierten auf den Einsatz von D-Dimer POCT in der Primärversorgung.

Settings: ambulante Versorgung (3 SRs + 2 Primärstudien) Krankenhaus-Setting: 2 SRs NR in 1 SR

Insgesamt mangelt es an zuverlässigen und qualitativ hochwertigen Nachweisen für die Nicht-Unterlegenheit gegenüber CL-Tests und für die Überlegenheit gegenüber der üblichen Versorgung (ohne sofortige CL-Tests) in der Notfallversorgung oder ambulanten Versorgung (insb. AllgemeinmedizinerInnen und FachärztInnen).

Ambulante Versorgung (insb. AllgemeinmedizinerInnen und FachärztInnen)

ambulante Versorgung: POCT + klinische Entscheidungsregel führt zu genauerer Diagnose bei Verwendung von oligosymptomatischen Pts

Im Setting der ambulanten Versorgung deutet die Evidenz darauf hin, dass die Kombination von D-Dimer POCT (insbesondere der quantitativen Testungen) mit einer klinischen Entscheidungsregel (z. B. durch die Hausärztin/den Hausarzt) bei Verwendung bei oligosymptomatischen PatientInnen mit geringer Wahrscheinlichkeit für VTE zu einer genaueren Diagnose von VTE führt als ohne POCT. Der negative prädiktive Wert des kombinierten D-Dimer POCT und der klinischen Entscheidungsregel ist hoch (>95 %), was bedeutet, dass unnötige Bildgebung in einem Krankenhaus vermieden werden könnte. Der effiziente Einsatz eines D-Dimer POCT in Kombination mit einer klinischen Entscheidungsregel erfordert jedoch Training, Expertise und Praxis.

keine direkte Evidenz aus SRs

Es wurde jedoch keine Evidenz gefunden, die die Auswirkungen der Einführung von D-Dimer-POCT auf Mortalität/Morbidität, Lebensqualität oder PatientInnenmanagement in der ambulanten Versorgung direkt untersucht.

2 NRCTs
TAT: <5 min-34 min
Überweisungsraten: keine s. s. Unterschiede zwischen IG und CG

Zwei identifizierte Primärstudien, die die Evidenz aus systematischen Übersichtsarbeiten aktualisierten, berichteten von Daten in Bezug auf Turnaround-Zeit (1 Studie: <5 min-34 min) und Überweisungsraten (1 Studie: kein s. s. Unterschied zwischen Intervention und üblicher Versorgung). Aufgrund des erhöhten Verzerrungspotenzials der Studien konnte der Evidenzkörper jedoch nicht maßgeblich verändert werden.

Notfallambulanz (Krankenhaus)

Notfallmedizin: unzureichende Evidenz in Notfallambulanz: 1 SR

Reduktion TAT & Krankenhauseinweisungen, Aufenthaltsdauer

Evidenzbasis: Beobachtungsstudien

Hinsichtlich der möglichen Auswirkungen der Implementierung von D-Dimer POCT in der Notfallambulanz berichtete eine identifizierte systematische Übersichtsarbeit von Evidenz zur Auswirkung der Implementierung von D-Dimer POCT auf das PatientInnenmanagement. Die Qualität des Berichts war jedoch moderat. Basierend auf Beobachtungsstudien konnte festgestellt werden, dass die Implementierung von D-Dimer POCT womöglich mit einer Reduzierung der TAT, der Anzahl der Krankenhauseinweisungen und der Aufenthaltsdauer einhergehen könnte. Eine weitere systematische Übersichtsarbeit identifizierte Evidenz in der Notaufnahme berichtete aber ausschließlich über nicht-vergleichende Daten in Bezug auf „failure rates“ und Effizienz. Keine der in diesen Settings identifizierten Übersichtsarbeiten berichtete über die diagnostische Testgenauigkeit für D-Dimer POCT.

Allgemein war daher die Evidenz unzureichend, um einen positiven Einfluss auf das PatientInnenmanagement nachweisen zu können. Es wurde zudem keine Evidenz gefunden, die eine mögliche Auswirkung der Implementierung auf die patientInnenrelevanten Endpunkte Mortalität/Morbidität sowie Lebensqualität überprüft.

Sicherheit: nicht direkt gemessen Eruieren der Vor- und Nachteile auf Basis indirekter Evidenz (DTA)

Schaden/Nachteile

Im Hinblick auf die Sicherheit hat keine der identifizierten systematischen Übersichtsarbeiten Nebeneffekte/Nachteile als solche hervorgehoben. Die in diesem Bericht dargestellten Daten zur diagnostischen Genauigkeit können jedoch indirekt darauf hinweisen, ob Schäden durch falsch positive/falsch negative Befunde zu erwarten sind.

Die Evidenz bestätigt, dass D-Dimer POCT einen hohen negativen prädiktiven Wert hat, sehr sensitiv, aber nicht sehr spezifisch ist. Die Sensitivität des D-Dimer POCTs wird verbessert, wenn er mit einem klinischen Wahrscheinlichkeitswert vor dem Test kombiniert wird. Die systematischen Übersichtsarbeiten und Leitlinien stimmen überein, dass D-Dimer POCT ohne diesen nicht verwendet werden sollte. Die Spezifität von D-Dimer nimmt mit zunehmendem Alter stetig ab, so dass bei älteren Menschen altersgerechte Cut-offs erforderlich sind.

D-Dimer POCT sehr sensitiv, aber nicht sehr spezifisch

zum Ausschluss von VTE geeignet

Leitliniensynopse

Die Empfehlungen der zehn eingeschlossenen Leitlinien sind hinsichtlich der Verwendung von D-Dimer Tests konsistent: Acht von zehn Leitlinien kommen zu dem Schluss, dass D-Dimer POCT verwendet werden kann, um eine vermutete Lungenembolie oder eine tiefe Venenthrombose auszuschließen. Nur eine Leitlinie gibt aufgrund fehlender oder schwacher Evidenz gar keine Empfehlung ab und eine Leitlinie empfiehlt indirekt, dass kein Ultraschall erforderlich ist, wenn der D-Dimer Wert mit POCT gemessen werden kann.

10 Leitlinien

konsistente Leitlinienempfehlungen: 8/10 Leitlinien: D-Dimer POCT als Ausschlussdiagnostik

Die empfohlenen Settings für die Verwendung von D-Dimer POCT sind dagegen in den Leitlinien weniger konsistent erwähnt: Drei Leitlinien haben relevante Settings nicht definiert, drei Leitlinien definierten Allgemeinmedizin/Primärversorgung als mögliches Setting und eine weitere Leitlinie beschreibt, dass D-Dimer POCT in vielen Settings zur Anwendung kommen kann (Primär-, Sekundär-, Tertiärversorgung). Zwei weitere Leitlinien beschreiben, dass der Test in der Notfallambulanz und in weiteren ambulanten Settings zum Einsatz kommen kann. Eine weitere Leitlinie beschreibt sowohl ambulante als auch stationären Settings als mögliche Einsatzgebiete.

inkonsistente Empfehlungen hinsichtlich relevanter Settings

Zwei Leitlinienempfehlungen sind in Bezug auf die empfohlene Sensitivität des D-Dimer Tests inkonsistent. Eine Leitlinie besagt, dass der einfache qualitative D-Dimer POCT in Kombination mit der klinischen Wahrscheinlichkeit im Vergleich zum quantitativen ELISA-Test bei PatientInnen mit geringem Risiko in seinem Wert vergleichbar sein kann, während eine andere Leitlinie sich gegen die Verwendung von qualitativer oder semi-quantitativer Tests in der Primärversorgung ausspricht.

inkonsistente Empfehlungen hinsichtlich des Einsatzes qualitativer Tests

ExpertInnenbefragung

Im Hinblick auf die österreichische Situation gab es keinen klaren Konsens zum potentiellen Nutzen von D-Dimer POCT. Es ist festzuhalten, dass entsprechende Ausbildung und Fachwissen notwendig ist, um die Ergebnisse von POC-Diagnostika neben den Ergebnissen der Vortestwahrscheinlichkeit korrekt interpretieren zu können. Darüber hinaus ist die Kenntnis klinischer Entscheidungsregeln Voraussetzung für die Anwendung des Tests. Während zwei der ExpertInnen deshalb eher kritisch zum D-Dimer POCT im niedergelassenen Bereich in Österreich stehen, war eine Expertin der Ansicht, dass D-Dimer POCT eine unentbehrliche Rolle spielt und HausärztInnen die entsprechende Expertise mitbringen, um D-Dimer POCT richtig anwenden zu können.

5 Diskussion

Evidenz unzureichend, um Nicht-Unterlegenheit im Vergleich zu CL-Tests und Überlegenheit im Vergleich zur Standardversorgung nachweisen zu können

Ziel dieses Berichts war es, den klinischen Nutzen und die Sicherheit von Tn-POCT und D-Dimer POCT in der ambulanten Versorgung und der Notfallmedizin bei symptomatischen PatientInnen zu bewerten. Sowohl für Tn-POCT als auch für D-Dimer POCT gibt es keine ausreichenden Beweise, um eine Nicht-Unterlegenheit gegenüber CL-Tests und eine Überlegenheit gegenüber der aktuellen Situation (ohne sofortige CL-Tests) in der Notfallversorgung oder ambulanten Versorgung (insb. AllgemeinmedizinerInnen und FachärztInnen) nachzuweisen.

Limitationen: Evidenz zu DTA stammt aus systematischen Übersichtsarbeiten (mit ev. älteren POCTs)

Obwohl der Schwerpunkt dieses HTA-Berichts auf dem klinischen Nutzen liegt, wurde auch Evidenz für die diagnostische Genauigkeit, die in den eingeschlossenen systematischen Übersichtsarbeiten identifiziert wurde, berichtet. Diese Evidenz ist möglicherweise nicht aktuell, da neuere Tests nicht inkludiert waren. Verbesserungen im Bereich der diagnostischen Genauigkeit zeigen jedoch nur indirekt, ob der Einsatz der POCTs auch zu patientInnenrelevanten Vorteilen – wie dem Vermeiden unnötiger Interventionen und Krankenhausaufenthalte – führt.

Heterogenität der Produkte

verringert Aussagekraft der Evaluation

Des Weiteren wurden in den – diesem Bericht zugrundeliegenden – Übersichtsarbeiten sehr viele, oft heterogene, Produkte als Intervention definiert: Es wurden im Zuge der manuellen Suche nach relevanten Produkten 26 POC-Diagnostika identifiziert. Davon messen 15 Geräte Troponin und elf Produkte D-Dimer. Die meisten Produkte messen die Biomarker quantitativ (Tn: 14/15; D-Dimer: 8/11). Diese Heterogenität der Produkte – gepaart mit einer Unwissenheit darüber, welche dieser Tests nun in Österreich eigentlich zum Einsatz kommen – stellt eine wesentliche Limitation für die Validität der Aussage dieser Evaluierung dar.

laufende Studien: 5 Studien zu Tn-POCT

keine Studien zu D-Dimer POCT

Die Suche nach laufenden Studien ergab, dass es derzeit fünf laufende Studien zur Evaluierung der Verwendung von Tn-POCT in der Notfallambulanz gibt. Zwei davon sind RCTs und weitere drei identifizierte Studien sind NRCTs. Ergebnisse zum PatientInnenmanagement (z. B. LOS, TTD) werden in drei Studien gemessen, und zwei weitere Studien bewerten ausschließlich die diagnostische Performanz dieser Diagnostika. Für D-Dimer POCT wurden keine laufenden NRCTs oder RCTs identifiziert.

Übertragbarkeit der Ergebnisse, settingabhängigkeit, Limitationen klassischer EbM Methoden

Darüber hinaus ist zu erwähnen, dass alle Vorteile, die sich aus der Implementierung von Tn-POCT und D-Dimer POCT ergeben, stark vom Setting und dem Gesundheitssystem abhängig sind. Aus diesem Grund könnten Evaluierungsstudien im Bereich der Versorgungsforschung, im Vergleich zu traditionellen randomisierten Kontrollstudien, besser geeignet sein, um den klinischen Nutzen in bestimmten Settings vollständig zu eruieren.

6 Schlussfolgerungen

Weitere konkrete Anwendungsforschung zu spezifischen Tests (quantitativ mit prä-definierten weiteren technologischen Charakteristika) ist jedenfalls notwendig: Die Versorgungsforschung kann hier gezielt eingesetzt werden, um den klinischen Nutzen in unterschiedlichen österreichischen Settings zu überprüfen.

konkrete Versorgungsforschung spezifischer Tests in spezifischen Settings erforderlich

EUnetHTA Joint Action 3 WP4

**Rapid assessment of other technologies using the HTA Core Model®
for Rapid Relative Effectiveness Assessment**

POCT/ POINT OF CARE TESTS: D-DIMER AND TROPONIN

Project ID: OTCA022

Version 1.4, 26.11.2019

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Disclaimer

The content of this assessment represents a consolidated view based on the consensus within the assessment team, it cannot be considered to reflect the views of the European Network for Health Technology Assessment (EUnetHTA), EUnetHTA's participating institutions, the European Commission and/or the Consumers, Health, Agriculture and Food Executive Agency or any other body of the European Union. The European Commission and the Agency do not accept any responsibility for use that may be made of the information it contains.

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Conflict of interest

All authors, co-authors, dedicated reviewers, external experts and patients or patient representatives involved in the production of this assessment have declared they have no conflicts of interest in relation to the technology and comparator assessed according to the EUnetHTA declaration of interest and confidentiality undertaking (DOICU) statement form.

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LIST OF ABBREVIATIONS

ACC	American College of Cardiology
ACS	Acute Coronary Syndrome
AGREE	Appraisal of Guidelines, Research and Evaluation
AHA/ACC	American Heart Association/American College of Cardiology
AMSTAR-2	Assessing the Methodological Quality of Systematic Reviews-2
ASERNIP-S	Royal Australasian College of Surgeons
AT	Austria
AWMF	Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften
CADTH	Canadian Agency for Drugs and Technologies in Health
CINAHL	Cumulative Index to Nursing and Allied Health Literature
CK-MB	Creatin-Kinase Muscle-Brain
CL	Central Laboratory
COI	Conflict of Interest
CPGs	Clinical Practice Guidelines
CRD	Centre for Reviews and Dissemination
CTEPH	Chronic Thromboembolic Pulmonary Hypertension
cTnI	cardiac Troponin I
cTnT	cardiac Troponin T
CTPA	Computerized Tomography Pulmonary Angiography
CV	Coefficient of Variation
DEGAM	Deutsche Gesellschaft für Allgemeinmedizin und Familienmedizin
DGK	Deutsche Gesellschaft für Kardiologie
DNT	Door-to-Needle Time
DTA	Diagnostic Test Accuracy
DVT	Deep Vein Thrombosis
ECG	Electrocardiography
ED	Emergency Department
EFF	Effectiveness
ESC	European Society of Cardiology
EU	European Union
EUnetHTA	European Network for Health Technology Assessment
FDA	Food and Drug Administration
FU	Follow Up
GP	General Practitioner
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HIV	Human Immunodeficiency Virus

HTA	Health Technology Assessment
ICD	International Classification of Diseases
IHD	Ischemic Heart Disease
ISO	International Organisation for Standardisation
IVD	In-Vitro Diagnostics
KCE	Belgian Healthcare Knowledge Centre
LBI-HTA	Ludwig Boltzmann Institute for Health Technology Assessment
LOS	Length of Stay
MeSH	Medical Subject Headings
n. s.	not statistically significant
N/A	Not Applicable, Not Available
NACB	National Academy of Clinical Biochemistry
NCGC	National Clinical Guideline Centre
NHMRC	Australian National Health and Medical Research Council
NICE	National Institute for Health and Care Excellence
NPV	Negative Predictive Value
NRCT	Non Randomised Controlled Trial
NSPHMPDB	National School of Public Health, Management and Professional Development
NSTEMI	Non-ST Elevation Myocardial Infarction
NZGG	New Zealand Guidelines Group
PE	Pulmonary Embolism
PHEM	Pre-Hospital Emergency Medicine
PICO	Population – Intervention – Comparison – Outcome
POC	Point Of Care
POCT	Point of Care Test
PPV	Positive Predictive Value
PTS	Post-Thrombotic Syndrome
QoL	Quality of Life
RCT	Randomised Controlled Trial
REA	Relative Effectiveness Assessment
RO	Romania
RR	Referral Rates
s. s.	statistically significant
SEN	Sensitivity
SIGN	Scottish Intercollegiate Guidelines Network
SNHTA	Swiss Network for Health Technology Assessment
SPEC	Specificity
SR	Systematic Review
STEMI	ST-Elevation Myocardial Infarction

TAT	Turnaround Time
TCD	Time to Clinical Decision
Tn	Troponin
Tn-POCT	Troponin-Point Of Care Testing
TTD	Time To Discharge
UA	Unstable Angina
URL	Upper Reference Limit
VTE	Venous Thromboembolism

1 SUMMARY OF RELATIVE EFFECTIVENESS OF TN-POCT AND D-DIMER POCT

Scope

This rapid assessment 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) settings or emergency care settings is more effective and/or safer than current diagnostic practice. Subsequently, the following research questions can be formulated:

- How do evidence-based guidelines recommend the use of Tn-POCT (position in the diagnostic path, threshold values in different patient populations, 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, 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)
- Can a theoretical benefit of POCT (D-dimer and Tn) be realized in the Austrian and Romanian context? (expert consultation)

Introduction

Description of technology and comparators

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 [1]. POCTs provide rapid feedback of 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 [2, 3]. [**B0001**]

For Tn-POCT, 15 devices were identified for this assessment. Of these, 14 devices measure troponin quantitatively and one further device measures it qualitatively. For D-dimer POCT, eleven devices were identified, eight of which measure D-dimer quantitatively. When reviewing the characteristics of the identified devices, it is notable that these are heterogeneous between devices 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). [**A0020**]

Tn-POCT and D-dimer POCT can be used to aid the diagnosis of patients with symptoms suggestive of suspected acute coronary syndrome and venous thromboembolism respectively. Theorectical advantages of POCT include faster turnaround time, reduced length of stay and reduced unnecessary hospitalisation/further testing. Tn-POCT is especially sought to be beneficial in this context; in settings where CL testing is not onsite or not available 24 hours per/every day, because time is critical in the diagnosis of acute coronary syndrome. Furthermore it may, especially in the context of implementing D-dimer POCT, reduce hospital admissions [4]. [**B0002**]

Both of the technologies under evaluation are used by healthcare professionals. Tn-POCT and D-dimer POCT may be used in emergency care settings such as EDs as well as in primary care settings [5-7]. Tn-POCT may further be used in other pre-hospital emergency medicine settings such as in ambulance vehicles [5]. [**B0004**]

For D-dimer assays, the commercially available devices approved by the Food and Drug Administration vary greatly when it comes to reference values and clinical cut-offs [7]. Similarly, Tn assays are – regardless of whether tested in a CL or at the point of care – neither standardised nor are they harmonised. That is to say; every assay uses a distinct set of antibodies for capturing and detecting Tn in the blood [8]. [**B0018**]

Test kits and/or analysers and adequate know-how are required to use the POCT devices. However, the required equipment and supplies strongly depend on the type of POCT being implemented. If fixed devices (benchtop-instruments) are implemented, one has to further think of where the analysers are to be positioned because these tests technically cannot be moved but have a specific location, e.g., in doctor's office or ambulance [9]. [**B0008**] [**B0009**]

Health problem and current use

Tn-POCT: Acute coronary syndrome

The target population for the use of Tn-POCT is adult patients presenting with signs and symptoms of acute coronary syndrome. Acute coronary syndrome is a health condition encompassing means and spectrum of signs and symptoms caused by a decreased blood flow in the coronary arteries (myocardial ischemia). The term acute coronary syndrome is used for patients that present with suspected or confirmed acute myocardial ischemia or infarction. There are different types of acute coronary syndrome such as non-ST elevation myocardial infarction, ST-elevation myocardial infarction or unstable angina [10, 11]. [**A0002**]

Ischemic heart disease is one of the leading causes of mortality globally. In Europe, approximately 1,800,000 persons die due to ischemic heart disease yearly. This is 20 per cent of all deaths in Europe, although the variation among countries is substantial [12, 13]. [**A0005**] [**A0006**]

The treatment of myocardial ischemia is time-critical as the condition can lead to death. It is, therefore, crucial to rapidly identify the cause of the chest discomfort, which is the main 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") [11]. This involves the following steps [14]: initial physical examination and obtaining the medical history of the patient, resting 12 lead electrocardiography, and finally cardiac troponin measurement. [**A0004**] [**A0024**]

The target population for the use of Tn-POCT is adult patients presenting with signs and symptoms of acute coronary syndrome. Tn-POCT can spare the referral of patients to an inpatient unit in cases where there are no ischemic electrocardiography changes, if there is clinical ambiguity, and if symptoms last for more than 12 hours [15]. All patients who present to the emergency department with symptoms suggestive of cardiac ischaemia should be evaluated with cardiac biomarkers as part of the initial evaluation. Cardiac specific troponin is the most widely utilized diagnostic biomarker for myocardial infarction and is the preferred laboratory test [16]. [**A0007**] [**A0023**] [**A0011**]

The standard of care for patients who present with acute coronary syndrome, including those with recurrent symptoms, ischemic electrocardiography changes, or positive cardiac troponins, is admission to hospital. The primary focus in the first 12 hours is the immediate relief of ischemia and the prevention of myocardial infarction and eventually death. [**A0025**]

D-dimer: Vyenous Thromboembolism

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; this is then 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, which in some cases may be fatal. [**A0002**]

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. If pulmonary embolism is symptomatic, symptoms include, but are not limited to, dyspnoea, chest pain, pre-syncope or syncope, fever, cough, unilateral leg pain [17, 18]. 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. [**A0004**] [**A0005**]

Venous thromboembolism is the third most frequent cardiovascular disease. The overall annual incidence is 100-200 per 100.000 inhabitants in Europe [17]. Venous thromboembolism is likely to be an escalating public health problem due to the prominence of age as a risk factor and the increasing age of the population [19]. Patients older than 40 years are at increased risk and risk doubles with each decade. Hence an increasing number of patients are expected to be diagnosed and treated to avoid fatal pulmonary embolism [17]. [**A0006**]

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 [18] [17]. [**A0024**]

The target population for the use of D-dimer POCT is adult patients at low to moderate risk for presenting with deep vein thrombosis or pulmonary embolism [18]. The standard diagnostic workup for deep vein thrombosis includes imaging: the costs of imaging modalities and the increasing number of negative tests lead to a reconsideration of the diagnostic strategies. In some patients, there is no need for diagnostic imaging to exclude the disease, the diagnostic workup relies then only on the pre-test probability assessment, complemented by the D-dimer test results [18]. [**A0007**] [**A0023**] [**A0011**]

The current standard practice for the treatment of venous thromboembolism is anticoagulation. These drugs "thin" the blood and prevent further clotting. There is a wide variation in practice, but patients are usually given a brief course of heparin treatment initially while they start on a 3–6-months course of warfarin. [**A0025**]

Methods

The EUnetHTA Core Model® was used as a reporting standard. Assessment elements from the Rapid Relative Effectiveness Assessments Version 4.2 were utilised. Where applicable, further assessment elements from the HTA Core Model® Application for Diagnostic Technologies version 3.0. were used.

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). To identify primary studies updating or extending the evidence derived from available systematic reviews, two further searches were conducted in four databases (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 following databases: 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.

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 [20, 21]. 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).

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 admission, treatment initiation, referral rates, door-to-needle time, turnaround time, time to discharge, length of stay, further diagnostic testing, and time to clinical decision. Safety outcomes included side effects/disbenefits.

Data extraction and analyses

One researcher from LBI-HTA extracted the data and another researcher from NSPHMPDB checked the extracted data. The evidence was qualitatively synthesised.

Quality rating

The quality of the eligible studies was assessed using the following tools: For systematic reviews, the AMSTAR-2 checklist [22] was utilised, whilst for non-randomised controlled trials (NRCTs) the quality was assessed using the Robins-I tool [23]. To assess the quality of the included guidelines, the Appraisal of Guidelines, Research and Evaluation (AGREE II) reporting checklist [24] was used.

Results

For Tn-POCT, we identified 15 devices for this rapid relative effectiveness assessment, 14 of which measure troponin quantitatively. For D-dimer POCT, eleven devices were identified, eight of which measure D-dimer quantitatively. It was not possible to identify which type of POCT product is actually used in the Austrian or Romanian health care system.

Tn-POCT

Available evidence

For the evaluation of the effectiveness of implementing Tn-POCT, two systematic reviews were included [25, 26] of which one was a report [25] 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 [25], but no further eligible primary studies were identified. The included systematic reviews reached a moderate [26] to high [25] certainty according to AMSTAR-2.

In addition, eight clinical practice guidelines met our inclusion criteria and were included in the guideline synopsis [11, 14-16, 27-30]. Concerning quality (AGREE-II), three guidelines are recommendable [11, 14, 28], and recommendable with modification [15, 29, 30] respectively. The remaining two guidelines [16, 27] are not fully recommendable.

Clinical Effectiveness and safety

Results relating to diagnostic test accuracy shows that there are significant inconsistencies in estimates measured across setting as evident in the comparison of DTA estimates of the eleven studies included in the CADTH report [25] and significant limitations with study quality (e.g., solely non comparative studies in the other review [26]). Evidence found by the CADTH report [25] relating to 11 studies on diagnostic test accuracy shows, that compared with CL testing, Tn-POCT tended to have a lower sensitivity, lower negative predictive value, higher specificity and higher positive predictive value.

The included systematic reviews [25, 26] included 32 studies investigating the clinical utility of Tn-POCT, of which seven were randomised controlled trials. Broadly, the identified evidence was insufficient to show non-inferiority in comparison 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 clearly show superiority when compared to usual care in settings without or delayed CL testing (e.g., certain ambulatory settings, pre-hospital emergency medicine).

In the **emergency department**, evidence from the CADTH report [25] showed limited evidence that implementing Tn-POCT in the emergency department may reduce turnaround time (reduction in 2 RCTs), time to discharge (reduction in 2 RCTs & 1 observational study), and length of stay (reduction in 3 RCTs and 2 observational studies, increase in 1 RCT). However, the use of Tn-POCT did not statistically change mortality (2 RCTs, 3 observational studies) or adverse events (2 RCTs, 2 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 (1 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 [25].

In **ambulatory (primary and community) care**, insufficient evidence was found indicating 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 [25, 26] 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.

In **pre-hospital emergency medicine**, there is also insufficient evidence indicating 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 [25] 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 emergency department or admission to hospital. The same review found evidence consisting of one non-comparative observational study showing a median turnaround time of 83 minutes (range: 46-187). Concerning the outcome mortality, the CADTH report [25] found evidence consisting of 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.

Concerning safety, none of the identified reviews highlighted side effects/disbenefits as such. However, data on diagnostic accuracy can indirectly indicate as to whether harms of false-positives and false negatives can be expected. Only one study identified in both systematic reviews [25, 26] directly reported on the harm of discharged patients with an 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 out patients with an acute MI or UA. 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.

Guideline synopsis

Eight clinical practice guidelines met our inclusion criteria and were included in the guideline synopsis [11, 14-16, 27-30]. Six guidelines [11, 14-16, 28, 30] were developed for the outpatient setting (emergency department, pre-hospital, primary care, ambulance), one guideline was developed for disaster medicine [29], one guideline did not specifically define the setting but states the guideline is applicable for all cardiac caregivers [27].

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 hospital dependent. One guideline [15] specifically states that no recommendations can be made due to lack of or weak evidence. Five guidelines only mention that POCT can be used for the measurement of cardiac troponins [11, 19, 27, 29, 30]. One guideline [15] recommends not to use qualitative troponin test routinely in primary care to exclude an acute myocardial infarction and one guideline recommends the use of sensitive or high-sensitivity assays only [14]. Three guidelines stress that the cardiac marker testing turnaround time (TAT) should be a maximum of one hour [14, 27, 30]. Two guidelines come to the (consistent) conclusion that if institutions cannot comply with this requirement, POCT should be implemented [27, 30]. One guideline [30] suggest that troponin tests should provide not only qualitative but also quantitative information. According to two guidelines, the sensitivity of Tn-POCT is considered to be below that of CL assays and they cannot be considered sensitive or high-sensitivity [11, 14]. On the other hand, one guideline states that Tn-POCT licensed

in the United Kingdom are equivalent in sensitivity to the 12 hour laboratory-based standard Tn assays [28]. Also, one guideline [14] states that Tn-POCT values may provide initial diagnostic information, but the advantage of shorter turnaround time is counterbalanced by lower sensitivity, lower diagnostic accuracy and lower negative predictive value. Furthermore, the rigorous quantitative assay standardisation that is needed for routine diagnosis favours CL testing [11]. A major limitation of the guideline synopsis is that recent guidelines, published in the last three years, could not be identified.

Expert consultation

In terms of the Austrian situation, the experts we consulted believed that there is a theoretical potential value of Tn-POCT in settings where a CL would not be available or would take too long to supply results. However, there is a doubt as to whether such scenarios actually exist in Austria.

In the Romanian context, the potential value of Tn-POCT was considered positive by all consulted experts. Rural areas with no access to CL testing were highlighted as particularly relevant settings, as it was thought that use of these tests would change referral practices and release the burden on very crowded highly specialised hospitals. If this occurs, the experts expect that it would allow for better spending of funds and better health outcomes.

Upcoming evidence

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

D-dimer POCT

Overall, six systematic reviews [26, 31-35] were identified. The reviews identified between four and 52 primary studies and the total number of patients from individual studies included in the reviews ranged from 199 [32] to 55,268 [34]. Two primary studies [36, 37] were additionally included that specifically considered deep vein thrombosis, that had not been adequately addressed in the reviews.

The included systematic reviews reached a moderate [26, 32, 35] to high [31, 33, 34] quality according to the AMSTAR-2 assessment. In terms of risk of bias of the primary studies (assessed with the ROBINS-I tool), one study [37] was considered to have a moderate risk of bias for the patient management outcomes while the risk of bias of the other study [36] was rated as severe.

Ten guidelines [15, 17-19, 29, 38-42] met our inclusion criteria and included some form of recommendation or mentioning of D-dimer POCT. With regard to quality (AGREE-II), five guidelines were fully recommendable [18, 38, 39, 42, 43] and the remaining guidelines were recommendable with modifications [15, 19, 29, 40, 41].

Clinical effectiveness & Safety

Evidence was identified in ambulatory (primary and community) care and emergency care. Three systematic reviews [26, 31, 33] reported on evidence in ambulatory care (primary and community care), whilst two reviews [34, 35] restricted their review to the emergency department or hospital emergency care settings. One further review [32] did not specify the setting and only mentioned the outpatient setting (without further description). Two primary studies [36, 37] 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 type) with a sensitive clinical decision rule (e.g. when general practitioners use a D-dimer POCT in combination with the more sensitive Wells clinical decision rule) leads to a more accurate diagnosis of venous thromboembolism than without POCT. The negative predictive value of the combined D-dimer POCT and clinical decision rule can be quite high (>95%) which means some patients may avoid referrals to imaging within a hospital setting. However, efficient use of a D-dimer POCT combined with a clinical decision rule requires training, expertise and practice. No direct comparative evidence was found elaborating the effect of implementing D-dimer POCT on mortality/morbidity, quality of life, or patient management in ambulatory care settings. Two primary studies [36, 37] updating the evidence from systematic reviews reported on data with regard to turnaround time (1 study: <5min-34 min) and referral rates (1 study: no statistically significant. difference between intervention and usual care) but did not change the available body of evidence identified within the overview of reviews.

Concerning the potential effect of implementing D-dimer POCT in **emergency care**, one systematic review [35] 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, considering the emergency department setting. Based on observational studies, this review found a reduction of turnaround time, number of hospital admissions and length of stay. Another review [34] included evidence in the emergency department, but reported solely on non-comparative data in relation to failure rates and efficiency. None of the reviews identified in the emergency department setting reported on diagnostic test accuracy for D-dimer POCT. 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.

As a consequence, there is a lack of reliable, good quality evidence to show non-inferiority compared to CL testing and superiority compared to the current situation (with no immediate CL testing) in emergency care or ambulatory (primary and community care) settings.

With regard to safety, none of the identified reviews highlighted side effects/disbenefits as such. However, data on diagnostic accuracy can indirectly indicate as to whether harms of false-positives and false negatives can be expected.

Broadly, the reviews [26, 31-35] confirm that D-dimer testing is very sensitive with a high negative predictive value, but it is 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.

Guideline synopsis

Ten guidelines [15, 18, 19, 29, 38-43] 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 [18, 19, 29, 38, 39, 41-43]. Only one guideline [40] 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 [29]. The recommended settings are somewhat inconsistent in the included guidelines: three guidelines did not define the setting [29, 39, 42], three guidelines are applicable only in the community or primary care setting [15, 19, 43], one guideline is applicable in numerous settings (primary, secondary, tertiary care) [18], two guidelines only in the emergency department [40] or in emergency department and outpatient settings [41], and one guideline both in the ambulatory and inpatient setting [38]. Two guidelines are inconsistent in terms of the recommended sensitivity of the D-dimer test. One guideline [38] states that the simple qualitative D-dimer POCT in combination with clinical probability may be comparable in its value when compared to the quantitative ELISA test in low-risk patients, while another guideline [15] recommends not to use qualitative or semi-quantitative tests in primary care.

Expert consultation

In terms of the Austrian situation, some experts believed that D-dimer POCT could only have a limited role outside the hospital setting at present, 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. This expert mentions that the goal is hereby to avoid unnecessary hospitalisations, and the test would be able to do that to a certain extent. The time element is not considered to be as crucial for D-dimer as there is less danger in the patient waiting to attend hospital and have further tests there.

In the Romanian context, the potential value of these D-dimer POCT was considered positive by all consulted experts. Rural areas with no access to CL testing were highlighted as particularly relevant settings, as it was thought that use of these tests would change referral practices and release the burden on very crowded highly specialised hospitals. If this occurs, the experts expect that it would allow for better spending of funds and better health outcomes.

Upcoming evidence

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

Discussion

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 emergency care or ambulatory (primary and community care) settings.

Although the focus of this health technology assessment is on clinical utility, we did include the evidence related to diagnostic accuracy as reported in the identified systematic reviews. This evidence may not be up-to-date. However, improvements in diagnostic test accuracy only indirectly show whether implementation would result in patient-relevant benefits. The aim of this review is evaluating clinical utility as a final endpoint, as recommended in diverse methodological guidelines [44].

Furthermore, this assessment included a variety of – often somewhat heterogeneous – products: 26 POCT diagnostics were identified through manually searching for relevant POCT devices. Of these, 15 devices measure troponin and eleven D-dimer products. Most products measure the biomarkers quantitatively (Tn: 14/15; D-dimer: 8/11). Further differences in technological characteristics are present. This heterogeneity of the products is further paired with not knowing about which tests are actually used in Austria and Romania – an essential limitation for a meaningful evaluation.

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, evaluation studies in the field of health service research might be better suited to fully determine the clinical benefit in specific settings than traditional randomised controlled trials.

Conclusion

Should such tests be considered for implementation or their use extended, prior further research on specific point of care tests (quantitative, with certain pre-defined analytical characteristics) in specific settings in Austria and Romania would be needed. Here a health services research approach might be more appropriate than traditional evidence-based medicine to assess potential benefits in different settings from a systems approach.

Table 1: Summary table of the results on the use of Tn-POCT

Effectiveness and diagnostic accuracy of Tn-POCT: Summary of the evidence						
Author, year	**Study design**	**Included studies/ included pts**	**Setting**	**Quality**	**Summary of the results**	**Authors' Conclusion**
CADTH, 2016 [25]	SR	41/NR	Diverse (incl. ED and primary care settings)	High	**DTA results (at admission: range of POCT vs. range of CL):** SEN: 26%-88% vs. 68%-100% SPEC: 84. %-98. % vs. 75%-94% PPV: 31. %-85. % vs. 10%-82% NPV: 90%-99% vs. 95%-100% **Clinical utility:** "In Settings Where a Central Laboratory is Available [Tn-POCT] tended to shorten *turnaround time (TAT)*, *length of hospital stay*, and *time to discharge.* The use of [Tn-POCT] did not statistically change *mortality rates* or severe adverse events compared with a central laboratory in most studies, in up to one year of follow-up. There was no difference in *quality of life among* patients who were tested using POC or central laboratory within up to three months' follow-up. Subgroup analyses of clinical-utility studies based on study design, setting, the level of sensitivity of the central laboratory methods, the types of cTn (I or T), and funding status did not show any differences in findings. (…). In Settings Where No Central Laboratory is Available In pre-hospital or ambulance settings, limited evidence points to the potential use of [Tn-POCT] for the diagnosis and management of patients. [Tn-POCT] may *reduce the percentage of patients referred to the emergency department from a primary health care centre.* [Tn-POCT] testing was shown to be feasible and reliable for patients transported by ambulance, and can s*horten the time from first medical contact to patient disposition* (…)."	"Overall, given the limitations with the data and the inconsistency in DTA estimates, the usefulness of [Tn-POCT[1]] in settings with access to central laboratories may be limited." "In settings with no access to a central laboratory, such as in rural health care centres or remote settings, [Tn-POCT] may be useful due to the potential to help reduce unnecessary transfer of patients to larger centres."

[1] Note: The synonymous term "POC cTn testing" was used instead of the term Tn-POCT in the report.

Effectiveness and diagnostic accuracy of Tn-POCT: Summary of the evidence						
Author, year	**Study design**	**Included studies/ included pts**	**Setting**	**Quality**	**Summary of the results**	**Authors' Conclusion**
Schols, 2018 [26]	SR	2/545	Primary Care	Moderate	DTA results (range of 2 studies, results of MI/MI+unstable angina): SEN: 67%-83%/21%-29% SPEC: 98-100%/98-100% PPV: 40%-100%/40%-100% NPV: 99%-99.7%/94%-96% Clinical utility: Limited evidence (1 comparative cohort study) was found that Tn-POCT would reduce the referral rate, but the identified cohort study noted that it may be on offset of potentially missing out on patients with an acute myocardial infarction or unstable angina.	No conclusion on Tn-POCT, highlighting the inconclusive available evidence.

Abbreviations: CADTH – Canadian Agency for Drugs and Technologies in Health; CL – central laboratory; cTn – cardiac troponin; DTA – diagnostic test accuracy; MI – myocardial infarction; NPV – negative predictive value; NR – not reported; POC – point of care; POCT – point of care test; PPV – positive predictive value; pts – patients; SEN – sensitivity; SPEC – specificity; SR – systematic review.

Table 2: Summary table of the results on the use of Tn-POCT in the emergency department

The use of Tn-POCT in the emergency department: Summary of the evidence			
Effect on patient management			
1 SR [25]	High	No. of hospital admission: N/A Treatment initiation: N/A RR: N/A DNT: N/A TAT (evidence base: 2 RCTs, 11 observational studies using a variety of different definitions of TAT[2]): RCTs (2 studies, cTnI or cTnT testing, 2,134 and 833 enrolled patients respectively): • Reduction in 2/2 studies: 43 min (median; p value not available) in one study, and 71 and 147 min in the other study[3] (median; s. s., with p<0.001) Observational studies (5 prospective, 1 retrospective and 5 pre-post studies respectively, cTnI or cTnT testing, 31 to 2,386 enrolled pts) • Reduction in 11/11 studies: 18-93 min (p values available for 5/11 studies, with s. s. differences in these studies) TTD (evidence base: 2 RCTs, 1 observational study): RCTs (2 studies, cTnT or cTnI testing, 487 and 2,134 enrolled pts respectively): • Reduction in 2/2 studies: 5 and 7 min (mean and median respectively; s. s. with p=0.04 and p value not available respectively) Observational studies (1 pre-post study, multiple biomarkers 4,886 enrolled pts): • Reduction in 1/1 study: 26 min (p value not available) LOS: Emergency room stay (evidence base: 3 RCTs, 2 observational studies): *RCTs* (3 studies, cTnI or cTnT testing, 487-912 enrolled pts): • Reduction in 2/3 studies: 0.2 and 0.8 h (mean and median; diff. n. s. in individual studies) • Increase in 1/3 studies: 0.1 h (median; diff. n. s.) *Observational studies* (2 pre-post studies, cTnI testing, 366 and 671 enrolled pts respectively): • Reduction in 2/2 studies: 1.9 h (mean; p value NR) and 2-2.7 h respectively (mean; diff. s. s.) Hospital stay in ED (evidence base: 1 RCT) *RCTs* (1 study, cTnI testing, 2,243 enrolled pts) • Reduction in 1/1 study: 2.2 h (mean; diff. n. s.)	Currently, the evidence is insufficient indicating non-inferiority of using a pathway with Tn-POCT compared to usual care if CL testing is timely available.

[2] E.g., time from blood draw to result.

[3] When using the definitions “time from collection to physician notification” and “time from presentation to anti-ischemic therapy” respectively.

The use of Tn-POCT in the emergency department: Summary of the evidence			
1 SR [25] *(continuation)*		Further testing: N/A TCD (evidence base: 1 RCT, 1 pre-post study): RCTs (1 study, cTnI testing, 2,134 enrolled pts) • Reduction in 1/1 study: 9 min (median; p value not available) Observational studies (1 pre-post study, multiple biomarker testing, 4,886 enrolled pts): • Reduction in 1/1 study (multiple biomarkers): 26 min (mean; p value not available)	
Effect on mortality/morbidity			
1 SR [25]	High	Mortality (evidence base: 2 RCTs and 3 observational studies) RCTs (2 studies; cTnT or cTnI testing, 487 and 2,243 enrolled pts respectively) • POC vs. CL: 0.5 vs. 0% in one study (p value NR) and 1% vs.0.2% in another study (n. s., with p=0.142) Observational studies (3 prospective studies; cTnI or cTnT testing; 508-1,410 enrolled pts) • None of the studies compared Tn-POCT with CL head-to-head (using statistical testing) Cardiac events (evidence base: 2 prospective studies, cTnI or cTnT testing) 30 day cardiac event rate (1 prospective study, 704 enrolled pts; POCT vs. CL): • Low risk pts: 0% (95%CI: 0-25.9) vs. 0% (95%CI: 0-21.5), p value NR • High risk pts: 24.8% (95%CI: 20.1-30.1) vs. 28.6% (95%CI: 23.4-34.4), p value NR Cardiac events after 1 year (1 prospective study, 1,410 enrolled pts; POCT vs CL): • 2.1% (95%CI: 1.5-3) vs. 2.2% (95%CI: 1.6-3.1), p value NR Other Adverse events (AE) and composite end points in ED (evidence base: 2 RCTs, cTnT or cTnI testing) Major AE after 3 m FU (1 RCT, 2,243 enrolled pts; POCT vs CL): 3% vs. 2%, diff. n. s., with p=0.313 CEP events[4] at 6 m (1 RCT, 487 enrolled pts; cTnT testing, POCT vs. CL): 10.4% vs. 5.4%, p value NR	
Effect on QoL			
1 SR [25]		QoL (evidence base: 1 RCT, cTnI testing, 2,243 enrolled pts using the EQ-5D questionnaire): POC vs. CL: • After 1 m: 0.742 vs. 0.759 (n. s., with p=0.614) • After 3 m: 0.752 vs. 0.759 (n. s., with p=0.638)	

Abbreviations: CL – central laboratory; DNT – door-to-needle-time; LOS – length of stay; m – month(s); n. s. – not statistically significant; N/A – no evidence available; pts – patients; QoL – quality of life; RCT – randomised controlled trial; RR – referral rates; SR – systematic review; s. s. – statistically significant; TAT – turnaround time; TCD – time to clinical decision;TTD – time to discharge.

[4] AMI, coronary revascularization, cardiac arrest, or mortality in patients with a negative first cTn test at 3 m FU

Table 3: Summary table of the results on the use of Tn-POCT in ambulatory (primary or community care)

The use of Tn-POCT in primary care settings: Summary of the evidence			
Evidence base	**Quality**	**Results**	**Conclusion**
Effect on patient management			
2 SRs [25, 26]	Moderate to High	No. of hospital admission: N/A Treatment initiation: N/A RR (evidence base: 1 comparative cohort study identified by both SRs): • Reduction in 1/1 study (TnT testing, 196 enrolled pts): 32/128 pts (25%) vs. 29/68 pts (43%), p value not reported[5] DNT: N/A TAT: N/A TTD: N/A LOS: N/A Further testing: N/A TCD: N/A	Currently, the evidence is insufficient indicating superiority of using a pathway with Tn-POCT compared to usual care in ambulatory care (primary or community care) if CL testing is not timely available.
Effect on mortality/morbidity			
No evidence identified	N/A	-	
Effect on QoL			
No evidence identified	N/A	-	

Abbreviations: CL – central laboratory; DNT – door-to-needle-time; LOS – length of stay; N/A – no evidence available; pts – patients; QoL – quality of life; RR – referral rates; SR – systematic review; TAT – turnaround time; TCD – time to clinical decision; TTD – time to discharge.

[5] Yet, it is mentioned in the review that the authors of the primary study noted that there were some two patients that were not referred and missed cases (one AMI and one unstable angina respectively). It is therefore concluded that the use of Tn-POCT in pts with chest pain "may reduce emergency referrals, but probably at the cost of an increased risk to miss patients with an acute myocardial infarction or unstable angina".

Table 4: Summary table of the results on the use of Tn-POCT in pre-hospital emergency medicine (PHEM)

Effectiveness of implementing Tn-POCT in pre-hospital emergency medicine: Summary of the evidence			
Evidence base	**Quality**	**Results**	**Conclusion**
Effect on patient management			
1 SR [25]	High	No. of hospital admissions (ambulance; evidence base: 1 RCT with 601 enrolled pts): No difference between Tn-POCT and usual care (no further information provided) Treatment initiation: N/A RR: N/A DNT: N/A TAT (ambulance; evidence base: 1 observational study; 928 pts): 83 min (median, range: 46-167) TTD (ambulance; evidence base: 1 RCT): • Reduction in 1/1 study (median time Tn-POCT vs CL): 8.8 hours (range: 6.2 h to 10.8 h) vs. 9.1 h (range 6.7 hours to 11.2 hours), *P* = 0.05. LOS: N/A Further testing: N/A TCD: N/A	Currently, the evidence is insufficient indicating superiority of using a pathway with Tn-POCT compared to usual care in pre-hospital emergency medicine if CL testing is not timely available.
Effect on mortality/morbidity			
1 SR [25]	High	Mortality: (ambulance; 1 RCT, 601 enrolled pts) • Death in the next 30 days: no difference between groups (no further information provided)	
Effect on QoL			
No evidence identified	N/A	N/A	

Abbreviations: CL – central laboratory; DNT – door-to-needle-time; LOS – length of stay; N/A – no evidence available; pts – patients; QoL – quality of life; RR – referral rates; SR – systematic review; TAT – turnaround time; TCD – time to clinical decision; TTD – time to discharge; RCT – randomised controlled trial.

Table 5: Summary table of the results on the use of D-dimer POCT

Effectiveness and diagnostic accuracy of D-dimer-POCT: Summary of the evidence of SRs						
Author, year	**Study design**	**Included studies/ included pts**	**Setting**	**Quality**	**Summary of the results**	**Authors' Conclusion**
Schols, 2018 [26]	SR	2/892	Primary care	Moderate	DTA: SEN: stand alone D-dimer 84%; Wells ≤4 + D-dimer 94-95%; Wells ≤2 + D-dimer 97%. SPEC: stand-alone D-dimer 62%; Wells ≤4 + D-dimer 38-51%; Wells ≤2 + D-dimer 32%. PPV: stand alone D-dimer 24%; Wells ≤4 + D-dimer 21-37%; Wells ≤2 + D-dimer 20%. NPV: stand alone D-dimer 96%; Wells ≤4 + D-dimer 94-99%; Wells ≤2 + D-dimer 99%. Effectiveness: NR	No studies assessed the effects of D-dimer on treatment initiation or referral rates. All studies were considered at high risk of bias. Evidence suggests combining D-dimer with a clinical decision rule (e.g. when GP use of a D-dimer POCT is combined with the Wells clinical decision rule) leads to more accurate diagnosis. Further research on clinical effectiveness is necessary.
Geersing, 2009 [31]	SR & meta alanysis	23/13,959	Primary or secondary care	High	DTA: SEN: 0.85 (95%CI 0.78-0.90) for SimpliRED D-dimer; 0.87 (0.81-0.91) for Clearview Simplify D-dimer; 0.93 (0.88-0.97) for Triage D-dimer; 0.96 (0.91-0.98) for Cardiac D-dimer. SPEC: 0.48 (95% CI 0.33-0.62) for Triage D-dimer; 0.57 (0.52-0.62) for Cardiac D-dimer; 0.62 (0.54-0.69) for Clearview Simplify D-dimer; 0.74 (95%CI 0.69-0.78) for SimpliRED Likelihood ratio of a negative test result: 0.07 (95%CI 0.04-0.16) for Cardiac D-dimer; 0.18 (95%CI 0.08-0.43) for Triage D-dimer; 0.21 (0.15-0.29) for SimpliRED D-dimer; 0.22 (95% CI 0.15 to 0.29) for Clearview Simplify D-dimer. Effectiveness: NR	The two quantitative tests (Cardiac D-dimer and Triage D-dimer) scored most favourably. In outpatients suspected of VE, D-dimer POCT can contribute important information and guide patient management, especially in low-risk patients (i.e. with low score on a clinical decision rule).

Effectiveness and diagnostic accuracy of D-dimer-POCT: Summary of the evidence of SRs						
Author, year	**Study design**	**Included studies/ included pts**	**Setting**	**Quality**	**Summary of the results**	**Authors' Conclusion**
Pasha, 2010 [32]	SR	4/199	Not specified[6]	Moderate	DTA: Incidence of VTE despite negative testing and unlikely clinical probability: 2% (95% CI: 0.1-10.1%)? Effectiveness: In 49/199 (25%) patients with unlikely clinical probability and normal D-dimer CT scans could be withheld. Mortality/Morbidtidy: 1 person (2%)	Overall (across POCT and lab tests) pooled incidence of morbidity was 0.34% (95%CI 0.036-0.96%) and combined incidence of death (across POCT and lab tests) was 0.1% (95% CI 0.0-0.5%). Combined 3-month mortality risk of PE (across POCT and lab tests) was 0.10% (95%CI 0.002-0.46%). 1 death occurred across all studies (this was in the POCT study). Ruling our PE on basis of unlikely clinical probability and normal D-dimer is very safe.
Hendriksen, 2015 [33]	SR	10/598	Primary care	High	Sensitivity*: *(* Data are ordered by values of the test accuracy rate)* 88% (78%-94%) for simplified revised Geneva ≤2 model 90% (81-96%) for original revised Geneva ≤5 95% (87%-98%) for original Wells ≤4; 95% (87-98%) for modified Wells ≤2 96% (88%-99%) for simplified Wells ≤1 Specificity*: 48% (44%-53%) for original revised Geneva ≤5; 49% (45-53%) for the simplified Wells ≤1; 50% (46-55%) for the modified Wells ≤2; 51% (47-55%) for the original Wells ≤4; 53% (49%-57%) for simplified revised Geneva ≤2. PPV*: 20% (15%-24%) for original revised Geneva ≤5; 21% (17-26%) for original Wells ≤4; 21% (17-26%) for modified Wells ≤2; 21% (17-25%) for simplified Wells ≤1; 21% (16-26%) for simplified revised Geneva ≤2. NPV*: 97% (95-99%) original revised Geneva ≤5; 97% (94-99%) simplified revised Geneva ≤2; 99% (96-100%) original Wells ≤4; 99% (96-100%) modified Wells ≤2; 99% (97-100%) simplified Wells ≤1.	Efficiency was comparable across all models but the Wells rules combined with D-dimer POCT gave the best performance in terms of lower failure rates

[6] Only "outpatients" stated in one study in this review that used a POCT but not defined further (i.e. if primary care or ED)

Effectiveness and diagnostic accuracy of D-dimer-POCT: Summary of the evidence of SRs						
Author, year	**Study design**	**Included studies/ included pts**	**Setting**	**Quality**	**Summary of the results**	**Authors' Conclusion**
					Effectiveness: Failure rates across all models: 1.2% (95%CI 0.2%-3.3%) for simplified Wells ≤1 1.5% (95%CI 0.4-3.7%) for original Wells ≤4 1.5% (95%CI 0.4-3.8%) for modified Wells ≤2 2.7% (95%CI 1.1-5.4%) for original revised Geneva ≤5 3.1% (95%CI 1.4%-5.9%) for simplified revised Geneva ≤2 Efficiency across all models: 43% (95%CI 39%-48%) for simplified Wells ≤1 44% (95%CI 40-48%) for original revised Geneva ≤5 45% (95%CI 41-49%) for modified Wells ≤2 46% (95%CI 41-50%) for original Wells ≤4 48% (95%CI 44%-52%) for simplified revised Geneva ≤2	
Lucassen, 2011 [34]	SR	52/55,268	Hospital setting (emergency department, outpatients or inpatients)	High	DTA: NR for D-dimer POCT Effectiveness: Failure rate (across all studies with qualitative d-dimer testing): 1.0% (95%CI 0.8-1.3%) combined with gestalt 0.7% (95%CI 0.4-1.2%) combined with Wells cutoff value ≤4: 1.7% (95%CI 1.0-2.8%) combined with Wells cutoff value <2: 0.9% (95%CI 0.6-1.5%) Efficiency (across all studies with qualitative d-dimer testing): 45% 95%CI 39-52%); Combined with gestalt: 52% (95%CI 40-64%) Combined with Wells cutoff value ≤4: 42% (95%CI 32-52%) Combined with Wells cutoff value <2: 40% (95%CI 33-48%)	Combining a decision rule and gestalt[7] can safely exclude PE when combined with sensitive D-dimer testing except when the less sensitive Wells rule (cutoff value ≤4) is combined with qualitative D-dimer POCT

[7] Note: Physician's unstructured estimate ("gestalt").

Effectiveness and diagnostic accuracy of D-dimer-POCT: Summary of the evidence of SRs						
Author, year	**Study design**	**Included studies/ included pts**	**Setting**	**Quality**	**Summary of the results**	**Authors' Conclusion**
Marquardt, 2015 [35]	SR	7/3,279	ED	Moderate	DTA: NR Effectiveness: No. of hospital admissions (1 before-after study, 462 pts) decreased by 13.8% TAT in ED (evidence base: 7 observational studies[8], 3,279 pts): • Reduction in 5 studies (comparative; prospective and retrospective): 10-101.5 min (using different measures of central tendency; p-values and information on stat. testing not reported) • No comparative data shown from 2 studies[9]	D-dimer POCT can safely improve patient journey times

Abbreviations: ED – emergency department; NPV – negative predictive value; NR – not reported; pts – patients; POCT – point of care test; PPV – positive predictive value; SEN – sensitivity; SPEC – specificity; SR – systematic review; TAT – turnaround time.

[8] While the review reported initially on seven included studies on TAT, data are only presented for six studies.

[9] Non-comparative data was shown in one study (time to result: 10-38 min) and not reported at all in another study that the review described.

Table 6: Summary table of the results on the use of D-dimer POCT derived from primary studies updating the overview of reviews

Effectiveness of implementing D-dimer-POCT: identified studies updating the evidence from SRs						
Evidence base	**Study design**	**Included pts**	**Setting**	**Risk of Bias**	**Summary of the results**	**Conclusion**
Effect on patient management						
2 studies [36, 37]	NRCT	971	Primary care	Moderate to severe	TAT (1 study): <5min to 34 min RR (1 study): no statistically significant difference in patients referred, not referred between intervention and usual care group	The identified evidence updating the overview of reviews is insufficient to suggest that implementing D-dimer POCT is non-inferior in comparison to CL testing and superior in comparison to usual care if CL is not (timely) available.
Effect on mortality/morbidity						
No studies identified	-	-	-	-	-	
Effect on QoL						
No studies identified	-	-	-	-	-	

Abbreviations: CL – central laboratory; NRCT – non randomised controlled trial; pts – patients; RR – referral rate; SRs – systematic reviews; TAT – turnaround time.

2 SCOPE

This rapid assessment addresses the research question whether using the point of care tests (POCT) for D-dimer and troponin in symptomatic populations presenting at ambulatory care (primary or community care settings) or emergency care settings is more effective and/or safer than current diagnostic practice. This topic was chosen based on a request from the representatives of the federal states in Austria who commissioned our agency to do a health technology assessment (HTA) on two POCTs, D-dimer and troponin (Tn), in symptomatic patients. POCT is expected to enable testing during a consultation and to enable triage of patients in need of further examination and a transfer to a hospital, while sparing other unnecessary tests or hospital admissions

In order to assess the evidence on the POCTs under evaluation, we conducted an overview of reviews on the clinical utility of Tn-POCT and D-dimer POCT. We also extracted information on the surrogate endpoints related to diagnostic test accuracy (DTA) if these were also included in the reviews on clinical utility.

In addition, the scope of this assessment was limited to two broad categories: ambulatory care (primary and community care) and emergency medicine.

Table 7: Inclusion criteria (PICO) for Tn-POCT

Population	Adult patients ≥18 years with signs and or symptoms of acute coronary syndrome (ACS) and/or other symptoms such as chest pain or breathlessness that are potentially indicative of acute myocardial infarction which is suspected and has not been ruled out. Specific high-risk groups of patients will be excluded. The intended use of the biomarker cardiac troponin is for use in patients who present with chest pain and/or suspected myocardial infarction (MI). MeSH-terms: acute coronary syndrome, myocardial infarction, unstable angina pectoris, cardiac troponin. ICD-10: I20-I24
Intervention	Point of care cardiac troponin products that are available on the market are as follows: i-STAT cTnI (Abbott Point of Care), Roche CARDIAC Troponin T, Cobas h232 (Roche), Stratus® CS Analyzer (Siemens), Minicare I-20 Troponin-I (cTnI) assay (Philips), LABGEO^{IB} TnI analyser (Samsung), ADEXUSDx® Troponin I Test (NowDiagnostics), RAMP® Cardiac Troponin I test (Response Biomedical), Troponin I Test (Eurolyser), mLabs Troponin I (Micropoint), PATHFAST^{TM} (LSI Medience Corporation; former Mitsubishi), Triage Troponin I Test (Quidel), AQT90 FLEX cTnI and AQT90 FLEX cTnT (Radiometer), troponin I test (PBM), i-CHROMA Diagnostics (Sycomed)
Comparison	All comparators will be included. For the impact of POCT on patient management, usual care (incl. central laboratory methods) will be used. In the diagnostic performance testing, reference standard tests are likely to include echocardiography, angiography and laboratory testing (as opposed to the near-patient testing devices).
Outcomes	Evidence-based clinical recommendations regarding the use of Tn-POCT Effectiveness/clinical utility: • *Patient management:* Number of hospital admissions, treatment initiation, referral rates (RR), door-to-needle time (DNT), turnaround time (TAT), time to discharge (TTD), length of stay (LOS), further diagnostic testing, time to clinical decision (TCD) • Mortality and morbidity • patient quality of life (QoL) Safety: side effects/disbenefits

Study design	At the first stage, systematic reviews and meta-analyses as well as HTA reports and evidence-based guidelines will be included. Publications published from 2009 onwards will be included (to identify recently published systematic reviews). For the search to identify relevant guidelines, no filter with regard to publication date applied. In a 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.

Table 8: Inclusion criteria (PICO) for D-dimer POCT

Population	Adult patients ≥18 years with symptoms such as leg swelling, chest pain or trouble breathing that are potentially indicative of deep vein thrombosis or pulmonary embolism. Specific high-risk groups of patients (e.g. those with a previous VTE or those with cancer) will be excluded. 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.[10] The intended use of the technology is for use as a diagnostic tool to rule out the presence of venous thromboembolism often in conjunction with use of a clinical prediction rule (such as Wells or Geneva). MeSH-terms: Pulmonary Embolism, venous thrombosis, thromboembolism, "fibrin fibrinogen degradation products"
Intervention	D-dimer POCTs included the following products: SimpliRED D-dimer (Agen Biomedical), NycoCard™ D-dimer Single Test (Abbott), Triage D-dimer (Alere), Clearview Simplify D-dimer (Alere), Roche Cardiac D-dimer (Roche), Dade Dimertest (Siemens) Stratus CS Acute Care D-dimer (Siemens), mLabs D-dimer (Micropoint Bioscience), PATHFAST D-dimer (Pathfast), i-CHROMA D-dimer (Boditech), AQT90 FLEX D-dimer (Radiometer)
Comparison	All comparators will be included. For the impact of POCT on patient management, usual care (incl. central laboratory methods) will be used. In the 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	Evidence-based clinical recommendations regarding the use of D-dimer POCT Effectiveness/clinical utility: • *Patient management:* Number of hospital admissions, treatment initiation, referral rates (RR), door-to-needle time (DNT), turnaround time (TAT), time to discharge (TTD), length of stay (LOS), further diagnostic testing, time to clinical decision (TCD) • Mortality and morbidity • patient quality of life (QoL) Safety: side effects/disbenefits
Study design	At the first stage, systematic reviews and meta-analyses as well as HTA reports and evidence-based guidelines will be included. Publications published from 2009 onwards will be included (to identify recently published systematic reviews). For the search to identify relevant guidelines, no filter with regard to publication date applied. In a 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.

[10] https://bmjopen.bmj.com/content/suppl/2015/11/11/bmjopen-2015-008864.DC1/bmjopen-2015-008864supp_tables.pdf

3 METHODS AND EVIDENCE INCLUDED

3.1 Assessment Team

LBI-HTA (lead authors):

- Developed first draft of EUnetHTA project plan
- Identified and contacted manufacturers
- Performed the literature search, literature selection, data extraction and risk of bias assessment (in agreement with co-author).
- Performed interviews with stakeholders in AT to ascertain context factors.
- Carried out the assessment: answered assessment elements, filled in checklist regarding potential “ethical, organisational, patient and social and legal aspects” of the HTA Core Model® for rapid REA.
- Sent “draft versions” to reviewers, compiled feedback from reviewers and performed changes according to reviewer’s comments.
- Prepared final assessment and wrote the executive summary of the assessment

NSPHMPDB (co-authors):

- Contributed to the development of the EUnetHTA project plan
- Reviewed the project plan draft.
  Supported the production of all domains and quality checked all steps (relating to data, information, sources).
- Co-authored the report (e.g, collaboration in the literature selection, independent quality assessment, and verification of the data extraction)
- Performed interviews with stakeholders in RO to ascertain context factors.
- Approved/endorsed conclusions drawn as well as all draft versions and the final assessment including the executive summary.
- Made substantial contributions to the conception, and revision of the report (especially Romanian context)
- Gave final approval of the version to be published

Dedicated reviewers:

- Guaranteed quality assurance by thoroughly reviewing the project plan and the assessment drafts.
- Reviewed methods, results, and conclusions based on the original studies included.
- Provided constructive comments in all the project phases

External expert:

- Guaranteed quality assurance by thoroughly reviewing the project plan and the assessment drafts.
- Reviewed methods, results, and conclusions based on the original studies included
- Provided constructive comments in all project phases

The project was split into two parts: D-dimer POCT and Tn-POCT. One researcher from the LBI-HTA was in charge of these projects respectively (LS, GG). From the co-authors, there were four researchers involved: two researchers for D-dimer (SF, MC) and troponin (SGS, CS) respectively. One further researcher from LBI-HTA (JE) was in charge of the guideline synopsis on the use of these biomarker tests and was assisted by all other researchers.

Co-authors were involved for all decisions and discrepancies were resolved by consensus.

3.2 Source of assessment elements

Assessment elements were taken from the latest version of the EUnetHTA Core Model ® (Version 4.2) [45]. Due to the fact that safety was not reported by most of the included studies, we combined presentation of the results of both of these domains in one chapter.

3.3 Search

To identify relevant clinical practice guidelines (CPGs), systematic searches were carried out in the following databases:

- Trip database
- Guidelines International Network (G-I-N) database

In addition, manual searches were carried out on the websites of the following HTA institutes and professional organizations:

- National Institute for Health and Care Excellence (NICE)
- Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften e. V. (AWMF, Association of the Scientific Medical Societies in Germany)
- Deutsche Gesellschaft für Kardiologie – Herz- und Kreislaufforschung e.V. (DGK, German Cardiac Society)
- European Society of Cardiology (ESC)
- American Heart Association/American College of Cardiology (AHA/ACC)
- Canadian Agency for Drugs and Technologies in Health (CADTH)
- Scottish Intercollegiate Guidelines Network (SIGN)
- New Zealand Guidelines Group (NZGG)
- Australian National Health and Medical Research Council (NHMRC)
- Belgian Healthcare Knowledge Centre (KCE)
- Royal Australasian College of Surgeons (ASERNIP-S)
- UpToDate database: https://www.uptodate.com/home

To identify potentially relevant systematic reviews and meta-analyses, systematic searches in the following four databases were performed:

- The Cochrane Library
- Centre for Reviews and Dissemination (CRD)
- Embase via Elsevier
- Medline via Ovid

To identify primary studies updating or extending the evidence derived from available systematic reviews, a further search was conducted in the following databases:

- Medline via Ovid
- Embase via Elsevier
- The Cochrane Library
- Cumulative Index to Nursing and Allied Health Literature (CINAHL)

Detailed tables on search strategy are included in Appendix 1.

Table 9 gives a broad overview of the research questions and the methods used to answer these.

Table 9: Research questions and the related method used

Research questions	Method
How do evidence-based guidelines recommend Tn-POCT be used (position in the diagnostic path, threshold values in different patient populations, settings)?	Synopsis of recommendations from CPGs (included in health problem and current use)
How do evidence-based guidelines recommend D-dimer-POCT be used (position in the diagnostic path, threshold values in different patient populations, settings)?	Synopsis of recommendations from CPGs (included in health problem and current use)
What are the clinical benefits of Tn-POCT in the management of symptomatic patients (adults)?	A systematic review of effectiveness and safety
What are the clinical benefits of D-dimer POCT in the management of symptomatic patients (adults)?	A systematic review of effectiveness and safety
Can a theoretical benefit of POCT (D-dimer and Tn) be realized in the Austrian and Romanian context?	Consultation with experts in AT and RO to reflect on context factors (expert input)

3.4 Study selection

Searching and study selection occurred separately for each POCT. Study selection was undertaken by two independent researchers for each POCT in accordance with the PRISMA statement [20, 21].

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).

For guidelines, no limitation was applied for the year of publication and systematic reviews were only included if published after 2009. Relevant guidelines/systematic reviews and primary studies published in English and German language were included.

Given the broad variety of definitions, we classified the device according to POCT or laboratory method following assignment by the study authors (whether they classified it as a POCT or not). If the study authors did not mention whether or not it is a POCT and we were familiar with the test, which was classified as a POCT elsewhere, we also classified it as POCT. If uncertainty persisted, we asked a clinical expert for his/her view for the final judgement. We used several sources guiding our decision as to whether a test was POCT or not [4, 8, 46, 47].

Tn-POCT

For the guideline synopsis, we searched for potentially eligible guidelines on the use of Tn-POCT in clinical practice. A total of 231 references were identified through database searching and manual searching. After title and abstract screening, 43 were identified as being potentially relevant. Of these, 35 were subsequently excluded based on the full-text review. We included eight guidelines in the synopsis. The study selection process is depicted in Figure 1.

For synthesising the evidence on the clinical utility of Tn-POCT, we firstly searched for systematic reviews of high quality that could be used for the qualitative synthesis of the evidence. The database search yielded 178 unique entries. After the abstract screening phase, 134 records were excluded and one further eligible publication was identified through a web-based hand-search, resulting in 45 publications eligible for full-text screening. Five studies met the inclusion criteria, of which only two had a sufficient (moderate or high) methodological quality according to the Assessing the Methodological Quality of Systematic Reviews-2 (AMSTAR-2) assessment and, hence was included for the synthesis of the evidence. The study selection for systematic reviews and meta-analyses is depicted in Figure 2.

In a second step, we searched for primary studies to update the evidence derived from systematic reviews and meta-analyses. The time period was chosen based on the last systematic search conducted within the identified systematic reviews (2016-2019). The database search yielded 983 unique entries that we screened on a title and abstract level. Of these, 890 articles were excluded and 93 records were eligible for the full-text screening. However, the full-text review revealed that none of these studies fulfilled our inclusion criteria. The study selection process is depicted in Figure 3.

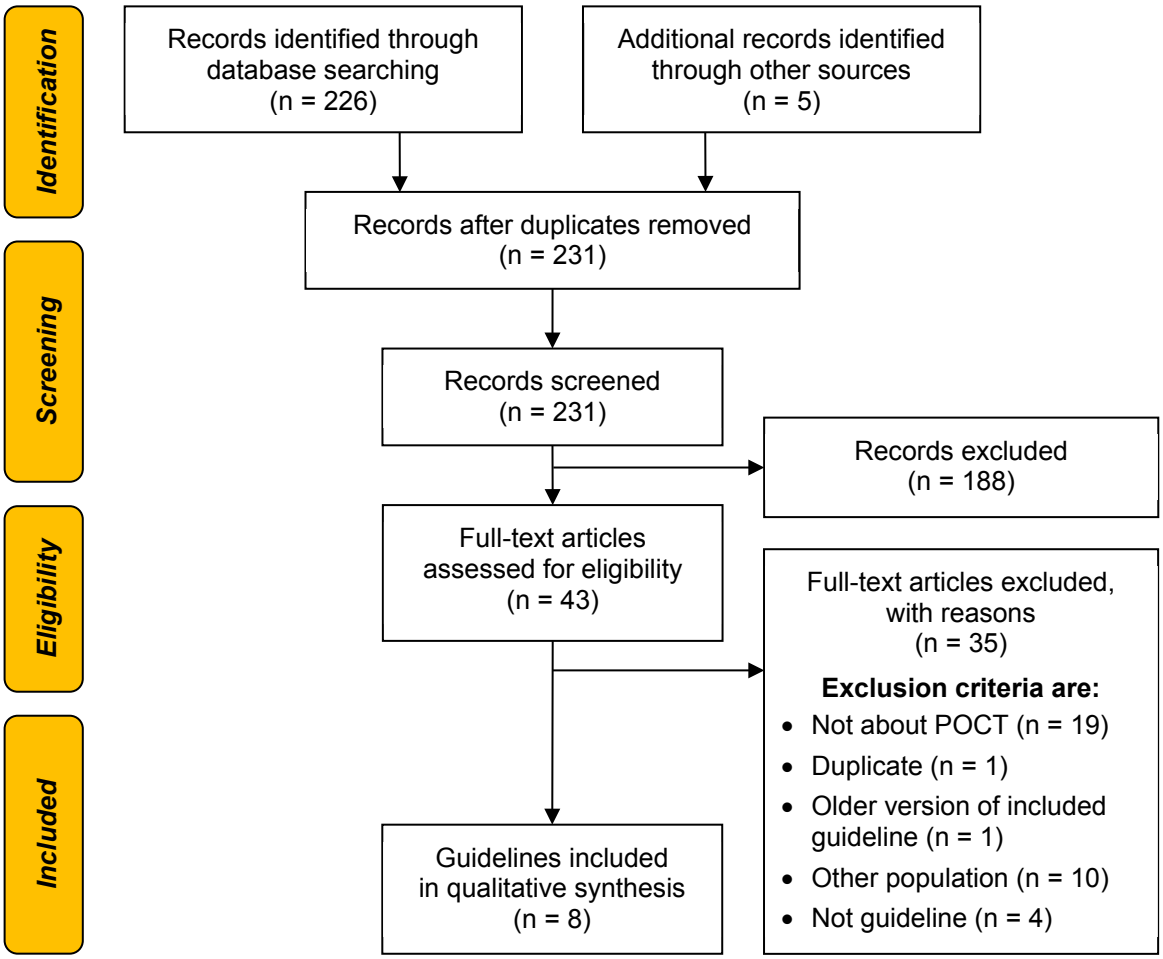


Figure 1: Flow chart to identify clinical practice guidelines on the use of Tn-POCT

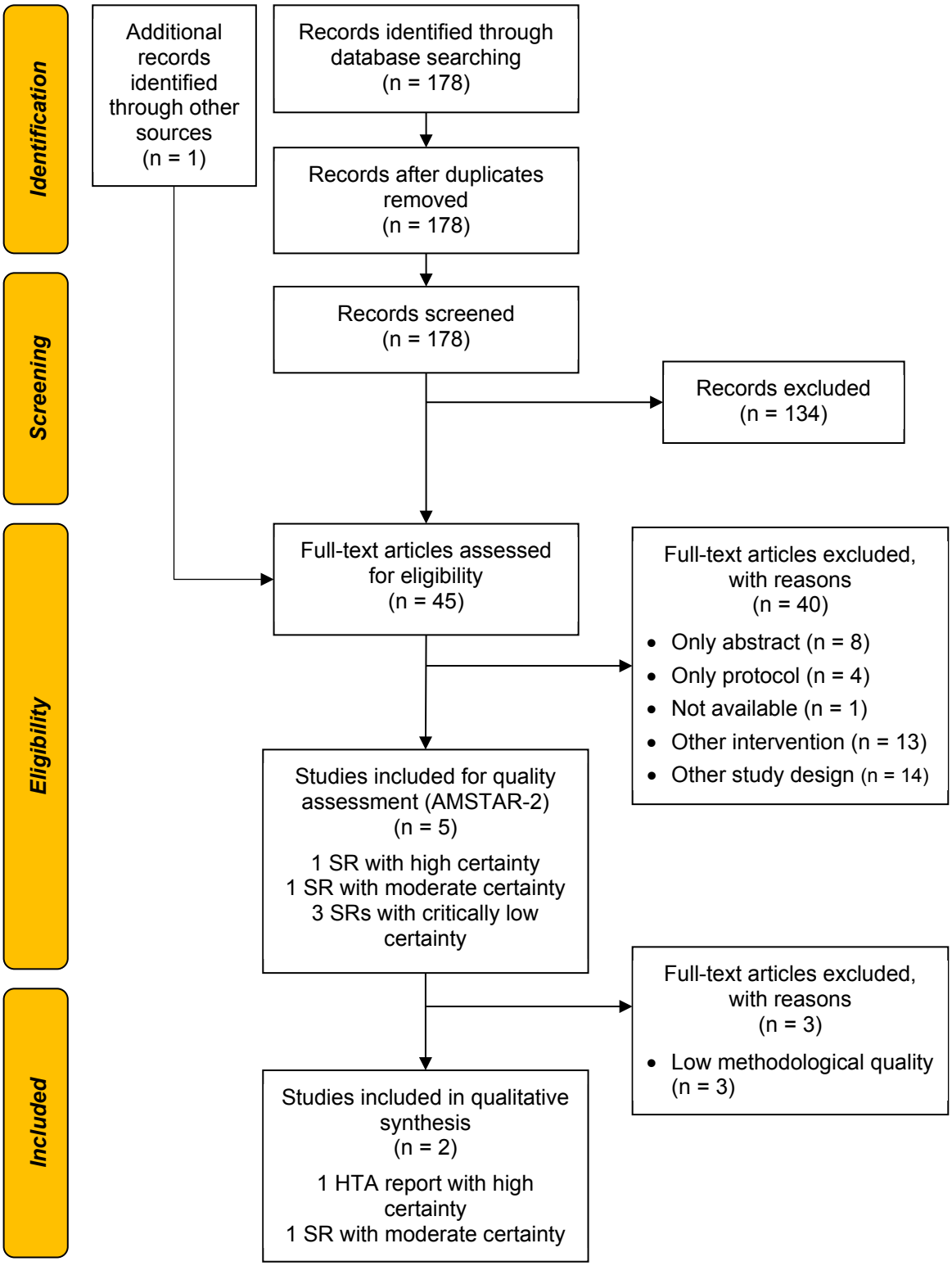


Figure 2: Flow chart to identify systematic reviews and meta-analyses for Tn-POCT

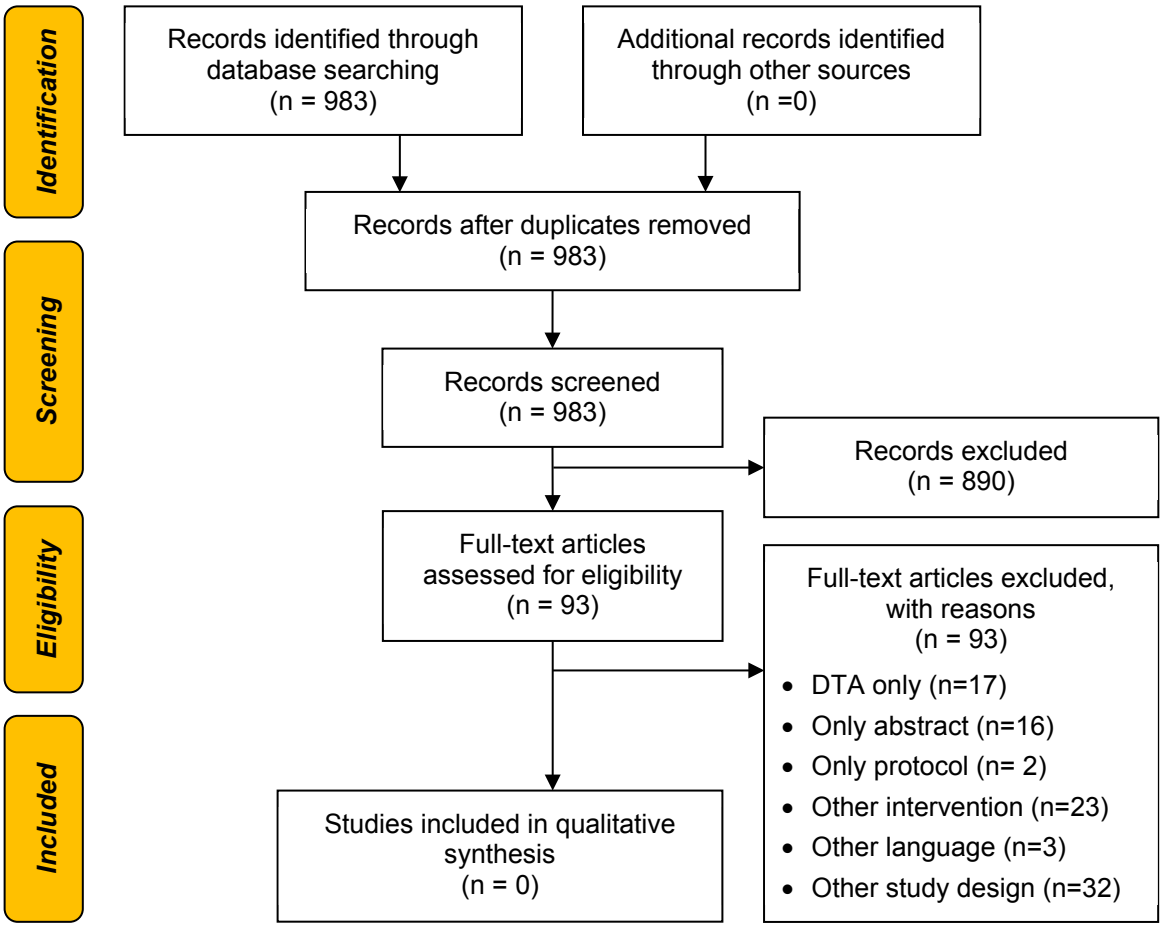


Figure 3: Flow chart to identify primary studies for Tn-POCT (publication period: 2016-2019)

D-dimer POCT

For the guideline synopsis, we searched for potentially eligible guidelines on the use of D-dimer POCT in clinical practice. A total of 149 references were identified through database searching and manual searching. After title and abstract screening, 37 references were identified as being potentially relevant. Of these, 27 were subsequently excluded due to the reasons listed in Figure 4. We included ten guidelines in the synopsis.

For synthesising the evidence on the clinical utility of D-dimer POCT, as a first step we searched for systematic reviews of high quality. The database search yielded 151 unique entries. After the abstract screening phase, 117 records were excluded and four further eligible publications were identified through other sources, resulting in 38 publications eligible for full-text screening. Nine reviews met the inclusion criteria, of which six had a sufficient (moderate or high) methodological quality according to the AMSTAR-2 assessment and, hence, were included for the synthesis of the evidence. The study selection for systematic reviews and meta-analyses is depicted in Figure 5.

One systematic review [26] was found to be the most relevant in terms of assessing clinical utility however it did not consider the emergency care setting (only primary care settings) nor deep vein thrombosis (but cardiopulmonary symptoms, pulmonary embolism) so a search of primary studies was conducted to cover these areas, using an amended search strategy based on this systematic review [26].

For deep vein thrombosis in ambulatory care (primary and community care), the database search yielded 259 unique entries that we screened on a title and abstract level. Of these, 254 articles were excluded and five records were eligible for the full-text screening. The full-text review revealed that two of these studies fulfilled our inclusion criteria. The study selection process is depicted in Figure 6.

For emergency care settings, the database search yielded 696 unique entries that we screened on a title and abstract level. Of these, 675 articles were excluded and 21 records were eligible for the full-text screening. The full-text review revealed that none of these studies fulfilled our inclusion criteria. The study selection process is depicted in Figure 7.

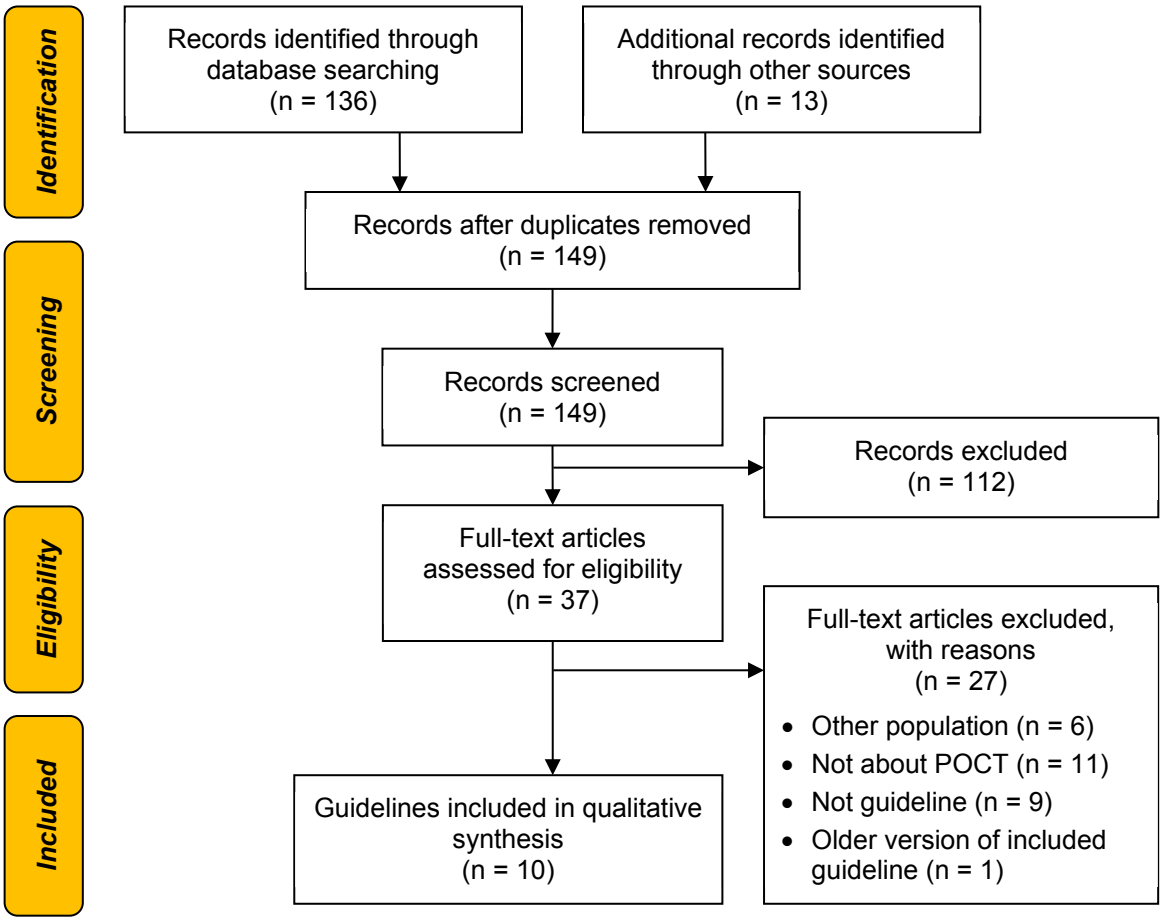


Figure 4: Flow chart to identify clinical practice guidelines on the use of D-dimer POCT

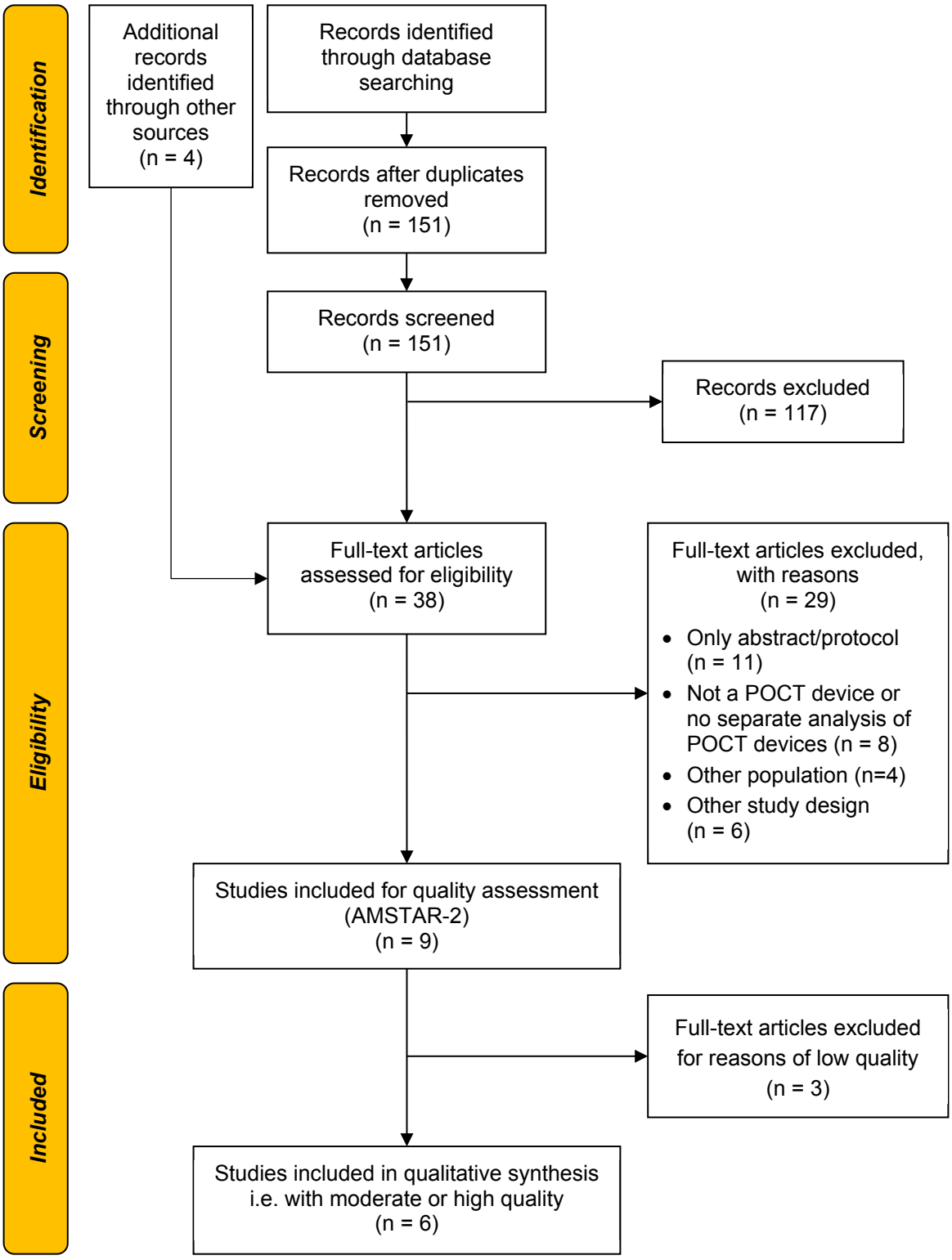


Figure 5: Flow chart to identify systematic reviews and meta-analyses for D-dimer POCT

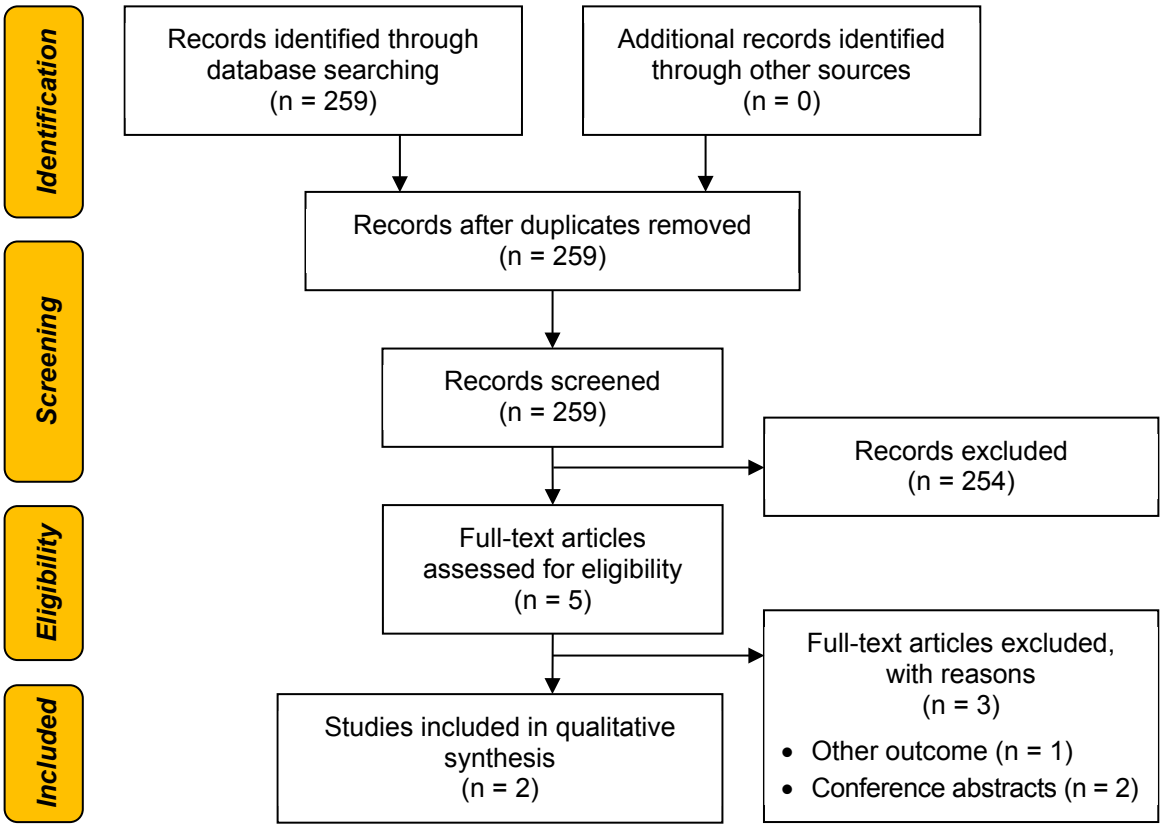


Figure 6: Flow chart to identify primary studies for D-dimer POCT in ambulatory care (primary and community care) settings

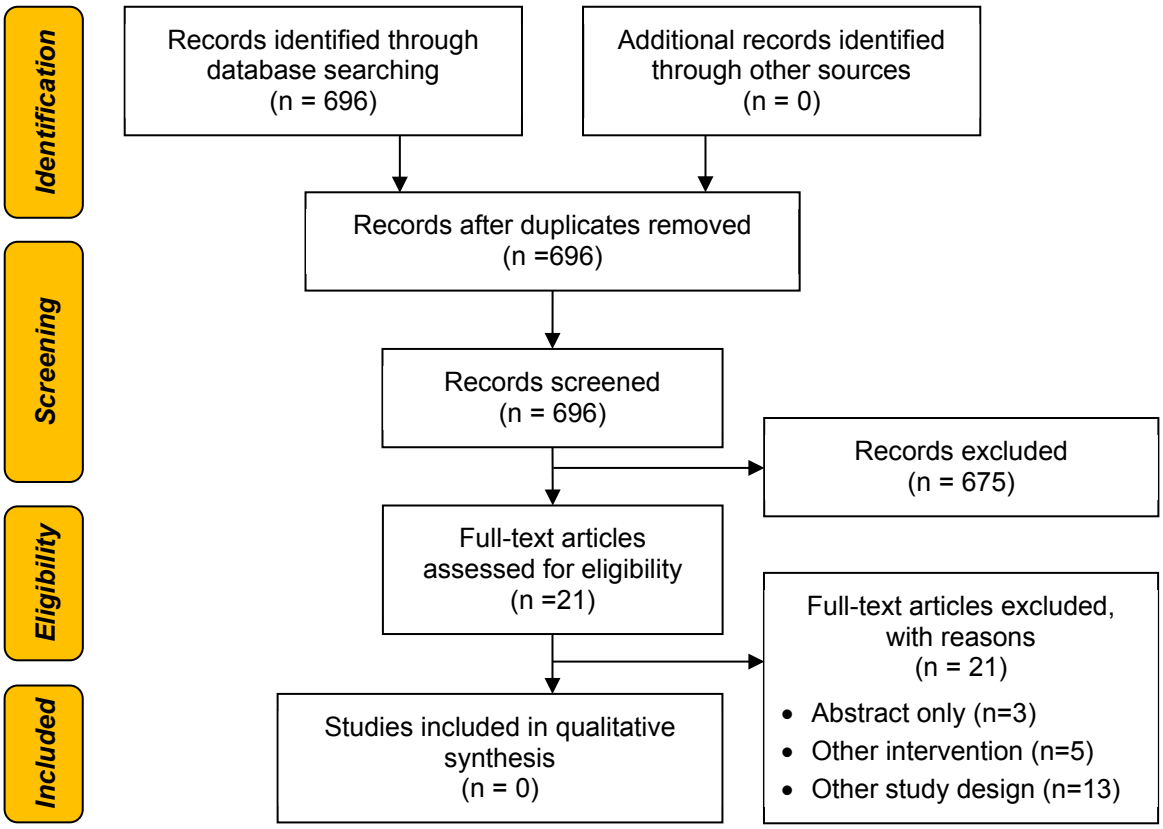


Figure 7: Flow chart to identify primary studies for D-dimer POCT in emergency care settings

3.5 Data extraction and analyses

One researcher from LBI-HTA extracted the data and another researcher from NSPHMPDB checked the extracted data. The evidence was qualitatively synthesised.

3.6 Quality rating

The quality of the eligible studies was assessed using the following tools: For systematic reviews, the AMSTAR-2 checklist [22] was utilised, whilst for randomised controlled studies and non randomised controlled trials (NRCTs) the quality was assessed using the Cochrane risk of bias tool [48] and the Robins-I tool [23] respectively.

To assess the quality of the included guidelines, the Appraisal of Guidelines, Research and Evaluation (AGREE II) reporting checklist [24] was used.

3.7 Description of the evidence used

Table 10: Main characteristics of reviews included for Tn-POCT

Author and year or study name	Study type	Quality (AMSTAR-2)	Number of included studies (Tn)/Number of included pts	Intervention (s)	Main endpoints	Included in clinical effectiveness and/or safety domain
CADTH, 2016 [25]	SR	High	41/NR	Tn-POCT	DTA and Clinical utility	EFF
Schols, 2018 [26]	SR	Moderate	2/545	Various POCT (including Tn-POCT)	DTA and clinical utility	EFF

Abbreviations: DTA – diagnostic test accuracy; EFF – effectiveness; NR – not reported; POCT – Point of Care; SAF – safety; SR – systematic review; Tn – Troponin; Tn-POCT – Troponin Point of Care.

Table 11: Main characteristics of reviews included for D-dimer POCT

Author and year or study name	Study type	Quality (AMSTAR-2)	Number of included studies (D-dimer)/ Number of included pts	Intervention (s)	Main endpoints	Included in clinical effectiveness and/or safety domain
Schols, 2018 [26]	SR	Moderate	2/892	Various POCT (including D-dimer)	Clinical effectiveness, DTA and/or effect on treatment and referral rates to secondary care	EFF
Geersing 2009 [31]	SR & meta-analysis	High	23/13,959	D-dimer POCT	DTA (sensitivity and specificity)	EFF
Pasha, 2010 [32]	SR & meta-analysis	Moderate	1/199	Lab & D-dimer POCT	Incidence of PE or DVT and its attributable mortality	EFF
Hendriksen, 2015 [33]	SR and validation of prediction models in primary care	High	10/598 [11]	Diagnostic (Pulmonary embolism) prediction models with D-dimer POCT	Discriminative ability of models, efficiency (proportion of patients in the whole cohort stratified to the group with low predicted probability of PE) and failure rate	EFF

[11] Total number of patients of the database used to test various models identified.

Author and year or study name	Study type	Quality (AMSTAR-2)	Number of included studies (D-dimer)/ Number of included pts	Intervention (s)	Main endpoints	Included in clinical effectiveness and/or safety domain
Lucassen, 2011 [34]	Meta-analysis	High	52/55,268	Physician's unstructured estimate ("gestalt") and clinical decision rules in combination with quantitative and qualitative D-dimer testing	DTA, failure rates, successful avoidance of imaging	EFF
Marquardt, 2015 [35]	SR	Moderate	7/3,279[12]	POCT in emergency departments	Turnaround time, time to diagnosis, referral or discharge	EFF

Abbreviations: SR – systematic review; POCT – Point of Care Test; DTA – diagnostic test accuracy; EFF – effectiveness, PE – pulmonary embolism.

Table 12: Main characteristics of primary studies included for D-dimer POCT & DVT

Author and year or study name	Study type	Risk of Bias	Number of included pts	Intervention (s)	Main endpoints	Included in clinical effectiveness and/ or safety domain
Oude Elferink, 2015 [37]	NRCT	Moderate	290	8 different D-dimer tests, one of which was POCT (Simplify)	DTA and clinical utility (turnaround time)	EFF
Kingma, 2017 [36]	NRCT	Severe	681	Implementation of a guideline consisting of clinical decision rule combined with negative D-dimer test	Proportion of non-referred pts, proportion of missed DVT cases, proportion of pts in whom guideline incorrectly applied	EFF

Abbreviations: DTA – diagnostic test accuracy; DVT – deep vein thrombosis; EFF – effectiveness; NRCT – non randomised controlled trial, POC – point of care.

[12] Total number of d-dimer patients on which data on turnaround time is available.

3.8 Deviations from project plan

Due to the fact that an overview of reviews was primarily conducted, Grading of Recommendations Assessment, Development and Evaluation (GRADE) [49] was not used within this assessment. Also, the included systematic reviews did not use GRADE, hence as a consequence and for consistency reasons, neither did we use GRADE when updating the evidence of these reviews.

Additional assessment elements from the HTA Core Model® for the full assessment of Diagnostic Technologies [50] were added to the effectiveness assessment elements.

There were slight adaptations of the PICO table based on the input from the clinical experts and dedicated reviewers.

Outcomes: Effectiveness and safety outcomes were changed: Harms from false positives and false negatives were initially considered as a safety outcome but is now considered as an effectiveness outcome. Safety outcomes were revised to focus on side effects/disbenefits.

4 DESCRIPTION AND TECHNICAL CHARACTERISTICS OF TECHNOLOGY (TEC)

4.1 Research questions

Element ID	Research question
B0001	What are the technology and the comparator(s)?
A0020	For which indications have the technology received marketing authorisation or CE marking?
B0002	What is the claimed benefit of the technology in relation to the comparator(s)?
B0003	What is the phase of development and implementation of the technology and the comparator(s)?
A0021	What is the reimbursement status of the technology?
B0004	Who administers the technology and the comparator(s) and in what context and level of care are they provided?
B0018	Are reference values or cut- off points clearly established?
B0008	What kind of special premises are needed to use the technology and the comparator(s)?
B0009	What equipment and supplies are needed to use the technology?

4.2 Results

Features of the technology and comparators

[B0001] – What are Tn-POCT and D-dimer POCT and usual care?

The biomarkers troponin (Tn) and D-dimer can be measured using a central laboratory (CL; e.g., in the hospital or non hospital centered medical loboratories) or by using POCT. The term usual care or standard care describes pathways that may or may not include CL. By contrast, a care pathway with Tn-POCT or D-dimer POCT is the intervention in this assessment.

POCTs, near the patient or bedside testing are diagnostic tests that are performed near patients rather than in central laboratories [1]. POCTs provide rapid feedback of 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 [2, 3].

Yet, it appears that there is no standardised robust definition of POCT within medical literature and in clinical practice. The International Organisation for Standardisation (ISO) defines POCT as *"(...) testing that is performed near or at the site of a patient with the result leading to possible change in the care of the patient" [51].*

While the ISO definition of POCT primarily refers to the geographical point (near the patient), there are further aspects that characterise POCT such as the time point (e.g., fast results). The following typical characteristics are central for a POCT device [1].

- Conducting the testing in the immediate vicinity of the patients
- Conducting the testing outside of the CL or satellite laboratory
- No sample preparation and use of full-blood instead

- No pipetting steps
- “Ready to use” reagents
- Special measuring devices that are specifically designed or used for single sample measurement
- No need for extensive medical-technical training to use the devices
- Short turnaround time (TAT)
- Possibility to immediately derive a diagnosis and draw therapeutical consequences from the results.

There are numerous different distinctions of devices in the context of POCT. There are four notable characteristics when it comes to the available devices in the context of POCT [9]:

- **Hand-held devices [9]:** These devices can be qualitative (discrimination against plus/minus results) or quantitative (usually this test needs a further analyser; see description of other unit-use systems below).
- **Other unit-use or multi-use systems [9]:** For each testing, there is a packed strip to be used for single-use; whole blood is hereby used. These systems can be designed only for one parameter or for different multiple parameters by using different test strips [9]. An example of aunit-use POCT systems is the i-STAT manufactured by Abbott [9].
- **Fixed devices (benchtop-instruments):** These devices are complex analytical systems that usually need more space than unit-use systems. These analytical systems may be described as highly optimised, more compact and user-friendly systems that still use the same technology as is used in central laboratories [9]. Examples of small bench-top analysers include, for instance, the PathfastTM, AQT90 FLEX, and the Stratus® CS 200 Acute Cardiac Care device [52].
- **Lab-on-a-chip systems:** This new instrument is aimed to have the whole laboratory testing within one chip, but is insufficiently developed and evaluated to be used in clinical practice [9].

The intervention (implementing Tn-POCT or D-dimer POCT) covers not only the test per se, but also, for instance, the training of personnel. The comparator of this assessment (usual care) also consists of the same biomarker testing but in a medical laboratory, not at the point of care.The reader is referred to chapter 5 for a nuanced description of the potential comparators currently used in clinical practice.

Table 13: Overview of available Tn-POCT and D-Dimer POCT systems

	Technologies	
Name	**Tn-POCT**	**D-dimer POCT**
Proprietary name (Manufacturer)	i-STAT cTnI (Abbott Point of Care) CARDIAC Troponin T, cobas h 232 (Roche) Stratus® CS Analyzer (Siemens) Minicare I-20 Troponin I (cTnI) assay (Philips) LABGEO^{IB} TnI analyser (Samsung) ADEXUSDx® Troponin I Test (NowDiagnostics), RAMP® Cardiac Troponin I test (Response Biomedical), mLabs Troponin I (Micropoint) PATHFAST^{TM} (LSI Medience Corporation; former Mitsubishi), Triage Troponin I Test (Quidel) AQT90 FLEX cTnI and AQT90 FLEX cTnT (Radiometer), Troponin I Test (Eurolyser), LifeSign MI TnI (PBM/Lifesign) i-CHROMA Diagnostics (Sycomed)	SimpliRED D-dimer (Agen Biomedical) NycoCard™ D-dimer Single Test (Abbott) Triage D-dimer (Quidel) Clearview Simplify D-dimer (Alere) Roche Cardiac D-dimer (Roche) Dade Dimertest (Siemens) CS Acute Care D-dimer (Siemens) mLabs D-dimer (Micropoint Bioscience) PATHFAST D-dimer (LSI Medience Corporation; former Mitsubishi), i-CHROMA D-dimer (SYCOmed) AQT90 FLEX D-dimer (Radiometer)

Note: products were identified using a web-based search. The list of these devices is not exhaustive.

Abbreviations: Tn-POCT – Troponin point of care testing; D-dimer POCT – D-dimer point of care testing.

Sources: [53-74]

For Tn-POCT, 15 devices were identified for this assessment. Of these, 14 devices measure troponin quantitatively and one further device measures it qualitatively. For D-dimer POCT, eleven devices were identified, eight of which measure D-dimer quantitatively. When reviewing the characteristics of the identified devices, it is notable that these are heterogeneous between devices when it comes to both analytic performance (see differences in analytical range and sample size) and further technological characteristics (e.g., as to whether they can be connected to another device on which diagnostic data can be stored). For a nuanced description of the available devices according to information from the manufacturers and online resources, the reader is referred to Table 14 and Table 15 for Tn-POCTs and to Table 16 and Table 17 for D-dimer POCTs.

The identification of all available POCT devices was challenging due to a number of factors: first, the vague definition of POCT, which was particularly problematic when the author or manufacturer did not use the term POCT as such; second, there are numerous POCT devices on the market (as a result, the reader is reminded that the tables are not exhaustive); and third, there are some products that measure multiple biomarkers[13] in one test. These POCT systems were deemed to be beyond the scope of this assessment.

[13] Products are among others: *Samsung LABGEO* IB SOB Cardiac 3 Panel Test (Troponin I/NT-proBNP/D-dimer), *Samsung LABGEO* IB CHF Plus Test Troponin I/NT-proBNP, *Samsung LABGEO* IB Cardiac 3-in-1 Panel Test Troponin I/CK-MB/Myoglobin, ADEXUSDx® Troponin I/Myoglobin Test, Quidel Triage® Cardio 2 Panel (Trop, BNP), Quidel Triage® Cardio 3 Panel (CK-MB, Trop, BNP), Quidel Triage Meter Pro (Troponin I, CK-MB, Myoglobin, BNP and D-dimer), Quidel Triage Cardiac Panel (Myoglobin, CK-MB und Troponin)

Table 14: Features of Tn-POCT systems

Product name (manufacturer)	i-STAT cTnI (Abbott Point of Care)	CARDIAC Troponin T, cobas h 232 (Roche)	Stratus® CS Analyzer Tropo-nin-I (Siemens)	Minicare I-20 Troponin-I (cTnI) assay (Philips)	LABGEO^{IB} TnI analyser (Samsung)	ADEXUSDx® Troponin I Test (NowDiagnostics)	RAMP® Cardiac Troponin I test (Response Biomedical)
Source(s)	[53] and information from manufacturer, [75]	Information from manufacturer, [75]	[54, 75]	[55, 75]	[56, 75]	[57, 75]	[58, 75]
Qualitative/ quantitative or semi-quantitative	Quantitative	Quantitative	Quantitative	Quantitative	Quantitative	Qualitative	Quantitative
Sample size	17 µL	150 µL	N/A	N/A	N/A	N/A	75µL
Analytical range (expected)	Reportable: 0.00 to 50.00 ng/mL (µg/L). Reference range: 0.00-0.08 ng/mL	40-2,000 ng/L	0.03-50 ng/mL	N/A	0,05-30 ng/mL	N/A	N/A
Cut-off value (ng/l)	80	50	70	N/A	100	N/A	N/A
Coefficient of Variation	10-20% (99th percentile)	N/A	<10% (99th percentile)	N/A	10-20% (99th percentile)	N/A	N/A
Storage requirements	Refrigerated at 2 to 8 ºC until expiration date. Up to 14 days at room temperature (20 to 25ºC). Individual cartridges may be used after standing five minutes at room temperature. All cartridges should be used immediately after opening pouch.	Until the printed expi-ration date at 2-8 °C. Up to 1 week at room temperature (15-25 °C). The test can be used immediately after removal from the refrigerator. The test must be used within 15 minutes once the pouch has been opened.	N/A	N/A	N/A	4-30 °C	N/A
Performance time	10 min	<12 min	14 min	10 min	20 min	15 min	19 min

Product name (manufacturer)	i-STAT cTnI (Abbott Point of Care)	CARDIAC Troponin T, cobas h 232 (Roche)	Stratus® CS Analyzer Tropo-nin-I (Siemens)	Minicare I-20 Troponin-I (cTnI) assay (Philips)	LABGEO^{IB} TnI analyser (Samsung)	ADEXUSDx® Troponin I Test (NowDiagnostics)	RAMP® Cardiac Troponin I test (Response Biomedical)
Connectivity	Wireless or wired data transfer (pending on i-STAT analyzer used) with flexible connectivity and interfacing software solutions, e.g. Abbott Info HQ.	Wireless technology (COBAS ®Technology required)	N/A	Minicare's built-in connectivity auto-matically updates the information in a patient's electronic file as soon as the reading has been obtained.	N/A	N/A	N/A
Print function	Yes (via separate i-STAT printer)	N/A	N/A	N/A	Yes	N/A	N/A
Data storage on device	Up to 1,000 test records	2,000 patient test results 500 QC test results 200 IQC test results	N/A	N/A	N/A	N/A	N/A

Note: All cut-off values and coefficient of variation values were used from a recent publication [75] that tried to standardise these using ng/l instead of µg/l; NA – not applicable or not available.

Abbreviations: IQC – internal quality control; QC – quality control.

Table 15: Features of Tn-POCT systems (continued)

Product name (manufacturer)	mLabs Troponin I (Micropoint)	PATHFAST™ High Sensitivity POC Troponin I (LSI Medience Corporation; former Mitsubishi),	Triage Troponin I Test (Quidel)	AQT90 FLEX cTnI (Radiometer),	AQT90 FLEX cTnT (Radiometer)	Troponin I test (Eurolyser)	LifeSign MI TnI (PBM/ Lifesign)	i-CHROMA Tn-I Diagnostics (Sycomed)[14]
Source(s)	[59, 75]	[60, 75]	[61, 62, 75]	[63, 75]	[63, 75], information from manufacturer	[64, 75]	[65, 75]	[66, 75]
Qualitative/ quantitative or semi-quantitative	Quantitative	Quantitative	Quantitative	Quantitative	Quantitative	Quantitative	Qualitative	Quantitative

[14] The only identified information was retrieved from a company called KIN Diagnostics. In the medical literature, the test is referred to be considered as belonging to Sycomed. It was unclear to the review authors which company lastly sells this device.

Product name (manufacturer)	mLabs Troponin I (Micropoint)	PATHFAST™ High Sensitivity POC Troponin I (LSI Medience Corporation; former Mitsubishi),	Triage Troponin I Test (Quidel)	AQT90 FLEX cTnI (Radiometer),	AQT90 FLEX cTnT (Radiometer)	Troponin I test (Eurolyser)	LifeSign MI TnI (PBM/ Lifesign)	i-CHROMA Tn-I Diagnostics (Sycomed)[14]
Sample size	250 µl	100 µl	N/A	2 mL whole blood (for up to 5 tests)	2 mL whole blood (for up to 5 tests)	N/A	120 µL	N/A
Analytical range (expected)	0.02 to 50 ng/ml	2.33-50,000 ng/L	N/A	Reportable range: 0.01-25 µg/L (ng/mL)	Reportable range: 0.01-25 µg/L	1,00-10.00 ng/ml	N/A	0.01-15.00 ng/mL
Cut-off value (ng/l)	N/A	20	N/A	99th percentile: 23 ng/L	99th percentile: 17 ng/L	1,500	N/A	N/A
Coefficient of Variation	N/A	< 10% (99th percentile)	N/A	0.021 µg/L: CV = 12.9 % 0.035 µg/L: CV = 7.7 % 9.2 µg/L: CV = 4.4 %	0.027 µg/L: CV = 9.6 % 0.21 µg/L: CV = 5.6 % 12.0 µg/L: CV = 5.4 %	N/A	N/A	N/A
Storage requirements	2-8 °C	N/A	N/A	Whole blood: 2 hours at 18-25 °C Plasma: 2 hours at 18-25 °C Plasma: 24 hours at 2-8 °C Plasma: >24 hours at -18 °C	Whole blood: 3 hours at 18-25 °C Plasma: 3 hours at 18-25 °C Plasma: 24 hours at 2-8 °C Plasma: >24 hours at -18 °C	2-8 °C.	2-30 °C.	4-30 °C.
Performance time	< 8 min	< 17 min	20 min	< 19 min	< 13 Min	10 min	15 min	N/A
Connectivity	N/A	N/A	Quidel Triage Census®-Software	Yes	Yes	N/A	N/A	N/A
Print function	N/A	Yes	Yes	Yes	Yes	N/A	N/A	N/A
Data storage on device	N/A	Patient data: 1,000, QC data: 1800, CAL data: 300	Yes	Yes	Yes	N/A	N/A	N/A

Notes: All cut-off values and coefficient of variation values were used from a recent publication [75] that standardised these using ng/l instead of µg/l;
N/A – information was not available or not found within the online search

Abbreviations: IQC – internal quality control; QC – quality control.

Table 16: Features of D-dimer POCT systems

Product name (manufacturer)	SimpliRED D-dimer (Agen Biomedical)	NycoCard™ D-dimer Single Test (Abbott)	Triage D-dimer (Quidel)	Clearview Simplify D-dimer (Sekisui)	Roche CARDIAC D-DIMER (Roche)
Source	No source identified	Information from manufacturer, [76]	[67]	[77]	[68] and information from manufacturer
Qualitative/ quantitative or semi-quantitative	Qualitative [15]	Quantitative	Quantitative	Qualitative	Quantitative
Sample size	N/A	50 µL	N/A	N/A	150 µL
Analytical range (expected)	N/A	0.1-20.0 mg/L	100-5,000 ng/mL	N/A	0.1-4 µg/mL
Cut-off value	N/A	0.3 mg/L	N/A	N/A	0.5 µg/mL
Coefficient of Variation	N/A	≤ 15% in the measuring range below 10 mg/L > 15% in the measuring range above 10 mg/L	N/A	N/A	NA
Storage requirements	N/A	2-8 °C	2-8 °C	2-25 °C	2-8 °C.
Performance time	N/A	<3 min	Appr. 20 min	10 min	8 min
Connectivity	N/A	N/A	N/A	N/A	Wireless technology (COBAS® Technology required)
Print function	N/A	N/A	Yes	N/A	N/A
Data storage on device	N/A	N/A	Yes	N/A	2,000 patient test results 500 QC test results 200 IQC test results

Notes: N/A – information was not available or not found within the online search

[15] Information was retrieved from a secondary literature [47].

Table 17: Features of D-dimer POCT systems (continued)

Product name (manufacturer)	*Dade Dimertest* Latex assay (Siemens)	*Stratus* CS Acute Care D-dimer (Siemens)	mLabs D-dimer (Micropoint Bioscience)	PATHFAST D-dimer (LSI Medience Corporation; former Mitsubishi)	i-CHROMA D-dimer (Boditech)	AQT90 FLEX D-dimer (Radiometer)
Source	[78]	[71, 72]	[69]	[70]	[79, 80]	Information from manufacturer, [73]
Qualitative/ quantitative or semi-quantitative	Qualitative/ semi-quantitative	Quantitative	Quantitative	Quantitative	Quantitative	Quantitative
Sample size	N/A	N/A	250 µL	100 µl	N/A	2 mL whole blood (for up to 5 tests)
Analytical range (expected)	N/A	6 – 5,000 ng/mL	100-10,000 ng/ml	0.005-5 µg/mL	50~10,000 ng/mL	80-100,000 µg/L.
Cut-off value	NA	NA	NA	NA	500 µg/L	500 µg/L
Coefficient of Variation	NA	4.1 % at 412 ng/mL	NA	NA	NA	194 µg/L: CV = 15.3 % 572 µg/L: CV = 12.8 % 61,614 µg/L: CV = 7.4 %
Storage requirements	2-8°C	N/A	2-8°C	N/A	4-30°C.	Whole blood: 3 hours at 18-25 °C
Performance time	N/A	14 min	4-10 min	15 min	12 min	20 min
Connectivity	N/A	N/A	N/A	NR	N/A	Yes
Print function	N/A	N/A	N/A	Yes	N/A	Yes
Data storage on device	N/A	N/A	N/A	Patient data: 1,000 QC data: 1,800 CAL data: 300	N/A	Yes

Notes: N/A – information was not available or not found within the online search

Abbreviations: IQC – internal quality control; QC – quality control.

[A0020] – For which indications have the Tn-POCT and D-dimer POCT received marketing authorisation or CE marking?

Tn-POCT and D-dimer POCTs are in vitro diagnostic tests that are used in the diagnosis and treatment of myocardial infarction and pulmonary embolism (PE)/deep vein thrombosis (DVT) respectively [53-74]. The reader is referred to chapter 5 for the current use of, and indications for, the use of the diagnostics under evaluation.

Both of the POCTs are subject to in-vitro diagnostic regulation (IVDR) from the European Union (EU) 2017/746 [81]. The IVDR replaced the former directive on in-vitro diagnostics (IVD) directive 98/79/ec [82]. Currently, there is a transition period, making the regulation fully applicable in May 2022 [83]. The aim of the new regulation is to harmonise and strengthen the regulation within the EU. Substantial changes are notable such as the rule-based classification system as opposed to the list-based approach that was previously in place. Also, new concepts of both performance evaluation and the role of clinical evidence are being introduced [84].

[B0002] – What is the claimed benefit of a pathway with Tn-POCT and D-dimer POCT in relation to usual care?

Tn-POCT has the advantage to decrease the TAT when compared to a pathway with clinical adjudication and CL. POCT usually does not replace the CL but it may be described as having an "oversight" role. As a result, the timely results (due to shorter TAT) may leverage a clinically important advantage with regard to adequate decision making in comparison to CL testing/no immediate testing [4]. This can also lead to an optimisation of resource use [85].

For Tn-POCT and D-dimer POCT, it is expected that the decreased TAT also translates into a decrease of length of stay (LOS). In some settings (such as rural or remote areas), POCT devices are also expected to avoid expensive, unnecessary transportation costs, especially in the context of Tn-POCT, if timely testing leads to triage referrals to the main centres [4]. Tn-POCT is especially sought to be beneficial in settings where CL testing is not onsite or not available 24 hours per/every day, because time is critical in the diagnosis of acute coronary syndrome (ACS). Furthermore, POCT may, especially in the context of implementing D-dimer POCT, further reduce hospital imaging [4].

On the other hand, the claimed benefit of CL testing is that it usually has better diagnostic performance: Tn-POCT is, for instance, expected to have lower sensitivity, a lower diagnostic accuracy and a lower negative predictive value (NPV) in comparison to CL testing [4].

POCT devices may also be further harmful when compared to CL testing, if quality standards are not upheld. Incorrect results may lead to undesirable effects that could have otherwise been prevented [86]. Therefore, analytical and diagnostic performance is of great importance in the context of POCT devices. These may suffer from increased risk of error in the pre-, intra-, and post-analytical period. In the pre-analytical period, for instance, one problem may be that further parameters are measured that are beyond the scope of the actual clinical question. For instance, the biomarkers myoglobin and Creatin-Kinase Muscle-Brain (CK-MB) are often used with Tn-POCT devices even though there is proof that they do not exhibit valuable additional information [86]. In the intra-analytical period, some POCT devices' measurements may be more inconclusive [86]; e.g., POCT devices measuring cardiac Tn have been critiqued to not meeting recommended quality standards [87]. In the post-analytical period, risks of error may include the poorer documentation (that is often handwritten), and, in combination with the fast accessibility of the results, can lead directly to harms to the patients [86]. As a result, it is mandatory to reflect on strategies with regard to quality assurance when implementing these devices [88].

[B0003] – What is the phase of development and implementation of Tn-POCT and D-dimer POCT and the comparators?

[A0021] – What is the reimbursement status of Tn-POCT and D-dimer POCT?

The manufacturers were asked for information on the reimbursement status of the POCT devices under evaluation. However, we only received some information on the reimbursement status. For products of the company radiometer, Tn-POCT and D-dimer POCT are currently reimbursed in Italy, Belgium, Netherlands, Czech Republic, Germany, France, Hungary, Switzerland and Turkey (see Table 18).

Table 18: Overview of countries providing reimbursement for the AQT90 Flex analyser

Country	cTnI	cTnT	D-dimer
Austria			
Italy	Y	Y	Y
Lithuania			
Belgium	Y	Y	Y
Netherlands	Y	Y	Y
Czech Rep.	Y	Y	Y
Denmark			
Germany	Y	Y	Y
Spain			
France	Y	Y	Y
Hungary	Y	Y	Y
United Kingdom			
Schwitzerland	Y	Y	Y
Turkey	Y	Y	Y
Finland			
Norway			
Sweden			

Note: Radiometer kindly provided us with this information. “Y” means that it is currently reimbursed.

Abbreviations: cTnI – cardiac troponin I; cTnT – cardiac Troponin T; Y – yes.

[B0004] – Who administers Tn-POCT and D-dimer POCT and the comparator(s) and in what context and level of care are they provided?

Both of the technologies under evaluation are used by healthcare professionals. Tn-POCT[16] and D-dimer POCT may be used in emergency care settings such as emergency departments (ED) as well as primary care settings [5-7]. Tn-POCT may further be used in other pre-hospital emergency medicine (PHEM) settings such as in ambulance cars [5].

[16] For Tn-POCT, certain in-hospital settings such as intensive care units may also be a setting where Tn-POCT may be used, but these settings were beyond the scope of this assessment [4].

[B0018] – Are reference values or cut- off points clearly established?

Ideally, devices measuring cardiac Tn should meet a 10% coefficient of variation (CV) at the 99th percentile upper reference limit. However, for POCT devices in the context of Tn, a CV of ≤ 20% at the 99th percentile upper reference limit (URL) is regarded as being acceptable in the medical literature [46]. Tn assays are – regardless of whether tested in a CL or at the point of care – neither standardised nor are they harmonised. That is to say; every assay uses a distinct set of antibodies for capturing and detecting Tn in the blood [8]. In addition, most of the data on analytical characteristics stem from the manufacturers, as opposed to solid data from studies that have been published in peer-reviewed academic journals. This data often does not correspond to data in clinical laboratories in clinical practice [46].

For D-dimer assays, the commercially available devices approved by the Food and Drug Administration (FDA) vary greatly when it comes to reference values and clinical cut-offs [7]. When using CL testing, a normal range of D-dimer is considered to be less than 500 ng/ml [3, 89, 90]. Ideally, the clinical laboratory should establish the reference range and cut-off value. In case a cut-off value from the literature is used, it is mandatory that the methodology of measurement is identical – preferably also coming from the same manufacturer. Some POCT devices also test D-dimer semi-quantitatively based on latex agglutination. This testing, however, is less clinically valuable due to a high inter-observer variability [91].

[B0008] – What kind of special premises are needed to use the technology and the comparator(s)? Overlaps with: B0009

[B0009] – What equipment and supplies are needed to use POCT devices?

Test kits and/or analysers and adequate know-how are required to use the POCT devices. However, the required equipment and supplies strongly depend on the type of POCT being implemented. If fixed devices (benchtop-instruments) are implemented, one has to further think of where the analysers are to be positioned because these tests technically cannot be moved but have a specific location, e.g., in doctor's office or ambulance [9].

5 HEALTH PROBLEM AND CURRENT USE OF THE TECHNOLOGY (CUR)

5.1 Research questions

Element ID	Research question
A0002	What is the disease or health condition in the scope of this assessment?
A0003	What are the known risk factors for the disease or health condition?
A0004	What is the natural course of the disease or health condition?
A0005	What are the symptoms and the burden of disease or health condition for the patient?
A0006	What are the consequences of the disease or health condition for society?
A0024	How is the disease or health condition currently diagnosed according to published guidelines and in practice?
A0025	How is the disease or health condition currently managed according to published guidelines and in practice?
A0007	What is the target population in this assessment?
A0023	How many people belong to the target population?
A0011	How much are the technologies utilised?

5.2 Results Tn-POCT

Overview of the disease or health condition

[A0002] – What is acute coronary syndrome (ACS) in the scope of this assessment?

ACS is a health condition encompassing means and spectrum of signs and symptoms caused by a decreased blood flow in the coronary arteries (myocardial ischemia). The term ACS is used for patients that present with suspected or confirmed acute myocardial ischemia or infarction (MI). There are different types of ACS such as non-ST elevation myocardial infarction (NSTEMI), ST-elevation myocardial infarction (STEMI) or unstable angina (UA) [10, 11].

ACS can be categorized in terms of the ST-segment elevation into two groups:

- Persistent (>20 min) ST-segment elevation with acute chest pain. The persistent ST-elevation is indicative of immediate coronary angiography because patients normally have an acute total coronary occlusion and most of them develop an STEMI [14].
- No persistent ST-elevation with acute chest pain. This condition is suggestive of non-ST segment elevation ACS (NSTE-ACS) [14]. These patients present a broad clinical spectrum and can further be divided on the basis of cardiac biomarkers of necrosis to NSTEMI or UA. UA is characterised by myocardial ischemia without elevated biomarkers and means a potentially reversible phase [11, 14, 19].

[A0003] – What are the known risk factors for ACS?

Factors that could increase the probability of developing ACS are older age, male sex, positive family history of coronary artery disease (CAD), the presence of peripheral arterial disease, diabetes mellitus, hyperlipidaemia, hypertension, renal insufficiency, prior MI, and prior revascularization

[11, 14]. ACS occurs three to four times more often in men than in women below the age of 60 years, but after the age of 75, women represent the majority of patients. Women tend to present more often with atypical symptoms [12].

[A0004] – What is the natural course of ACS?

Most patients presenting with NSTE-ACS will develop NSTEMI, and most patients presenting with ST-elevation ACS will ultimately develop STEMI [14]. MI, whether STEMI or NSTEMI, is defined as the presence of acute myocardial injury detected by abnormal cardiac biomarkers in the setting of evidence of acute myocardial ischemia [92]. The treatment of MI is time-critical as the condition can lead to death. Overall, NSTEMI patients appear to have lower short-term mortality compared with STEMI individuals [11, 14], while at 1- or 2-years follow up the mortality rates become comparable (likely due to differences in baseline characteristics, including older age and a greater prevalence of co-morbidities in the NSTEMI population) [14]. Patients with UA do not develop myocardial necrosis and have a considerably lower risk of death [14].

Effects of the disease or health condition

[A0005] – What are the symptoms and the burden of ACS?

The main symptom of suspected ACS is chest pain. The clinical spectrum of NSTE-ACS may range from patients free of symptoms at presentation to individuals with ongoing ischemia, electrical or haemodynamic instability or cardiac arrest [14]. NSTE-ACS most commonly presents as a pressure-type chest pain (angina) that typically occurs at rest or with minimal exertion lasting at least 10 minutes [11], or according to the ESC definition [14] over 20 minutes, radiating to the left arm (or both arms or the right arm), neck or jaw [11, 14]. Patients with NSTE-ACS may also present with diaphoresis, sweating, dyspnoea, nausea, abdominal pain, or syncope [11, 14]. Atypical symptoms include epigastric pain, indigestion-like symptoms, stabbing or pleuritic pain and isolated dyspnoea. Atypical symptoms appear more frequently in women, older patients over 75 years, patients with diabetes mellitus and chronic renal disease or patients with dementia [11, 14].

Likewise, the main symptom of STEMI is chest pain, including various combinations of chest, upper extremity, mandibular, or epigastric discomfort during exertion or at rest, or an ischaemic equivalent such as dyspnoea or fatigue. Often, the discomfort is diffuse; not localized, nor positional, nor affected by movement of the region. However, these symptoms are not specific for myocardial ischaemia and can be observed in other conditions such as gastrointestinal, neurological, pulmonary, or musculoskeletal complaints. MI may occur with atypical symptoms such as palpitations or cardiac arrest, or even without symptoms [92].

[A0006] – What are the consequences of ACS for society?

Ischemic heart disease (IHD) remains among the leading causes of mortality globally. In Europe, approximately 1,800,000 persons die due to IHD yearly. This is 20 percent of all deaths in Europe, although the variation among countries is substantial [12, 13].

While the incidence of STEMI has decreased considerably over the last decade; the rate of NSTEMI has slightly increased [14]. The incidence rate of STEMI ranges from 43 to 144 per 100,000 per year in the various European countries [12].

STEMI mortality remains substantial; the inhospital mortality in the national registries in the ESC countries varies between 4 and 12 percent, while 1-year mortality among STEMI patients in angiography registries is approximately 10 percent [12].

The 28-day case mortality rate for ACS among patients in developed nations is approximately 10 percent, but varies with the severity of the disease and the treatment provided. Less than 15 to 30 percent of patients who present to the ED with nontraumatic chest pain have ACS (including MI and UA) [93].

Current clinical management of the disease or health condition

[A0024] – How is ACS currently diagnosed according to published guidelines and in practice?

The most common symptom suggestive of ACS is chest pain. It is important to rapidly identify the cause of the chest complaint to be able to promptly start appropriate therapy, as early intervention has shown to have better outcomes [11]. The causes of chest pain can be distinguished into two main categories: non-ischemic cardiovascular causes (aortic dissection, expanding aortic aneurysm, pulmonary embolism etc.) and non-cardiovascular causes (pulmonary, gastrointestinal, musculoskeletal, psychiatric disorders, other) [11].

The primary goal of early evaluation/initial assessment (within 15 minutes after presentation) is to confirm the diagnosis of ACS (“rule-in”) or exclude ACS as the cause of the symptoms (“rule-out”). In the course of the risk assessment, the likelihood that the symptoms represent ACS and the likelihood of adverse outcomes is evaluated and patients are assigned to low, intermediate, or high risk for ACS, based on information obtained from the patients’ medical history, physical examination, electrocardiogram (ECG) and cardiac troponins. The determination of the level of risk on initial evaluation is vital to guide patient management, including the need for additional diagnostic testing and treatment [11].

Several scoring systems and clinical prediction algorithms have been developed for risk assessment, and different guidelines have endorsed different systems. The AHA/ACC recommends for the assessment of patients presenting to the ED with undifferentiated chest pain the TIMI risk score, PURSUIT risk score, GRACE risk score, and the National Cardiovascular Data Registry’s Action Registry (NCDR-ACTION registry). The Sanchis score, Vancouver rule, Heart score and HEARTS3 score, and Hess prediction rule were developed specifically for the assessment of patients presenting with chest pain at the ED [11]. The ESC recommends the GRACE risk score or GRACE 2.0, and the TIMI risk score [14].

Steps of the initial assessment of patients with suspected ACS

Evaluation consists of an initial physical examination and medical history, which considers factors related to the likelihood of ACS such as age, sex, symptoms, prior history of coronary artery disease (CAD) and the number of traditional risk factors [11]. The initial physical examination focuses on findings that permit rapid triage and immediate diagnosis. Comorbid conditions and non-coronary causes of chest pain or extracardiac pathologies are identified [11, 14].

The resting 12 lead ECG is an important diagnostic tool in the initial assessment of patients with suspected ACS. Based on the ECG, the ST-segment elevation can be examined and the type of ACS decided on: STEMI in case of persistent ST-segment elevation or NSTE-ACS in case of non-ST-segment elevation. ECG should be done within 10 minutes of arrival to the ED or at first con-

tact with emergency medical services in the pre-hospital setting and must be interpreted by a qualified physician [11, 14, 15, 19, 27]. Outpatient facilities should have the capacity for ECG and cardiac troponin measurements with immediate ED referral because STEMI, as well as NSTEMI is a serious emergency and should be treated immediately [11]. ACS can often fail to be diagnosed with an initial ECG; the ECG results might be normal even when the patient has ACS. It is therefore recommended to obtain additional 12-lead ECGs in case of persistent or recurrent symptoms or diagnostic uncertainty [11, 19].

Biomarkers complement the clinical assessment and 12-lead ECG in the diagnosis, risk stratification and treatment of patients with suspected NSTE-ACS. Measurement of a biomarker, preferably high-sensitivity **cardiac troponin** I/T ((cTnI/cTnT) is mandatory in all patients with suspected NSTE-ACS to help to distinguish between UA and NSTEMI. Troponin should be measured at presentation and also later to identify a rising and/or falling pattern [14].

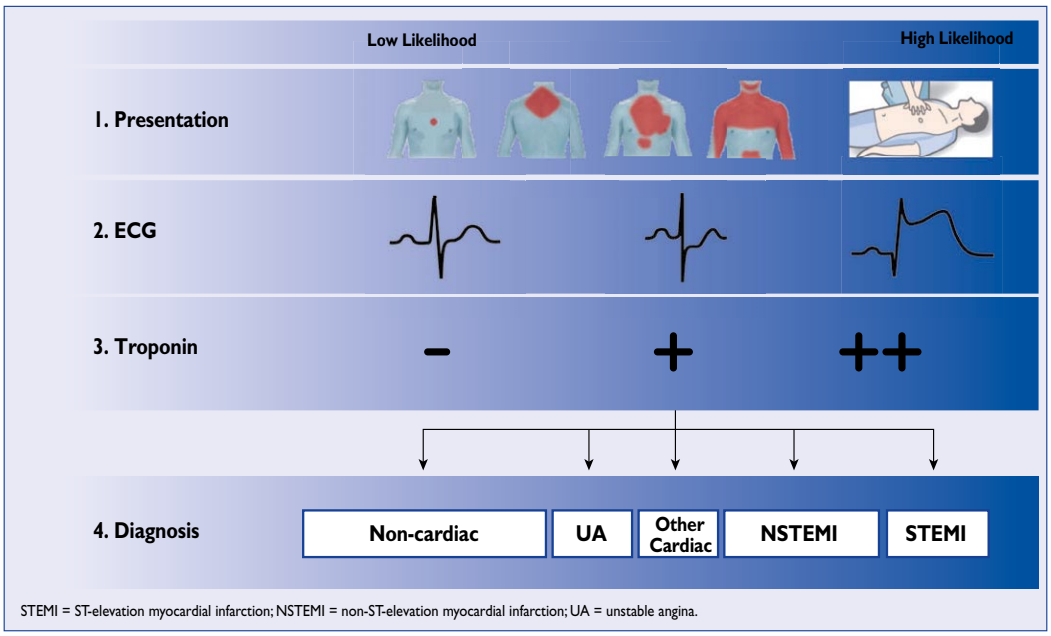


Figure 8: Initial assessment of patients with suspected ACS

Source: ESC [14]

Diagnostic algorithms (rule-in and rule-out algorithms)

Different guidelines recommend using different rule-in and rule-out algorithms for the diagnosis of ACS based on the initial risk stratification and the type of available **troponin** assay. Early rule-out protocols typically involve cardiac troponin measurements on presentation and 3 to 6 hours later with a high-sensitivity assay [11, 15, 19]. Moreover, the ESC recommends that the 0h/3h algorithm can be shortened to 0h/1h. The cut-off levels within the 0h/1h algorithm are assay dependent and always have to be accompanied by a detailed clinical assessment and ECG and repeat blood sampling if the chest pain is recurrent or ongoing [14].

The AHA/ACC recommends that additional **troponin** levels should be obtained beyond 6 hours after symptom onset in patients with normal troponins on serial examination when ECG changes and/or clinical presentation confer an intermediate or high index of suspicion for ACS. Patients with suspected ACS and high-risk features should be referred to the ED immediately. Patients with less severe symptoms may be considered for referral to the ED, a chest pain unit, or a facility capable of performing adequate evaluation [11]. In patients with possible ACS and a normal ECG, normal

cardiac troponins, and no history of CAD, it is reasonable to initially perform (without serial ECGs and troponins) coronary computerized tomography (CT) angiography to assess coronary artery anatomy (or rest myocardial perfusion imaging with a technetium-99m radiopharmaceutical to exclude myocardial ischemia) [11]. The ESC recommends that coronary angiography should be considered in high-risk patients, while in patients with low to intermediate likelihood of NSTE-ACS, CT coronary angiography should be considered [14]. Other life-threatening conditions presenting with chest pain, such as aortic dissection and pulmonary embolism, may also result in elevated troponin levels and should be considered as differential diagnoses [14, 19].

Guidelines on the use of Troponin POCT

Eight CPGs met our inclusion criteria and were included in the guideline synopsis [11, 14-16, 27-30]. Six guidelines [11, 14-16, 28, 30] were developed for the outpatient setting (ED, pre-hospital, primary care, ambulance), one guideline was developed for disaster medicine [29], one guideline did not specifically define the setting but states the guideline is applicable for all cardiac caregivers [27]. Two guidelines [15, 29] contain recommendations on the diagnosis of several health conditions including ACS. Therefore we included this guideline in the guideline synopsis on both troponin and D-dimer POCT. One of these guidelines was developed to make recommendations if the patients present with chest pain and this included the diagnosis of both pulmonary embolism (PE) and ACS [15]. The other guideline was developed for disaster medicine and includes recommendations on the diagnosis of both DVT and ACS [29]. The overview of the included guidelines including the issuing society, the date of issue, and the summary of the recommendation and the level of evidence/class of recommendation can be found in Table A2 in the appendix.

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 hospital dependent. One guideline [16] specifically states that no recommendations can be made due to lack of or weak evidence. Five guidelines only mention that POCT can be used for the measurement of cardiac troponins [11, 19, 27, 29, 30]. The German Society of General Practice and Family Medicine (DEGAM [15] recommends not to use qualitative troponin test routinely in primary care to exclude an acute MI and one guideline recommends the use of sensitive or high-sensitivity assays only [14]. Three guidelines stress that the cardiac maker testing TAT should be maximum one hour [14, 27, 30]. Two guidelines come to the conclusion that if institutions cannot comply with this requirement, POCT should be implemented [27, 30]. The National Academy of Clinical Biochemistry (NACB) [30] suggests that troponin tests should provide not only qualitative but also quantitative information.

According to the ESC and AHA guidelines, the sensitivity of Tn-POCT is considered to be below that of CL assays and they cannot be considered sensitive or highly-sensitive [11, 14]. On the other hand, SIGN states that Tn-POCT licensed in the UK are equivalent in sensitivity to the 12 hour laboratory-based standard Tn assays [28]. The ESC recommends high-sensitivity assays over less sensitive ones [14]. According to the ESC, Tn-POCT values may provide initial diagnostic information, but the advantage of shorter TAT is counterbalanced by lower sensitivity, lower diagnostic accuracy and lower NPV. Furthermore, the rigorous quantitative assay standardization that is needed for routine diagnosis favours CL testing [11].

Primarily, clinicians should be aware of the sensitivity of the tests used for troponin evaluation in their hospitals and cut-off point concentrations for clinical decisions [11]. The diagnostic thresholds depend not only on the type of the assay but also on the characteristics of the reference population (e.g. sex) [28].

The quality appraisal of the guidelines can be found in Table A11 in the Appendix. A major limitation of the guideline synopsis is that recent guidelines, published in the last three years, could not be identified. This must be taken into consideration when relying on the conclusions of the guidelines as there might be a need for update especially with the rapid technological developments in the field. Other limitations include a lack of clarity whether patients' views and preferences were sought, whether the guidelines were piloted among target users, missing procedures or plans for updating the guidelines, missing monitoring/auditing criteria, and potential cost implications of applying the recommendations was often not considered. There are some methodological weaknesses in terms of the rigour of development and missing information on editorial independence especially in two guidelines [15, 27].

[A0025] – How is ACS currently managed according to published guidelines and in practice?

The standard of care for patients who present with ACS, including those with recurrent symptoms, ischemic ECG changes, or positive cardiac troponins, is admission to hospital. The primary focus in the first 12 hours is the immediate relief of ischemia and the prevention of MI and eventually death. Patients undergo continuous ECG rhythm monitoring and observation for recurrent ischemia [11]. Patients with suspected ACS in the ambulance are assessed in the pre-hospital environment and receive treatment prior to admission to hospital, which may include administration of dual antiplatelet therapy [28].

Two treatment pathways are available for patients with NSTE-ACS: the invasive strategy triages patients to an invasive diagnostic evaluation (i.e., coronary angiography). The initial ischemia-guided strategy requires an invasive evaluation of only those who fail to respond to medical therapy, have objective evidence of ischemia, or have clinical indicators of very high prognostic risk. In both strategies, patients should receive anti-ischemic and antithrombotic medical therapy [11].

STEMI is a serious emergency and should be treated with immediate reperfusion. Primary PCI is the preferred reperfusion strategy within 12 hours of symptom onset, provided it can be performed 120min from STEMI diagnosis by an experienced team [12].

Target population

[A0007] – What is the target population of this assessment?

The target population for the use of Tn-POCT is adult patients presenting with signs and symptoms of MI. Troponin tests can spare the referral of patients to an inpatient unit in cases where there are no ischemic ECG changes, if there is clinical ambiguity, and if symptoms last for more than 12 hours [15].

[A0023] – How many people belong to the target population?

ACS is estimated to have an annual incidence rate of over 780,000 cases in the United States. Approximately 70% of these have NSTE-ACS [11]. While the incidence of STEMI has decreased appreciably over the last decade, the rate of NSTEMI has slightly increased [14].

In Europe, approximately 1,800,000 persons die due to IHD yearly. The incidence cases of IHD accounted for around 5,5 million in 2015 in Europe [13].

[A0011] – How much are the technologies utilized?

All patients who present to the ED with symptoms suspicious of cardiac ischaemia should be evaluated with cardiac biomarkers as part of the initial evaluation [16]. Cardiac specific troponin is the most widely utilized diagnostic biomarker for myocardial infarction and is the preferred laboratory test. (LOE I) [16]. In the general practitioner (GP) praxis (according to the DEGAM guideline), the measurement of the cardiac troponin is only useful in clinically ambiguous cases when the symptom onset exceeds 12 hours [15].

5.3 Results D-dimer POCT

Overview of the disease or health condition

[A0002] – What is venous thromboembolism (VTE) in the scope of this assessment?

Venous thromboembolism (VTE) 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; this is then called a DVT. Blood flow through the affected vein can be limited by the clot, 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 (PE), which in some cases may be fatal. VTE as a term includes both DVT and PE [18].

[A0003] – What are the known risk factors for VTE?

There are a number of environmental (also known as temporary or setting-related) as well as genetic (also called as permanent or patient-related) risk factors for VTE. These can also be grouped into strong, moderate and weak categories. Strong predisposing risk factors are (odds ratio >10): fracture of the lower limb, hospitalisation for atrial fibrillation or heart failure within the last 3 months, hip or knee replacement, major trauma, myocardial infarction within the last 3 months, previous VTE, spinal cord injury. Moderate risk factors (odds ratio 2-9): arthroscopic knee surgery, autoimmune diseases, blood transfusion, central venous illness, chemotherapy, congestive heart or respiratory failure, erythropoiesis-stimulating agents, hormone replacement therapy, in vitro fertilization, infection (especially pneumonia, HIV, urinary tract infection), inflammatory bowel disease, cancer, oral contraceptive therapy, paralytic stroke, postpartum period, superficial vein thrombosis, thrombophilia. Weak risk factors (odds ratio <2): bed rest longer than three days, diabetes mellitus, hypertension, immobility due to sitting e.g. due to prolonged air or car travel, increasing age, obesity, pregnancy, laparoscopic surgery and varicose veins [17].

[A0004] – What is the natural course of VTE?

VTE may be fatal in the acute phase or lead to chronic disease and disability. Acute PE is the most serious clinical presentation of VTE and is often the consequence of undiagnosed and/or untreated DVT [17]. Non-fatal VTE can cause serious longer-term conditions such as post-thrombotic syndrome (PTS) and chronic thromboembolic pulmonary hypertension (CTEPH). PTS is a chronic condition that may develop after DVT due to damage to the deep veins and their valves. It affects 20%-40% of patients after DVT of the lower limb, can be debilitating to patients, and have a significant impact on quality of life (QoL). CTEPH is less common and is caused by obstruction of the pulmonary arteries due to PE. This puts excessive pressure on the heart which can be harmful to some patients, causing heart failure [18]. The incidence of CTEPH after PE is currently estimated at

approximately 1.5% (with a wide range reported by mostly small-cohort studies), with most cases appearing within 24 months of the index event [17].

VTE can be recurrent. The rate of recurrence is highest during the first two weeks and declines thereafter. The risk of recurrence is predicted to be higher in the early period if the patient has active cancer or fails to rapidly achieve therapeutic levels of anticoagulation. The frequency of recurrence does not appear to depend on the clinical presentation (DVT or PE) of the first event, but recurrent VTE is likely to occur in the same clinical form as the index episode. Recurrence is more frequent after multiple VTE episodes as opposed to a single event, and after unprovoked VTE as opposed to if the patient is exposed to temporary (setting-related) risk factors, particularly surgery. It is also more frequent in women who continue hormone intake after a VTE episode and in patients who have had PE or proximal vein thrombosis compared to calf vein thrombosis. Elevated D-dimer levels also indicate an increased risk of recurrence [17].

Effects of the disease or health condition

[A0005] – What are the symptoms and the burden of VTE for the patient?

Clinical signs and symptoms of VTE are non-specific and often asymptomatic.

- DVT: if it is symptomatic, the most common symptoms are leg pain and/or swelling, redness and warmth in the leg.
- PE: it may be completely asymptomatic and may be discovered incidentally during diagnostic work-up for another disease or at autopsy. If PE is symptomatic, it is suspected in case of the following symptoms and signs: dyspnoea, chest pain, pre-syncope or syncope, fever, cough, unilateral leg pain, signs of DVT, tachypnoea, tachycardia, hypoxia, pyrexia, elevated jugular venous pressure, gallop rhythm, systemic hypotension, cardiogenic shock, widely split second heart sound, tricuspid regurgitant murmur, pleural rub and haemoptysis [17, 18]. Fatal PE is very often underdiagnosed, because of the non-specificity of symptoms and signs prior to death, which may be attributed to myocardial infarction, pneumonia, or other pathology [19].

VTE may be fatal. Non-fatal VTE may affect the patients' long-term QoL and functional capacity [42]. VTE has high mortality when untreated but the treatment also carries risks, principally haemorrhage [19].

[A0006] – What are the consequences of VTE for society?

VTE is likely to be an escalating public health problem due to the prominence of age as a risk factor and the increasing age of the population [19]. Patients older than 40 years are at increased risk and risk doubles with each decade. Hence an increasing number of patients are expected to be diagnosed and treated to avoid fatal PE [17]. In six European countries with a total population of 454,4 million, more than 370,000 deaths were related to VTE in 2004. Of these patients, 34% died suddenly or within a few hours of the acute event, before therapy could be started or before therapy took effect. Of the other patients, death resulted from acute PE that was diagnosed after death in 59% and only 7% of patients who died early were correctly diagnosed with PE before death [43].

Current clinical management of the disease or health condition

[A0024] – How is VTE currently diagnosed according to published guidelines and in practice?

The diagnostic algorithms differ for DVT and PE, hence they are presented separately.

A. Deep vein thrombosis (DVT)

1. The initial step if patients present with signs and symptoms suggestive of DVT is to assess the patients for their pre-test probability, i.e. the likelihood that they have DVT using a clinical probability score (also known as pre-test probability score or clinical prediction rule). Patients are stratified into different risk categories to help to choose the most appropriate diagnostic and treatment pathway. The most commonly used clinical probability score is the Wells score, which has several versions: the original, an updated and its simplified versions [17]. The original Wells score used three levels of risk: low, intermediate and high. The updated Wells score uses only two risk categories: DVT likely or DVT unlikely [18]. The simplified versions aim to facilitate adoption into clinical practice [17]. Obtaining general medical history and physical examination is part of the scoring process. It is also important to look for alternative diagnoses which would explain the symptoms. If DVT can be ruled out at this stage, additional, more costly tests and radiation exposure can be avoided [17, 18]. It is recommended by the National Clinical Guideline Centre (NCGC) [18] to use the two-level scoring system because it reduces the risk of confusion as to what to do with the moderate risk category patients. Physicians have to be trained how to complete the score, especially the item on “alternative diagnosis as likely as DVT” [18].
2. Measurement of the D-dimer level in the blood has a role in the exclusion of DVT in oligosymptomatic patients as a negative D-dimer assay implies that thrombosis is not occurring. On the other hand, a positive test can indicate not only thrombosis but also other causes, such as liver diseases, inflammation, malignancy, pregnancy, trauma, and recent surgery. With the change of the three-level scoring to the two-level scoring, the patients in the unlikely group can be more safely ruled out when the pre-test probability is combined with D-dimer testing [18].
3. Ultrasound is a non-invasive imaging modality which has high sensitivity and specificity for proximal DVT. However, ultrasound does not identify calf vein DVT reliably. Compression ultrasound uses a gentle probe pressure to try and compress the vascular lumen. If no residual lumen is observed the vein is considered to be fully compressible, indicating the absence of DVT. Duplex ultrasound is similar but a Doppler signal is used to determine blood flow characteristics. If the phasic pattern of venous blood flow is absent venous outflow obstruction is diagnosed [18].

Different guidelines propose different diagnostic workup based on the pre-test probability of patients. NCGC recommends the following algorithm (see Figure 9).

- Pre-test probability unlikely (low to moderate clinical probability): D-dimer should be tested. If the test is positive, a proximal leg vein ultrasound should be done within 4 hours of being requested. If the ultrasound cannot be done within 4 hours, parenteral anticoagulant should be taken in 24-hour doses and a proximal leg vein ultrasound should be done within the 24 hours. If the ultrasound is negative, alternative diagnoses should be considered.
- Pre-test probability likely (high clinical probability): there are two possibilities, depending on if a proximal leg vein ultrasound is available within 4 hours.
    - If a proximal leg vein ultrasound is available, it should be done within 4 hours of being requested. If the result is negative D-dimer should be tested additionally.

- If a proximal leg vein ultrasound is not available, D-dimer should be tested immediately and 24 hours dose parenteral anticoagulant should be given. A proximal leg vein ultrasound should be done within 24 hours of being requested.

If the D-dimer test is positive and the ultrasound is negative, the ultrasound should be repeated within 6-8 days. If the ultrasound and the D-dimer test are negative, or a repeated ultrasound is negative, an alternative diagnosis should be considered [18].

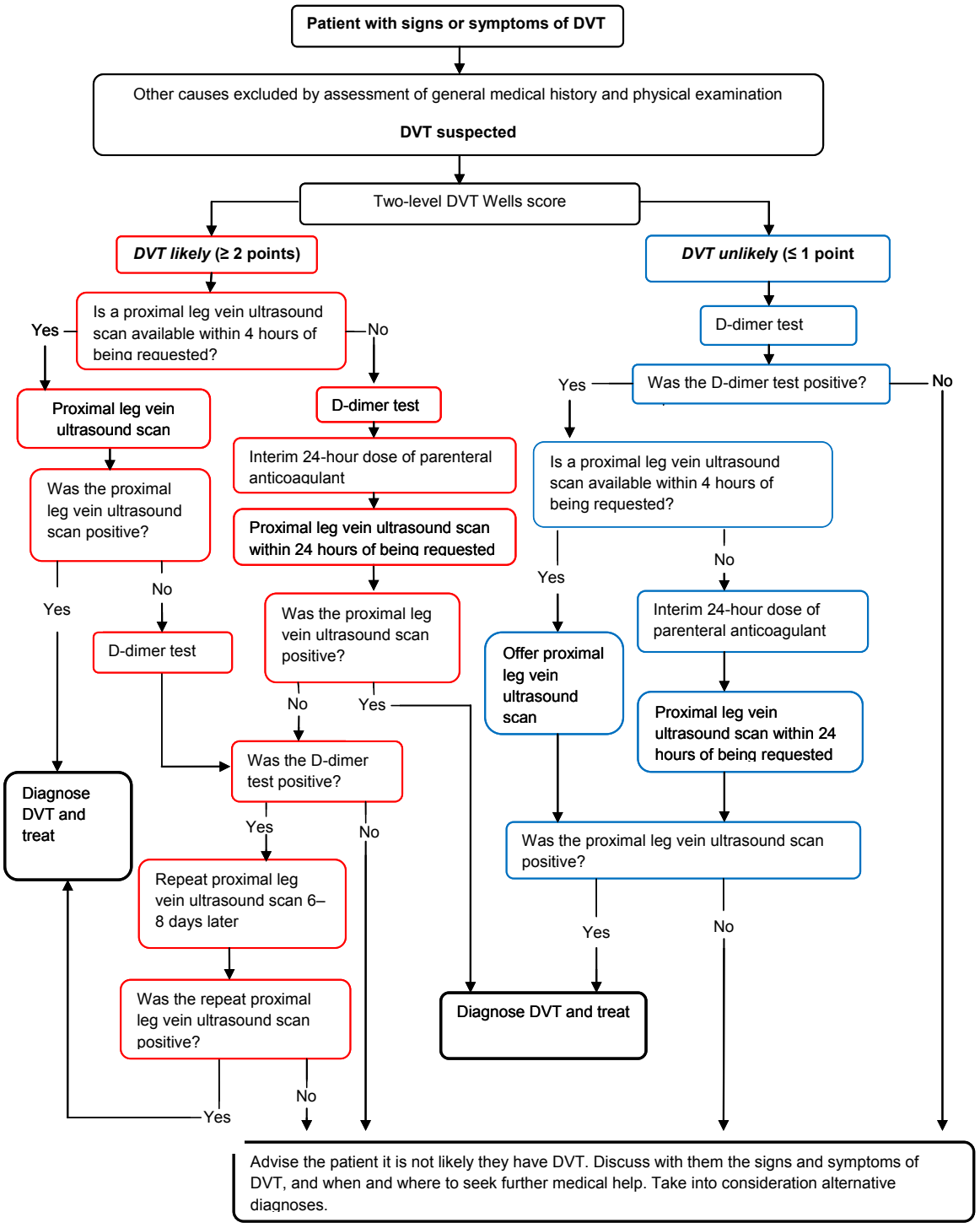


Figure 9: Diagnosis algorithm DVT [18]

SIGN and AWMF recommend that the D-dimer level should only be measured in patients with low or moderate clinical probability (or PE or DVT unlikely) only. In patients with a high clinical probability (PE or DVT likely), D-dimer should not be measured before imaging to exclude VTE, but patients should proceed immediately to imaging. A normal D-dimer test result does not safely exclude VTE, and therefore it has no value in this group. Patients with low or moderate clinical probability should be tested for D-dimer and if the test is positive, the patients should proceed to imaging. If the test is negative, the patients should be informed that VTE might be diagnosed in the upcoming three months, but no further thrombosis diagnosis is required [19, 38].

One guideline [41] recommends a slightly different algorithm. The difference is partly due to the fact that the three-level categories are used instead of the two-levels and that the type of the available D-dimer test is taken into consideration instead of the availability of ultrasound within 4 hours.

- If a highly sensitive D-dimer test is available, the first step in both the low- and moderate-risk categories is to test the D-dimer level.
    - If the test result is positive, the next step is to carry out an ultrasound scan.
      If the ultrasound is negative, a repeated ultrasound is suggested.
    - If the test result is negative, clinical follow up is recommended.
- If only moderately sensitive D-dimer test is available, it is recommended to use it as first-line diagnostic tool only for the testing of low-risk patients.
    - If the test result is positive, the patients should proceed to an ultrasound scan.
    - If the test result is negative, clinical follow up is suggested.

    In the moderate-risk category ultrasound is the first-line diagnostic tool. If the ultrasound is negative, D-dimer should be tested and if the test result is positive, ultrasound should be repeated. If the D-dimer test result is negative, clinical follow-up is recommended.

B. Pulmonary embolism (PE)

1. The initial step in the diagnosis of a patient presenting with signs and symptoms of PE is to assess the likelihood of having a PE. A number of clinical prediction scores have been developed to assess it, based on the signs, symptoms and the medical history of the patient. As clinical judgements lack standardization; several clinical prediction rules are in use, of which the most frequently used are the Wells score, the Geneva score and the Charlotte rule. The updated Wells score uses two-levels (PE likely, PE unlikely) instead of the original three levels (high, moderate and low risk). PE is likely if the score is greater than 4, PE is unlikely if the score is 4 or less. The Geneva score is based on risk factors and findings of a chest X-ray and arterial blood gases. The Charlotte rule stratifies patients into low and high-risk categories. The major difference compared to other scoring systems is that the Charlotte scoring system does not consider active cancer or a previous history of VTE a risk for developing PE [18].
2. **D-dimer** testing is combined with the clinical prediction scores to achieve additional diagnostic predictive value. The specificity of D-dimer for PE is poor, although the NPV is high [18].
3. Ventilation-perfusion (V/Q) scan consists of two parts; both involve the use of radioisotopes. In the ventilation part the patient breaths in isotopes; in the perfusion part the patient receives intravenous isotope injection. Thereafter it is detected with imaging where the isotope has gone into the lungs. This allows for the identification of areas that are ventilated but not perfused [18].
4. Computed tomography pulmonary angiography (CTPA) involves an intravenous contrast agent given to the patient and a CT of the chest afterwards. The advantage is that the CT cannot only detect pulmonary emboli but also other disorders that can be the cause of the patients' symp-

toms. The disadvantage is that the radiation is higher as compared to the V/Q scan [18]. CT angiography can confirm PE when it shows a clot at least at the segmental level of the pulmonary arterial tree [17].

It is recognized in the various guidelines that the diagnostic approach to suspected PE may vary, depending on the availability of, and expertise in, specific tests in various hospitals and clinical settings and depending on the risk score for developing PE. It needs to be mentioned that both the ESC guideline [17] and the NCGC guideline [18] refer to the ED setting only. It is emphasized in all included guidelines that D-dimer should be measured only after the prior estimation of clinical probability and that a pre-test probability score alone is not enough to rule out PE [17-19, 38-42]. The ESC differentiates suspected PE with hypotension (high-risk of PE) and without shock and hypotension (not high-risk of PE). After this initial risk stratification, the clinical probability is assessed again to distinguish between low or intermediate (PE unlikely) and high clinical probabilities (PE likely). NCGC distinguishes based on the two-level Wells score (PE likely or PE unlikely). In all guidelines, the assessment of the D-dimer level is only applicable in patients who have low or intermediate clinical probability or PE unlikely [17-19, 38-42].

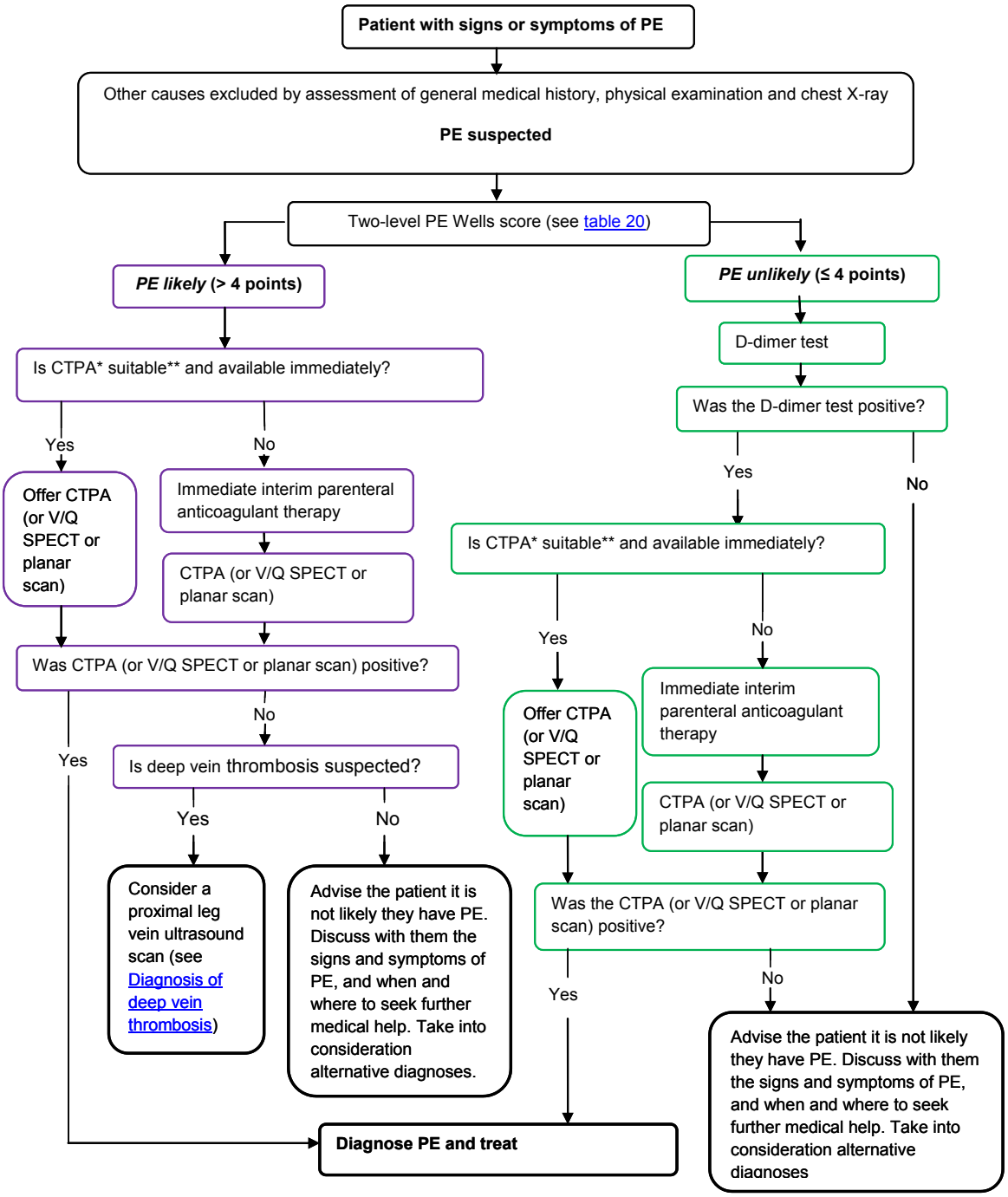
- Low or intermediate clinical probability or PE unlikely: a D-dimer test should be done immediately and if the result is positive either an immediate CTPA should be done, or if it is not available immediately, anticoagulation therapy should be started immediately and CTPA should be carried out later [17, 18]. In patients with unlikely PE score and a negative D-dimer or a positive D-dimer with a negative CTPA, an alternative diagnosis should be considered [18, 38]. The type of D-dimer test should preferably be highly sensitive [17, 40]. The ESC recommends that in low clinical probability patients, a highly, as well as a moderately, sensitive assay can be used [17].
- High clinical probability or PE likely (also suspected PE with shock or hypotension): the first-line diagnostic tools is CTPA (if CTPA is not available, ECG is first line) [17, 18]. If CTPA cannot be done instantly, immediate parenteral anticoagulation followed by CTPA later should be given. If the CTPA is negative, a proximal leg vein ultrasound should be considered [18]. In the PE-likely patient population, D-dimer has a low NPV, therefore D-dimer test is not recommended for them [17, 38]. It is also less useful in hospitalized patients because the number needed to test to obtain a clinically relevant negative result is high [17].

The NCGC diagnostic algorithm provides a good overview of this process (see Figure 10).

The use of combinations of clinical decision rules (CDRs) and D-dimer is generally applicable to ambulatory, non-hospitalised patients presenting with suggestive symptoms or signs of VTE; it should not be applied to the investigation of hospitalised patients, cancer patients, post-surgical patients and pregnant women in whom false-positive tests are more common and among whom initial investigation should be appropriate imaging [19].

The specificity, as well as the sensitivity of the assays, should be considered when making recommendations on their use and their application in the diagnostic algorithms.

- The specificity of D-dimer decreases steadily with age, to almost 10% in patients over 80 years. Evidence suggests using age-adjusted cut-offs to improve the performance of D-dimer testing in the elderly. In a meta-analysis referenced in the ESC guideline [17], age-adjusted cut-off values (age x 10 mg/L above 50 years) allowed increasing specificity from 34-46% while retaining a sensitivity above 97% [17].
- The sensitivity of the assay is affected by the duration of symptoms and the use of anticoagulants [19, 41]. The sensitivity of the D-dimer test is reduced if the duration of symptoms or signs exceeds 2 or 3 days prior to the test or with the use of heparin before testing [41].



*Computed tomography pulmonary angiogram
**For patients who have an allergy to contrast media, or who have renal impairment, or whose risk from irradiation is high , assess the suitability of V/Q SPECT† or, if not available, V/Q planar scan, as an alternative to CTPA.
†Ventilation/perfusion single photon emission computed tomography

Figure 10: Diagnostic algorithm PE [18]

Guidelines on the use of D-dimer POCT

Ten guidelines[15, 18, 19, 29, 38-43] met our inclusion criteria and included some form of recommendation or mention of D-dimer POCT. The overview of the included guidelines includes the issuing society, the date of issue, and the summary of the recommendation and the level of evidence/ class of recommendation and can be found in Table A3 in the appendix. Not all of the guidelines cover both DVT and PE. Three guidelines cover only PE [15, 40, 43], one guideline covers only

DVT [41], whilst four guidelines include recommendations both on PE and DVT [18, 19, 38, 42]. Two guidelines [15, 29] contain recommendations on the diagnosis of several health conditions including ACS. Therefore we included this guideline in the guideline synopsis on both troponin and D-dimer POCT. One of these guidelines was developed to make recommendations if the patients present with chest pain, which can include the diagnosis of both PE and ACS [15]. The other guideline was developed specifically for unusual conditions such as natural disasters and cardiovascular care and includes recommendations on the diagnosis of both DVT and ACS in these unusual conditions [29].

Different guidelines come to different conclusions regarding the use of these assays. Eight guidelines conclude that POCT can be used to exclude suspected PE or DVT [18, 19, 29, 38, 39, 41-43]. One guideline conclude that no recommendations can be made in terms of the use of POCT due to lack of or weak evidence [40]. Finally, one guideline makes recommendation for the inpatient setting and does not recommend using manual qualitative or semi-quantitative tests that are offered in doctors' offices [15].

Four guidelines highlight the importance of the type of assay chosen as different assays have different characteristics (sensitivities and specificities) and therefore require differing recommendations [15, 18, 40, 41]. Five guidelines[19, 38, 39, 41, 43] recommend the use of POCT only in low-risk patients (or PE-unlikely patients); one of these guidelines explicitly states that it is not recommended for moderate or high-risk pre-test probability patients [41]. One guideline makes recommendation indirectly on the use of D-dimer POCT, stating that there is no need for ultrasound imaging if D-dimer level can be determined with POCT [29]. Only three guidelines [19, 29, 40] indicate the level of evidence and/or class of recommendations. The quality appraisal of the guidelines can be found in Table A14. A major limitation of the guideline synopsis is that only one recent guideline [43], published in the last three years, could be identified. This must be taken into consideration when relying on the conclusions of the guidelines as there might be a need for an update especially given rapid technological developments in the field. Furthermore, there is little evidence from the primary care setting. Additionally, the guidelines used various terms to distinguish D-dimer test, such as qualitative, semi-quantitative and quantitative D-dimer assays, rapid D-dimer tests, highly-sensitive, moderate- and low-sensitivity assays, but failed to specify which tests are considered POCT based on these categories. The main focus of some guidelines was on the treatment, prevention or other diagnostic forms of VTE; here D-dimer testing is only mentioned and described briefly.

[A0025] – How is VTE currently managed according to published guidelines and in practice?

The current standard practice for the treatment of VTE is anticoagulation. These drugs "thin" the blood and prevent further clotting. There is a wide variation in practice, but patients are usually given a brief course of heparin treatment initially, while they start on a 3–6-month course of warfarin. Patients who have had recurrent VTE or who are at high risk of recurrence may be given indefinite treatment with anticoagulants to prevent further VTE episodes. However, anticoagulation treatment carries the risk of bleeding and requires the patient to have regular monitoring blood tests. In addition, there is a wide variation in practice regarding when to test for thrombophilia after VTE and controversy as to how thrombophilia should be managed if it is found on testing [18].

There is also the potential to dissolve the clots using drugs termed thrombolytics which can be used both for DVT and PE. Dissolving the clots in the pulmonary arteries may reduce the risk of fatal PE and longer-term problems with CTEPH. In the case of DVT, thrombolysis may reduce the risk of fatal PE and PTS. However, the use of thrombolytics may cause side-effects such as bleeding and guidance is needed as to which patients may benefit from their use [18].

Target population

[A0007] – What is the target population of this assessment?

The target population for the use of D-dimer POCT is adult patients at low to moderate risk for presenting with DVT or PE according to the three-level Wells score or PE or DVT unlikely according to the two-level Wells score. Specific high-risk groups, such as pregnant women are excluded from the analysis. In these selected patients, a negative D-dimer combined with the low pre-test probability score can safely rule out DVT and PE and therefore could reduce the need for further imaging and other diagnostics [18].

[A0023] – How many people belong to the target population?

VTE is the third most frequent cardiovascular disease. The overall annual incidence is 100-200 per 100,000 inhabitants in Europe [17]. DVT presents with clinical symptoms in about 1 per 1,000 people per year in the general population [19]. The estimated number of deaths due to VTE in the EU in 2004 was over 500,000 [18]. 34% of the deaths were due to sudden fatal PE, whereas 59% were due to PE that remained undiagnosed. Only 7% of the deaths were formerly diagnosed with PE before death [17]. In the United States, it is estimated that 650,000 to 900,000 individuals have acute PE each year of which 200,000 are fatal [40].

[A0011] – How much are the technologies utilized?

The standard diagnostic workup for DVT includes imaging. However, the costs of imaging modalities and the increasing number of negative tests has led to a reconsideration of the diagnostic strategies. In some patients there is no need for diagnostic imaging to exclude the disease; the diagnostic workup relies only on the information from the clinical history and examination (pre-test probability assessment), complemented by the D-dimer test results [18]. According to a Dutch primary care study referenced by the ESC guideline, PE could be ruled out in 46 percent of low-risk patients with suspected PE without proceeding to imaging tests (with a failure rate of 1.5 percent) [43].

6 CLINICAL EFFECTIVENESS (EFF) AND SAFETY (SAF)

6.1 Research questions

Element ID	Research question
D0001	What is the expected beneficial effect of the technology on mortality?
D0026	How does the technology modify the effectiveness of subsequent interventions?
D0032	How does the test-treatment intervention modify the magnitude and frequency of morbidity?
D0016	How does the use of the technology affect activities of daily living?
D0012	What is the effect of the technology on generic health-related quality of life?
D0013	What is the effect of the technology on disease-specific quality of life?
D0030	Does the knowledge of the test result affect the patient's non-health-related quality of life?
D0017	Were patients satisfied with the technology?
D0024	Is there an effective treatment for the condition the test is detecting?
D1001	What is the accuracy of the test against the reference standard?
D1002	How does the test compare to other optional tests in terms of accuracy measures?
D1003	What is the reference standard and how likely does it classify 'the target condition correctly?
D1004	What are the requirements for accuracy in the context the technology will be used?
D1005	What is the optimal threshold value in this context?
D1006	Does the test reliably rule in or rule out the target condition?
D1007	How does test accuracy vary in different settings?
D1008	What is known about the intra- and inter-observer variation in test interpretation?
D1019	Is there evidence that the replacing test is more specific or safer than the old one?
C0006	What are the consequences of false positive, false negative and incidental findings generated by using the technology from the viewpoint of patient safety?
C0008	How safe is the technology in relation to the comparator(s)?
C0002	Are the harms related to applying the technology?
C0004	How does the frequency or severity of harms change over time 'or in different settings?
C0005	What are the susceptible patient groups that are more likely to be harmed through the use of the technology?
C0007	Are the technology and comparator(s) associated with user-dependent harms?
B0010	What kind of data/records and/or registry is needed to monitor the use of the technology and the comparator?
D0020	Does use of the test lead to improved detection of the condition?
D0021	How does use of the test change physicians' management decisions?
D0010	How does the technology modify the need for hospitalisation?

The results will be reported – if possible – according to the setting: primary and community care or emergency medicine. The latter was split into ED [94] and pre-hospital emergency medicine (PHEM) that includes the ambulance emergency transport [95]. It needs to be highlighted that we expected that PHEM has no access, and primary or community care were also unlikely to have, access to a CL. The ED, on the contrary, is highly likely to have access to a CL.

6.2 Results for the use of Tn-POCT

Included studies

For the evaluation of the effectiveness of implementing Tn-POCT, two systematic reviews were included [25, 26]. One systematic review [25] from the CADTH evaluated, inter alia, the DTA and clinical utility of Tn-POCT in different settings.

The systematic search of the included systematic reviews covered the periods up until 2014 [26] and 2016 [25] respectively. As a result, an update search was conducted but we could not identify any additional primary studies for the update of these systematic reviews in the time period between 2016 and 2019 (see 3.4 Study selection).

The two systematic reviews [25, 26] consisted of a combined total of 42 primary studies. The CADTH report [25] identified 41 primary studies. Of these, nine studies investigated the DTA of Tn-POCT and 30 studies assessed clinical utility. Further two studies were included that investigated both DTA and clinical utility. The other included systematic review [26] identified two studies in the primary care settings, one of which was also included in the CADTH report [25].

The total number of patients was not reported by the CADTH report [25] and was 545 in the other systematic review [26].

Settings & outcomes measured

Evidence in the CADTH report [25] relating to the effects of Tn-POCT (clinical utility) consisted of seven randomised controlled trials (RCTs) and 25 observational studies.

The setting of these studies was dominated by the ED, with 21 included studies. Furthermore, the review identified three studies with a pre-hospital or ambulance setting and one study in primary health care centres and remote centres respectively. Besides, the CADTH report [25] included four studies conducted in coronary care units, a setting that is beyond the scope of this EUnetHTA assessment and was therefore excluded. Similarly, one study in the review looked at staff satisfaction that was not defined as a patient-relevant outcome in this assessment. The results of these studies will not be presented and, hence, the reader is referred to the original publication [25] for a detailed description of these results. The other included systematic review [26] focused only on primary care settings and included two prospective comparative cohort studies for Tn-POCT.

We selected mortality/morbidity, QoL as well as impact on patient management as relevant outcomes. For patient management, nine sub-categories of outcomes were identified: number of hospital admissions, treatment initiation, referral rates (RR), door-to-needle time (DNT), turnaround time (TAT), time to discharge (TTD), length of stay (LOS), further diagnostic testing, and time to clinical decision (TCD).

Methodological Quality/RoB assessment

The systematic reviews reached a moderate [26] and high [25] quality according to the AMSTAR-2 assessment respectively (see Table A10 in the appendix).

The methodological quality of the included studies was assessed using QUADAS-2 (diagnostic studies) in both systematic reviews for DTA studies [25, 26]. For RCTs, one systematic review used the Cochrane Risk of Bias tool [26] and the other systematic review used the Downs and Black checklist [25]. An overall score of the risk of bias of included studies was absent in both systematic reviews.

Synthesis

Both of the systematic reviews [25, 26] conducted a qualitative evidence synthesis and none of the identified systematic reviews used a standardised tool such as GRADE [49] to grade the identified evidence across studies. One systematic review rated the available evidence as limited and inconclusive [26] and the other systematic review also highlighted that the quality of the included studies is limited [25].

Index tests and reference standards

Both reviews [25, 26] used diverse types of index tests and types of reference standards. Neither of the reviews clearly described the algorithms for the diagnosis of ACS used within the primary studies. The reader is referred to the data-extraction table (Table A4) found in the appendix for more information.

Funding

In the CADTH report [25], it was reported that the organisation received funding from Canada's federal, provincial and territorial governments, with the exception of Quebec. Across all included studies, it was stated that 22/41 studies had authors with a conflict of interest (CoI) due to industry sponsoring. The other review [26] was funded by the Netherlands Organisation for Health Research and Development (ZonMw) but did not report the funding of the included primary studies.

Further notes

The inclusion criteria were, except for the aforementioned discrepancy regarding defined settings, aligned with the inclusion criteria of this overview of reviews.

Mortality

[D0001] – What is the expected beneficial effect of the technology on mortality?

The CADTH report [25] found limited evidence indicating that the use of Tn-POCT does not statistically change mortality compared with CL up to one year follow-up (FU) in the ED setting. The primary studies included in the CADTH report [25] consisted of two RCTs and three observational studies investigating the effect of implementing Tn-POCT on mortality in the ED. The two RCTs used cTnT or cTnI testing and enrolled 487 and 2,243 patients, respectively. Both of the studies compared POCT with CL result with one study finding a mortality rate of 0.5% and 0% respectively (p-value not reported). The other study found mortality data of 1% in the POCT group as opposed to 0.2% in the CL group (n. s., with p=0.142).

The remaining mortality data in the ED setting derived from observational studies were incompletely reported in the systematic review [25]. Besides, none of these observational studies compared Tn-POCT with CL devices directly.

Further, the CADTH report [25] found limited evidence that implementing Tn-POCT would not lead to a difference in 30-days mortality between Tn-POCT and usual care in the ambulance – a setting where CL testing is not available. The evidence base was one RCT with 601 enrolled patients. However, the reporting on this study was sparse[17].

The other included systematic review [26] did not identify studies reporting on mortality data in primary care settings.

[D0026] – How does the technology modify the effectiveness of subsequent interventions?

No evidence was found to answer this research question.

Morbidity

[D0032] – How does Tn-POCT modify the magnitude and frequency of morbidity?

The CADTH report [25] found evidence on the potential effect of implementing Tn-POCT on the magnitude and frequency of morbidity in the ED. Evidence from two RCTs and two prospective studies suggests that using Tn-POCT would not statistically change the frequency of severe adverse events when compared to conventional CL testing up to one year FU.

The same systematic review [25] reported on two prospective studies elaborating on cardiac events in the ED using cTnI or cTnT testing. Of these, one prospective study enrolled 704 patients and compared the 30 day cardiac event rate of Tn-POCT with conventional CL Tn testing (low-risk pts: 0% (95%CI: 0-25.9) versus 0% (95%CI: 0-21.5), p-value NR; high-risk pts: 24.8% (95%CI: 20.1-30.1) versus 28.6% (95%CI: 23.4-34.4), p-value NR). The other prospective study included 1,410 patients and compared Tn-POCT with CL testing with a cardiac event rate after one year of 2.1% (95%CI: 1.5-3) and 2.2% (95%CI:1.6-3.1) respectively.

Additionally, the systematic review [25] reported on other adverse events (AE) and composite endpoints in the ED consisting of two RCTs using cTnT or cTnI testing. Major AE after three months follow up was measured by one included RCT (2,243 enrolled patients) comparing Tn-POCT with CL testing, with a rate of 3% and 2% respectively (diff. n. s., with p=0.313). CEP events[18] at six months were measured by the other RCT (487 enrolled pts), with 10.4% (Tn-POCT) and 5.4% (CL) suffering from CEP events after six months respectively (p-value: NR).

The other identified systematic review [26] did not find evidence answering this research question in the primary care setting.

[17] Data on studies within settings where CL testing is unavailable where only briefly reported narratively in text of the SR without creating a data-extraction table for this evidence.

[18] AMI, coronary revascularization, cardiac arrest, or mortality in patients with a negative first cTn test at 3 m FU

Function

[D0016] How does the use of the technology affect activities of daily living?

No evidence was found to answer the research question.

Health-related quality of life

[D0012] – What is the effect of the technology on generic health-related quality of life?

[D0013] – What is the effect of the technology on disease-specific quality of life?

[D0030] – Does the knowledge of the test result affect the patient's non-health-related quality of life?

One included systematic review [25] identified evidence on the effect of implementing Tn-POCT on QoL in the ED setting. The evidence consisted of one RCT (2,243 enrolled patients, cTnI testing), comparing the QoL between Tn-POCT and CL testing and found no statistically significant difference in the QoL scores (measured with the EQ-5D) between groups, with 0.742 and 0.759 QoL scores after one month and 0.752 and 0.759 after three months respectively ($p>0.05$).

The other systematic review [26] did not find any evidence regarding the effect of implementing Tn-POCT on QoL in primary care settings.

Satisfaction

[D0017] – Were patients satisfied with the technology?

No evidence was found to answer the research question.

Test-treatment chain

[D0024] – Is there an effective treatment for the condition the test is detecting?

Effective treatment does exist for the ACS. The reader is referred to chapter 5 for a nuanced description.

Test accuracy

Two systematic reviews assessed the test accuracy of Tn-POCT [25, 26].

[D1001] – What is the accuracy of the test against reference standard?

[D1002] – How does the test compare to other optional tests in terms of accuracy measures?

[D1003] – What is the reference standard and how likely does it classify the target condition correctly?

The CADTH report [25] assessed the DTA and included eleven DTA studies and two companion reports across numerous different settings. There were 16 different POCT devices with an analytical performance ranging from 0.014-0.08 mcg/L at the 99th percentile. The reference standard was clinical adjudication (e.g., final diagnosis using laboratory data, independent adjudication by a

cardiologist and cardiology research clinician). The reader is referred to the data extraction table to be found in the appendix (see Table A4) and the original publication [25] for more information.

Compared with CL testing, Tn-POCT tended to have a lower sensitivity, lower NPV, higher specificity and higher positive predictive value (PPV) in this systematic review [25]. This trend was generally seen across all of the identified studies and there appeared to be no systematic differences (e.g., depending on cTnI or cTnT). The sensitivity of Tn-POCT at admission ranged from 26% to 88% for Tn-POCT and 68% to 100% when using CL testing. The specificity for Tn-POCT ranged from 84% to 98% as opposed to a range of 75% to 94% for CL testing. In addition, the PPV of all included DTA studies ranged from 31% to 85% for Tn-POCT and 10%-82% for CL testing. Lastly, the NPV was 90% to 99% for Tn-POCT and 95% to 100% for CL troponin measurements.

The other systematic review [26] included two DTA studies in primary care settings. The brand names of the evaluated Tn-POCT devices were not reported. However, the cut-off values were 0.08ug/l and 0.03ug/l in the included studies respectively. The studies used either common practice, including follow up only or evaluation of hospital records, ECG and GP's clinical evaluation or telephone interviews as reference standards. The reader is referred to the data extraction table to be found in the appendix (see Table A4) and the original publication [26] for more information. This systematic review [26] did not identify clinical studies comparing the DTA between Tn-POCT and CL testing in primary care settings. Yet, two non-comparative clinical studies focusing on DTA were identified: For MI, the sensitivity was 67% and 83% in the two included studies respectively, while the specificity was 98% and 100% respectively. The PPV was 40% in one study and 100% in the other study. The NPV for MI was 99% and 99.7%. For the diagnosis of MI and UA, the sensitivity in these two studies was 21% and 29% respectively, while the specificity was 98% and 100% respectively. The PPV and NPV were 100% and 94% in one study, and 40% and 96% in the other study respectively [26].

[D1004] – What are the requirements for accuracy in the context the technology will be used?

[D1005] – What is the optimal threshold value in this context?

No evidence was identified to answer the research questions. It appears that different troponin cut-offs are currently used. The systematic review by CADTH [25] highlighted that different troponin cut-offs were used in their included studies leading to variations in DTA. The CADTH report [25], however, tried to minimise these variations by only including studies with the 99th percentile cut-off threshold (0.014-0.08 mcg/L). The other systematic review [26] identified studies that did not clearly report on whether the 99th percentile was used in their included studies, but reported on 0.03ug/L and 0.08ug/L in their included studies respectively.

[D1006] – Does the test reliably rule in or rule out the target condition?

The reader is referred to the results on diagnostic accuracy described above.

[D1007] – How does test accuracy vary in different settings?

None of the included studies included evidence that may answer this research question. However, in both systematic reviews [25, 26] there was a wide variability of the DTA performance.

[D1008] – What is known about the intra- and inter-observer variation in test interpretation?

No evidence found to answer the research question.

[D1019] – Is there evidence that the replacing test is more specific or safer than the old one?

The reader is referred to D1001-D1003.

Safety

[C0006] – What are the consequences of false-positive, false-negative and incidental findings generated by using the technology from the viewpoint of patient safety?

The potential harms of discharged patients with an acute MI was specifically reported in one systematic review [26], although the other systematic review [25] indirectly also highlighted the harm of discharged patients with an ACS. The evidence consisted of one cohort study in the primary care setting that reported a decrease in referrals that may increase the risk of missing out patients with an acute MI or UA. 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.

[C0008] – How safe is the technology in relation to (the) comparator(s)?

[C0002] – Are the harms related to applying the technology?

[C0004] – How does the frequency or severity of harms change over time or in different settings?

[C0005] – What are the susceptible patient groups that are more likely to be harmed through the use of the technology?

[C0007] – Are the technology and comparator(s) associated with user-dependent harms?

[B0010] – What kind of data/records and/or registry is needed to monitor the use of the technology and the comparator?

No evidence was found to answer these research question.

Change in management

[D0020] – Does the use of the test lead to improved detection of the condition?

[D0021] – How does use of the test change physicians' management decisions?

[D0010] – How does the technology modify the need for hospitalisation?

For the impact of implementing Tn-POCT on patient management, nine outcomes were selected: number of hospital admissions, treatment initiation, RR, DNT, TAT, TTD, LOS, further diagnostic testing, and TCD.

Number of hospital admission

The number of hospital admissions was reported in one out of two included systematic reviews [25]: The review identified one RCT with 601 enrolled patients, comparing Tn-POCT with usual care in the ambulance – a setting where no CL testing is available. No difference in hospitalisation between groups was found hereby. However, the systematic review sparsely reported on this study[19].

Treatment initiation

The outcome treatment initiation was not reported in any of the included studies.

Referral rates (RR)

The RR were reported in both included systematic reviews: One cohort study was identified by both reviews [25, 26]. This study used cTnT testing with 196 enrolled patients in the primary health care centres where CL testing was not available. The study found a reduction of 18% (p-value not reported); however, it is necessary to highlight that this study also noted that two patients were not referred and also missed cases: one acute myocardial infarction (AMI) and one UA respectively. As a consequence, this reduction may come at the cost of an increased risk of missing patients with an AMI or UA.

Door-to-needle time (DNT)

The DNT was not reported in any of the included systematic reviews.

Turnaround time (TAT)

The TAT was reported in one out of two included systematic reviews [25]: The review identified comparative evidence (Tn-POCT versus CL) in the ED setting, consisting of two RCTs and eleven observational studies (both prospective and retrospective). The evidence derived from RCTs indicates that it may reduce the TAT between 43 and 147 minutes (median). Yet, this reduction was only statistically significant in one RCT and not reported in the other RCT. The evidence derived from observational studies shows a reduction in all eleven studies, with a mean or median time ranging from 18 to 93 minutes, although the p-value was only reported in 5/11 studies, with statistically significant differences in these studies.

The same review [25] included an observational study investigating the use of Tn-POCT in the ambulance by paramedics. This uncontrolled study included 928 patients and measured a median time from symptom onset to blood sampling of 83 minutes (range: 46-167).

Time to discharge (TTD)

The outcome TTD was reported in one of the two included systematic reviews [25]: The review identified comparative evidence (Tn-POCT versus CL) in the ED setting, consisting of two RCTs (487 and 2,134 enrolled pts) and one observational study (n=4,886), using a test strategy including cTnT/cTnI and Tn in combination with other biomarker testing respectively. The evidence derived from RCTs shows a reduction in 2/2 studies, with a reduction of 5 minutes (mean; s. s., with $p<0.05$) and 7 minutes (median; p-value not available) when using Tn-POCT respectively. The evidence

[19] Data on studies within settings where CL testing is unavailable were only briefly reported by the included review (narratively without data presented in data-extraction table for this outcome).

derived from observational studies shows a mean reduction of 26 minutes in 1/1 study (p-value not available). However, it is to be highlighted that the observational study used multiple biomarker testing, which is not within the scope of this systematic review.

Additionally, further evidence for the outcome TTD was found from one of the systematic reviews [25] in a pre-hospital setting with no access to CL testing (ambulance). One RCT was included by the systematic review that found a reduction in TTD when comparing Tn-POCT to usual care, with a median time of 8.8 and 9.1 hours in these groups respectively (p=0.05).

Length of stay (LOS)

The outcome LOS was reported in one of two included systematic reviews [25]: The review identified comparative evidence (Tn-POCT versus CL) in the ED setting. All of the studies tested for cTnT or cTnI. The evidence consisted of three RCTs and two observational studies for ED[20] stay and one further RCT investigating hospital stay in the ED. For the former, the evidence derived from RCTs (487-912 enrolled pts) shows a non-statistically significant mean or median reduction in 2/3 studies (0.2-0.8h), while also a non-statistically significant median increase in 1/3 studies (0.1 h) was notable. The two observational studies (pre-post design) measured a reduction of 1.9 hours (mean; p-value not reported) and 2-2.7 hours (median; statistically significant). For the latter (hospital stay in ED), the evidence consisting of one RCT showed a non-statistical mean reduction of 2.2 hours.

Further Testing

The outcome of further diagnostic testing was not reported in any of the included systematic reviews.

Time to clinical decision (TCD)

The outcome time to TCD was reported in one out of two included systematic reviews [25]: The review identified comparative evidence (Tn-POCT versus CL) in the ED setting. The evidence consisted of one RCT and one further observational study. The evidence of the RCT (cTnI testing, 2,134 enrolled pts) shows a median reduction of TCD of nine minutes when using Tn-POCT, although the p-value was not available. The evidence of the observational study shows a reduction of 26 minutes (mean; p-value not available). However, the observational study used multiple biomarkers, which is not within the scope of this systematic review.

[20] In fact, the original study used the term emergency room stay, but it was judged to be the same as emergency department.

6.3 Results for the use of D-dimer POCT

Included studies

The search and selection process identified six systematic reviews for inclusion [26, 31-35]. The combined total number of patients from individual studies included in the reviews ranged from 199 [32] to 55,268 [34]. The publications of two primary studies [36, 37] were additionally included that specifically considered DVT, which had not been adequately addressed in the reviews.

Settings & outcomes measured

Evidence was identified in ambulatory (primary and community) care and emergency care. Three systematic reviews [26, 31, 33] reported on evidence in ambulatory care (primary and community care), whilst two reviews [34, 35] restricted their review to the emergency department or hospital emergency care settings. One further review [32] did not specify the setting and only mentioned the outpatient setting (without further description). Two primary studies [36, 37] were further identified that focused on primary care.

The two included primary studies took place in the Netherlands in the primary care setting and both evaluated clinical utility and DTA outcomes. One study [36] combined D-dimer testing with a clinical decision rule. In terms of primary endpoints, one study [37] looked at DTA and patient management (speed of testing) whilst the other study [36] considered the proportion of non-referred patients (efficiency) and proportion of missed cases (failure rate). Age and sex distributions were similar in both studies; in one study [36] there was some loss to follow up to note in the usual care group (11%).

We selected mortality/morbidity, QoL as well as impact on patient management as relevant outcomes. For patient management, nine outcomes were selected: number of hospital admissions, treatment initiation, referral rates (RR), door-to-needle time (DNT), turnaround time (TAT), time to discharge (TTD), length of stay (LOS), further diagnostic testing, and time to clinical decision (TCD).

Methodological Quality/RoB assessment

The included systematic reviews reached a moderate [26, 32, 35] to high [31, 33, 34] quality according to the AMSTAR-2 assessment (see Table A12).

In terms of risk of bias, one study [37] was considered to have a moderate risk of bias for the patient management outcomes while risk of bias of the other study [36] was rated as severe. The endpoints of mortality/morbidity, QoL and safety were not considered by either study (see Table A13).

Synthesis

Three reviews [31, 32, 34] included a meta-analysis although the combined meta-analytic results from one of these reviews [32] could not be reported as this incorporated laboratory and POCT. Another review [33] also conducted a primary validation of the models found in the systematic review using an available dataset.

None of the identified systematic reviews used a standardised tool such as GRADE [49] to grade the identified evidence across studies.

Index tests and reference standards

The included studies used diverse types of D-dimer POCTs (e.g., both qualitative and quantitative) as well as different types of reference standards. The reader is referred to the data-extraction tables for more information (see Table A5-A8).

Funding

Funding was not reported in two reviews [32, 35] and the remaining reviews were funded by the following institutions: Netherlands Organisation for Health Research and Development (ZonMw) [26], Dutch Heart Foundation [34], Netherlands Organisation for Scientific Research [33], Netherlands Heart foundation [31].

None of the included systematic reviews reported on source of funding of their included primary studies.

One of the included primary studies [36] was funded by the Netherlands Organization for Health Research & Development (ZonMw) and the other primary study [37] did not specifically report on funding but stated that no direct financial support was received.

Mortality

[D0001] – What is the expected beneficial effect of the technology on mortality?

Mortality was only mentioned in one of six reviews [32]. The review included one study that reported on one person who died (2%) due to VTE (despite a negative D-dimer test and low clinical probability).

Neither of the included primary studies [36, 37] reported on mortality.

[D0026] – How does the technology modify the effectiveness of subsequent interventions?

There is no evidence that the D-dimer test has an influence on subsequent interventions for venous thromboembolism. However, subsequent interventions (e.g. imaging) are likely to be influenced.

Morbidity

[D0032] – How does the test-treatment intervention modify the magnitude and frequency of morbidity?

No evidence was found to answer the research question.

Function

[D0016] – How does the use of the technology affect activities of daily living?

No evidence was found to answer the research question.

Health-related quality of life

[D0012] – What is the effect of the technology on generic health-related quality of life?

No evidence was found to answer the research question.

[D0013] – What is the effect of the technology on disease-specific quality of life?

No evidence was found to answer the research question.

[D0030] – Does the knowledge of the test result affect the patient's non-health-related quality of life?

No evidence was found to answer the research question.

Satisfaction

[D0017] – Were patients satisfied with the technology?

No evidence was found to answer the research question.

Test-treatment chain

[D0024] – Is there an effective treatment for the condition the test is detecting?

Effective treatment does exist. The reader is referred to chapter 5 for a nuanced description.

Test accuracy

[D1001] – What is the accuracy of the test against reference standard?

Two reviews looked at the DTA of a ***stand-alone D-dimer POCT*** [26, 31] and reported sensitivity of 84-96%, specificity of 48-74%, PPV of 24% (only reported by one review [26]) and NPV of 96% (only reported by [26]). Diagnostic accuracy was shown by one review [31] to vary widely depending on which POCT was used with Cardiac D-dimer showing the highest sensitivity and SimpliRED showing the highest specificity. PPV of the stand-alone D-dimer was 24% [26] and NPV was 96% [26]; and another review [31] did not report on these measurements.

In combination with the Wells rule, sensitivity of D-dimer was reported to be 94-95% for a cut-off of ≤4 and 97% for a cut-off of ≤2 in one review [26], which accords with the 95- 96% observed for the original (≤4), modified (≤2) and simplified (≤1) Wells models reported by another review [33]. The specificity of D-dimer in combination with the Wells rule was reported in one review [26] to be 38-51% (depending on which study) for a cut-off of ≤4 and 32% for a cut-off of ≤2. Another review [33] reported specificity rates between 49% (for the simplified Wells with a cut-off of ≤1) and 51% (for the original Wells with a cut-off of ≤4). PPV was 21-37% for a cut-off of ≤4 and 20% for a cut-off of ≤ 2 [26] and 21% for a cut-off of ≤4, ≤2 and ≤1 [33]. NPV was reported to be 94-99% for a cut-off of ≤4 and 99% for a cut-off of ≤2 [26] and 99% for all Wells cut-offs [33].

Regarding ***D-dimer in combination with other clinical decision rules (CDRs), one review [33]*** reports on the test accuracy results of D-dimer combined with either the original revised Geneva (cut-off of ≤5) or the simplified revised Geneva (cut-off of ≤2). This was associated with a worse

sensitivity than the Wells rule and D-dimer combination as follows: 88% (cut-off ≤2) and 90% (cut-off ≤2). In terms of specificity, the original revised Geneva ≤5 performed the worst of all test/CDR combinations (48%) but the simplified revised Geneva ≤2 performed slightly better than all Wells rules in combination with D-dimer (at 53%). The PPV of the original revised Geneva ≤5 scored the worst of all the tests (20%) whilst the ≤2 performed the best at 21%. The NPV of the Geneva ≤5 was 97%, whilst for the ≤2 it was 97%.

Of the primary studies, one study [37] reported on diagnostic accuracy for the stand-alone POCT Simplify and in combination with clinical decision rules. The Simplify test reached a sensitivity of 91%, which was further improved in combination with a clinical decision rule to 95% (76-100%). The specificity was between 60.8% (stand-alone) and 62.8% (in combination with a Wells cut-off of <2).

[D1002] – How does the test compare to other optional tests in terms of accuracy measures?

No evidence was found directly comparing the accuracy of D-dimer POCT to other ways of diagnosing venous thromboembolism.

[D1003] – What is the reference standard and how likely does it classify the target condition correctly?

One review [26] referred to a composite reference standard used by the included studies (noted in a footnote to be spiral CT, ventilation-perfusion scan, pulmonary angiography, leg ultrasonography and/or three months follow up). Another review [31] included studies either using compression ultrasonography, venography, impedance plethysmography or uneventful follow up (no VTE at three months) for DVT or CT pulmonary angiography, ventilation-perfusion lung scanning, pulmonary angiography or uneventful follow up for PE. One further review [33] refers to validation of the tests using the AMUSE-2 cohort and a composite reference standard of all diagnostic imaging tests performed at the hospital (spiral computed tomography, ventilation-perfusion scanning, pulmonary angiography, leg ultrasonography and clinical probability assessment).

The reference standard employed by one primary study [37] was compression ultrasonography whilst the other primary study [36] considered whether a DVT had taken place within the three months FU.

[D1004] – What are the requirements for accuracy in the context the technology will be used?

Among populations with a low clinical probability of PE or DVT, a test with a high NPV can be used to rule out the presence of the disease.

[D1005] – What is the optimal threshold value in this context?

No evidence was found to answer the research question.

[D1006] – Does the test reliably rule in or rule out the target condition?

The reader is referred to the results on diagnostic accuracy described above.

[D1007] – How does test accuracy vary in different settings?

No evidence was found to answer the research question. The reader is referred to chapter 5 for information on different settings where D-dimer POCT may be utilised.

[D1008] – What is known about the intra- and inter-observer variation in test interpretation?

No evidence was found to answer the research question. It is worth noting that each test has its own calibration and interpretation values.

[D1019] – Is there evidence that the replacing test is more specific or safer than the old one?

There is no alternative POCT for diagnosing VTE.

Safety

[C0006] – What are the consequences of false positive, false negative and incidental findings generated by using the technology from the viewpoint of patient safety?

See answers below on clinical utility, in particular a reduction in the use of imaging would have safety benefits for patients in terms of reduced radiation.

[C0008] – How safe is the technology in relation to (the) comparator(s)?

[C0002] – Are the harms related to applying the technology?

[C0004] – How does the frequency or severity of harms change over time or in different settings?

[C0005] – What are the susceptible patient groups that are more likely to be harmed through the use of the technology?

[C0007] – Are the technology and comparator(s) associated with user-dependent harms?

[B0010] – What kind of data/records and/or registry is needed to monitor the use of the technology and the comparator?

No evidence was found to answer these research question.

Change-in management

[D0020] – Does the use of the test lead to improved detection of the condition?

[D0021] – How does use of the test change physicians' management decisions?

[D0010] – How does the technology modify the need for hospitalisation?

For the impact of implementing D-dimer POCT on patient management, nine outcomes were selected: number of hospital admissions, treatment initiation, RR, DNT, TAT, TTD, LOS, further diagnostic testing, and TCD.

Number of hospital admissions

The outcome number of hospital admissions was reported by one review [35]: The review included one before-after study with 462 enrolled patients that found a decrease of 13.8% after implementing the D-dimer POCT in the ED. However, the review sparsely reported on the study and no p-values were reported.

Treatment initiation

The outcome treatment initiation was not reported in any of the included studies.

Referral rates (RR)

The RR was not reported in any of the included systematic reviews. One out of two identified primary studies [36] reported on this outcome: No significant differences in patients referred, not referred and the proportion of VTE in patients referred/not referred between the intervention and usual care groups were found.

Door-to-needle time (DNT)

The DNT was not reported in any of the included studies.

Turnaround time (TAT)

The TAT was reported in one systematic review [35] and one primary study [37]. There was no hard evidence on TAT although the systematic review [35] found evidence in the ED and concluded narratively (no data are shown) that there was a reduction in TAT that was reflected in reduced LOS and clinical decision-making times and overall shorter patient journey times. The evidence consisted of six observational studies with overall 3,279 patients. In four studies included in this review (comparative; both prospective and retrospective) a reduction of TAT average values between 10 and 95 minutes was found when comparing the use of D-dimer POCT versus conventional D-dimer testing in the ED. For the remaining studies, the review by Marquardt and Apau [35] either did not sufficiently report on data with regard to TAT or only provide non-comparative data respectively.

The included primary study [37] reported a faster TAT for Simplify than most of the CL tests.

Time to discharge (TTD)

The outcome TTD was not reported in any of the included studies.

Length of stay (LOS)

LOS was reported in one systematic review [35]: one before-after study, with 462 enrolled patients, was included. The study found a non-statistically significant decrease, with a change in mean LOS of 8.46 to 7.14 hrs before and after implementing D-dimer POCT in the ED respectively (p=0.16).

Further diagnostic testing

One review [32] reported on a study showing that in 25% of patients – those with an unlikely clinical probability and normal D-dimer results – CT scans could be withheld.

Time to clinical decision (TCD)

The outcome TCD was not reported in any of the included studies.

Further outcomes

In addition to the selected outcomes in this report, two reviews [33, 34] reported on efficiency, which assesses the successful avoidance of imaging, and failure rates, which assesses the proportion of missed cases. Results for D-dimer combined with the Wells CDR (in different versions) were similar across the two reviews: failure rates ranged between 0.9% and 1.7% and efficiency rates ranged between 40% and 46%. For D-dimer testing combined with the two versions of the Geneva CDR, somewhat higher failure rates of 2.7% and 3.1% but similar efficiency rates (44-48%) to D-dimer combined with the Wells CDR were reported.

7 EXPERT INPUT

To address country-specific context factors, experts were consulted about the potential benefit of POCTs in the health care sector at different service provision levels (primary care, office-based specialists in the community, emergency medicine).

All experts were asked pre-defined questions and the answers were recorded. After each consultation, a summary was written and verified by the expert. In case a face-to-face consultation was not possible, the questions were sent to the expert and directly answered in written form.

The pre-defined questions and the summary of all expert consultations can be found in Appendix 5.

7.1 Austria

In the Austrian context, three experts were consulted. Two experts with experience in an ambulatory care (primary or community care) setting and one expert with experience working in the ED. Of these, two had already experience with at least one of these POCTs under evaluation.

Current use of the tests

The three clinical experts highlight that it is not quite clear how these POCT are currently used in Austria. One expert states that these POCT devices are randomly (without a general refunding process) used in general practice. In this context, it is highlighted that the patient or the doctor pay the testing. Another expert stated that he may not be able to answer the question on the current use in detail but is willing to reflect on how it may be used. The explanations of the third expert also only reflect on the potential use of POCT in Austria.

For the use of Tn-POCT in general practice, one expert states GPs who perform acute medicine or emergency medicine or so-called “Gemeinde- und Sprengelärzte” could justifiably have access to troponin testing if they are far away from hospitals or centres. However, it is highlighted that Tn testing must not be interpreted without at least clinical history, presentation and ECG reading. Another clinical expert reflected on the Austrian system that is quite hospital-based, meaning that the patients are usually referred to the hospital quickly where no Tn-POCT is done. The ED would usually have access to CL testing. Another expert mentions that no quantification on the use of Tn-POCT is possible because it is not refunded.

For the use of troponin as a diagnostics in the context of ACS, one clinical expert specifically mentions that the current ESC guideline is to be followed [14].

For D-dimer POCT, one expert did not specifically reflect on the use of D-dimer POCT in general practice or ED and another expert mentioned that D-Dimer is being used, but no quantification is possible because the costs are not refunded. One further expert did not know if the D-dimer test is used currently in office-based practices in Austria.

According to one expert, there is potentially an alternative role for D-dimer as a biomarker screening tool as it can rule out many diseases. The same expert warned that

> *“D-dimer is a very unspecific marker, which may also be positive due to inflammation. Even uncomplicated infections often show positive test results. Therefore, POC D-dimer test should have a limited availability and should be used only in selected departments in hospitals, in the EDs and by selected community-based specialists”.*

However, one expert interprets the D-dimer test as highly valuable in general practice according to own experience, while this expert had no experience with Tn-POCT in general practice, highlighting that no exclusion is possible with this test:

D-dimer: yes (s. above; (fear or symptoms of) DVT and PE rather frequent reasons for encounter: highly valuable in daily practice, Troponin: no – no exclusion possible, applicable after hours after symptom onset, so rather infrequent and good chance or expiring unused (no refund either).

Settings for POCT diagnostics

The first expert is somewhat sceptical to the potential benefit of using D-dimer POCT while reflecting somewhat positively on the value of Tn-POCT. However, the specific settings in which these would be beneficial are only vaguely answered:

"(...) The main aim of POCT is to rule out the disease and if the physician has a strong suspect that the patient has the disease, the patient will be sent to the hospital, and no POCT will be done. There is not a high risk of treating DVT later (e.g. 3 hours) if you do not do POCT, the only risk is that the patient will get PE, but it is very unlikely. (...) Tn-POCT makes more sense because coronary artery syndrome is a more severe disease. Nevertheless, it is unlikely that a patient would have ACS and not present symptoms. In ACS, an ECG is done first. If the result is clear it is not necessary to do the Tn test."

The second clinical expert describes the use of Tn-POCT or D-dimer POCT useful depending on the setting. Tn-POCT may, for instance, to be seen as

"(...) one helpful tool in a bigger picture, for family practice and outpatient units. CL test take more than few hours in any extramural setting: patient at risk of DVT/PE or coronary heart disease (CHD) cannot be sent to CL, sending blood samples takes too much time: decisions have to be made within minutes. Unavailable POCT (D-dimer) means: either admission to hospital, or organisation of imaging: venous ultrasound also not generally refunded for outpatients, so mostly angiography is performed (for: refunded): higher potential harm, no higher benefit, invasive, painful."

The third clinical expert highlights that it is dependent on the setting if such a test may be useful. The blurry and unstandardized definitions make it challenging to describe the value of POCTs in the different settings: In Austria, for example, EDs are heterogeneous, central and decentral:

"(...) Settings for these POC tests may include hospital units, such as wards, perioperative units, intensive care units, and emergency departments, outpatient departments, specialist offices, GP offices and mobile units, such as ambulance vehicles. These settings itself are heterogeneous, centralised and decentralised, some very remote. Even some hospital settings do not have a central lab available 24/7".

Summing up the content of all three expert consultations, the potential value of these POCT devices was interpreted differently. For D-dimer POCT, for instance, one expert reflects on it positively, while another expert does not see the point in using this POC diagnostic test. Consensus exists regarding the potential value of Tn-POCT in settings where a CL would not be available or would take too long to get the results. However, one expert doubts whether these settings would actually exist in Austria (because of the hospital-based healthcare system).

7.2 Romania

In the Romanian context four experts were consulted: one cardiologist, one emergency doctor, and two family physicians.

Experts' opinion on current use of the tests

All four clinicians confirmed use of rapid D-dimer and Tn tests in the emergency context, referring mainly to the emergency hospital units, or medical centres. But these facilities use the services of laboratories in their own structure. They mentioned the use of POCTs in Romania, but they were not sure about the extent of their use. However the clinicians reported that these tests in POC form are not used in the primary care or community care setting.

Experts' opinion on the usefulness of the tests

Regarding the place of the two diagnostic tests and the thresholds that may apply, almost all consulted experts said that they are useful in both diagnosis and the monitoring of patients at risk. The utility of using troponin is underlined by one expert as follows: "These tests are useful in rapid diagnosis of ACS, especially in the absence of electrocardiographic changes". A limitation in using these tests in the Romanian context might be: insufficient number of kits; overcrowding in emergency rooms that might mean the emergency doctor refers the patient to another service straight away; and insufficient training of some physicians in use and interpretation of the tests.

Experts' experience of the tests

With regard to the experts' experience, the cardiologist and the emergency doctor had both used rapid D-dimer and Tn tests, whilst one of the family physicians had only used the D-dimer. They rather used the services of laboratories in their facility structure. The physician working in the ED of the university hospital mentioned that she has *"been using both tests for about 10 years daily"* and *"they are very useful in refuting the diagnosis, especially as about 30% of patients presenting at the ED report chest pain"*.

Experts' opinion on relevant settings

All consulted experts agreed on potential settings where POCT diagnostics might sensibly be used. These are mainly the Permanent Care Centres (24-hour care) where people with emergencies go to seek health care, especially in rural remote areas. These centres arise from the agreement among a group of family physicians in a certain area to perform on-duty calls for their patients. At these centres, family physicians provide emergency care and patients attend them when their family physician is off service. In the experts' opinion, the use of these tests could potentially save lives by enabling early diagnosis and treatment, and could potentially avoid unnecessary travel and use of resources for patients that are clinically suspected but in fact do not have the disease.

In addition, one expert considered that these tests might be used in ambulatory cardiology offices or even in the emergency units of small hospitals. This would give the possibility of a more accurate diagnosis of acute coronary artery disease and would avoid the referral of patients to the next level or even to university hospitals, hence reducing the burden on these services.

All consulted experts believed that use of these tests might change referral practice, but the cardiologist also recommended training for those who might use these tests, in order that they may be able to interpret them correctly.

Current clinical decision rules in Romania

The Romanian Society of Cardiology has developed national guidelines based on those of the ESC. Based on the national guidelines, each medical setting has to develop its own clinical practice protocol. In some settings these protocols are not yet developed, in other settings they exist but clinicians do not comply with them.

In summary, the potential value of these POCTs was considered positive by all consulted experts. Rural areas with no access to CL testing were highlighted as particularly relevant settings, as it was thought that use of these tests would change referral practices and release the burden on very crowded highly specialized hospitals. If this occurs, the experts expect that it would allow for better spending of funds and better health outcomes.

8 DISCUSSION

This report aimed to evaluate the clinical utility/effectiveness and safety of Tn-POCT and D-dimer POCT in patients presenting to ambulatory care (primary or community care) or emergency care with symptoms that may indicate acute coronary syndrome, suspected deep vein thrombosis or pulmonary embolism.

For Tn-POCT, we identified 15 relevant point of care devices for this rapid evidence synthesis. Of these, 14 devices measure troponin quantitatively. For D-dimer POCT, eleven devices were identified, eight of which measure D-dimer quantitatively (see chapter 4). POCT devices can be classified in different ways [9] e.g., hand-held devices, fixed devices, etc., and manifest differences in measurement methods (e.g., quantitative vs. qualitative, the sample size and analytical range), as described in chapter 4. The exact nature of POCT products in use in the Austrian and Romanian health care systems is unknown.

Tn-POCT

The available evidence is based on two systematic reviews [25, 26] with moderate to high certainty according to AMSTAR-2. These two systematic reviews included a total of 42 primary studies, looking at diagnostic test accuracy (10 studies) and clinical utility (30 studies). Two further studies looked at both clinical utility and diagnostic test accuracy.

The results for diagnostic test accuracy show that there are significant inconsistencies in estimates measured across settings as evident in the comparison of diagnostic test accuracy estimates of the 11 studies included in the CADTH report [25] and significant limitations with the data (e.g., solely non-comparative studies in one review [26]). The comparative evidence found by the CADTH report [25] shows that, compared with CL testing, Tn-POCT tended to have a lower sensitivity, lower negative predictive value, higher specificity and higher positive predictive value.

Of the 32 studies in the included reviews that investigated the clinical utility of Tn-POCT, seven were randomised controlled trials. The evidence was insufficient to show non-inferiority in comparison to CL testing when implementing Tn-POCT if CL testing is onsite or readily available (e.g., in the emergency department). The evidence is also insufficient to clearly show superiority when compared to usual care in settings without or with delayed CL testing (e.g., certain ambulatory care settings, pre-hospital emergency medicine).

In the emergency department setting, evidence from the CADTH report [25] showed some limited evidence that implementing Tn-POCT in the emergency department reduces turnaround time (a reduction was reported in 2 RCTs), time to clinical decision (reduction shown in 2 RCTs & 1 observational study), and length of stay (reduction shown in 3 RCTs and 2 observational studies, but an increase was reported in 1 RCT). Furthermore, the use of Tn-POCT did not statistically significantly influence mortality (results reported in 2 RCTs and 3 observational studies) or adverse events (results reported in 2 RCTs and 2 observational studies) compared with CL testing for a follow up of up to one year. Additionally, quality of life was also not statistically significantly different after up to three months of follow-up (1 RCT reported on this outcome). However, overall 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 [25].

In ambulatory (primary and community) care, insufficient evidence was found indicating 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 [25, 26] 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.

In pre-hospital emergency medicine, there is also insufficient evidence indicating superiority of using a pathway with Tn-POCT compared to usual care (without Tn-POCT) in the ambulance transport: The CADTH report [25] 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 emergency department or admission to hospital whilst one non-comparative observational study showed a median turnaround time of 83 minutes (range: 46-187). Concerning mortality, the CADTH report [25] found evidence consisting of one RCT showing no difference in death in the following 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.

The results of the guideline synopsis highlight a potential scenario for the use of Tn-POCT: Two out of eight included clinical practice guidelines recommend using Tn-POCT if a turnaround time of 60 minutes cannot be met [27, 30]. It appears that these two guideline recommendations in favour of using Tn-POCTs if a rapid turnaround time cannot be ensured are consistent. The other relevant guideline recommendations do not directly address whether to use/not use Tn-POCT. One guideline from the European Society of Cardiology, for instance, also recommends that the results should be obtained within 60 minutes (Level A, class I), without specifically recommending/not recommending a Tn-POCT device [14]. One guideline [15] recommends not to use qualitative troponin tests routinely in primary care to exclude an acute myocardial infarction. Another guideline from the United States [30] suggest that troponin tests should provide not only qualitative but also quantitative information (Level C, Class II). The remaining included guidelines are even less specific in their recommendations about the use of Tn-POCT.

In terms of the Austrian situation, the experts we consulted believed that there could theoretically be a potential value of Tn-POCT in settings where a CL would not be available or would take too long to supply results. However, one of the consulted experts doubts whether this situation would exist in Austria (because of the hospital-based healthcare system).

D-dimer POCT

For D-dimer POCT, six systematic reviews [26, 31-35], containing between four and nine studies relating to between 199 and 55,268 patients were included in this assessment. The quality, according to AMSTAR-2, was moderate to high for the included reviews. A further two non randomised controlled trials [36, 37] with moderate to severe risk of bias were included to update one systematic review to also include symptoms relating to deep vein thrombosis. One systematic review [35] reported evidence regarding the effect of implementing D-dimer POCT in emergency care on patient management. Based on observational studies only, this review of moderate quality at most, found D-dimer POCT to be associated with a reduction of turnaround time, a reduction in number of hospital admissions and shorter length of stay. However, given the absence of RCT data, 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. Similarly, only a few prospective studies evaluating the effect of GP use of POCT on clinical diagnostic accuracy and clinical management in primary care patients with cardiopulmonary symptoms have been performed [26]. As a consequence, there is a lack of reliable, good quality evidence to show non-inferiority compared to CL testing and superiority compared to the current situation

(with no immediate CL testing) in emergency care or ambulatory care (primary and community care) settings. There is however some evidence that using D-dimer POCT may prevent unnecessary referrals for imaging, with benefits for patients and budgets, however this assumes the correct use of D-Dimer POCT in combination with an established clinical prediction tool.

Ten guidelines [15, 18, 19, 29, 38-43] from different international institutions were identified on the use of D-dimer POCT. Eight out of ten guidelines conclude that POCT can be used to exclude suspected pulmonary embolism or deep vein thrombosis in combination with low pre-test probability [18, 19, 29, 38, 39, 41-43]. Only one guideline [40] 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 [29]. The recommended settings are somewhat inconsistent in the included guidelines: three guidelines did not define the setting [29, 39, 42], three guidelines are applicable only in the community or primary care setting [15, 19, 43], one guideline is applicable in numerous settings (primary, secondary, tertiary care) [18], one guideline in the emergency department [40], one guideline in emergency department and outpatient [41]), and one guideline both in the ambulatory and inpatient setting [38]. Two guidelines are inconsistent in terms of the recommended sensitivity of the D-dimer test. One guideline [38] states that the simple qualitative D-dimer POCT in combination with clinical probability may be comparable in its value when compared to the quantitative ELISA test in low-risk patients, while another guideline [15] recommends not to use qualitative or semi-quantitative tests in primary care.

In addition, a negative D-dimer can exclude venous thromboembolism in a low pre-test probability setting but a positive D-dimer can leave many diagnoses open. Combining D-dimer with pre-test probability leads to greater certainty when ruling out the condition. The reviews [26, 31-35] confirm that D-dimer testing is very sensitive with a high negative predictive value, but it is not very specific. The sensitivity of the D-dimer test is improved when it is combined with a pre-test clinical probability score. The specificity of D-dimer decreases steadily with age, so age-adjusted cut-offs are needed among the elderly.

The included reviews [26, 31-35] and guidelines [15, 18, 19, 29, 38-43] suggest that D-dimer levels- when considered for use in ambulatory care settings- should only ever be measured in patients with low or intermediate clinical probability of pulmonary embolism or deep vein thrombosis. In patients with a high clinical probability, D-dimer should not be measured but patients should proceed immediately to imaging. It is emphasized in all included guidelines and reviews that D-dimer should be measured only after the prior estimation of clinical probability.

In terms of the Austrian situation, some experts believed that D-dimer POCT could only have a limited role outside the hospital setting at present, 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. This expert mentions that the goal is hereby to avoid unnecessary hospitalisations, and the test would be able to do that to a large extent. The time element is generally not considered to be as crucial for D-dimer as there is less danger in the patient waiting to attend hospital and have further tests there.

Limitations

One limitation of our review is that, despite having included systematic reviews of moderate and high quality, the primary studies in the systematic reviews and those studies in the update assessment were only of limited quality. One further limitation of our assessment is that the identified evidence may also include evidence based on older models of the test devices that may not be on the market any longer [21].

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, evaluation studies in the field of health service research, than traditional randomised controlled trials, might be better suited to fully determine the clinical benefit in specific settings.

We did not assess the role of algorithms, for instance, in troponin testing or the clinical prediction rules to be used in conjunction with D-dimer POCT, as these aspects were beyond the scope of this review. Also, multi-biomarker tests that test numerous different biomarkers simultaneously were, as far as possible, excluded from the synthesis. These tests are promising and an evaluation of the clinical utility of these tests may further be necessary as these tests evolve over time [4].

We did not update the evidence on the diagnostic test accuracy of Tn-POCT and D-dimer POCT. As a consequence, the evidence of diagnostic accuracy is based on the identified systematic reviews and may, therefore, not be up-to-date. However, improvements in diagnostic test accuracy only indirectly show whether implementation would result in patient-relevant benefits. The aim of this review is evaluating clinical utility as a final endpoint, as recommended in diverse methodological guidelines [44]. In addition, we relied on the judgement of the reviews with regard to quality assessment of the diagnostic test accuracy studies being a further limitation.

Further considerations

Measuring the effect of implementing a POCT device is complex to evaluate since there are many other confounding variables that influence the outcomes of interest. In the context of diagnosis and treatment of acute coronary syndrome, for instance, there are different algorithms. Usually these are dependent on the sensitivity of the devices used to measure troponin and on when troponin is tested. Hence, with increasing sensitivity of devices measuring troponin, there may not only be an impact on clinical utility but also on the decisional algorithm that may be used [96, 97]. A recent study [98], for instance, measured how successful five Tn-POCT devices could rule out non-ST elevation myocardial infarction using the 0h/3h algorithm. It showed that some of the devices currently on the market could even acceptably measure high sensitive troponin. With increasing advancements in diagnostic performance (esp. the ability to measure high sensitive troponin), one has to be aware that these advancements could potentially also have its flipside: due to lower specificity when compared to conventional assays, unwarranted hospitalisations may be increased when using devices measuring high-sensitive troponin [97].

Currently, the European Society of Cardiology, for instance, recommends using the 0h/3h algorithm, and a newer faster approach (0h/1h) if high sensitive troponin assays are available, although the latter has not yet been rigorously validated through RCTs [14]. Studies are ongoing to validate the 0h/1h strategy [99], as well as to evaluate further risk stratification strategies e.g. the HEART score (History, ECG, age, risk factors and initial troponin) [100].

[21] e.g., the Clearview Simplify POCT system from Sekisui was researched but no information on whether it is still sold or even exists anymore is available for this product online.

In addition, it may be useful to identify the POCT devices with the best analytical and diagnostic performance, or the ones that are currently used in Austria/Romania, and conduct primary research on the clinical utility of these POCT devices.

Ongoing studies

The search for ongoing studies revealed that there are currently five ongoing studies evaluating the use of Tn-POCT in the emergency department. Two of these are RCTs and three are NRCTs. The estimated completion date of four of the studies has already passed (4/5 studies) and one study is expected to be completed in 2020. The comparators used to compare with Tn-POCT in these studies differ slightly but include mostly conventional diagnostic testing. The sample size ranges from 50 to 2,000 enrolled patients. Patient management outcomes (e.g., LOS, TTD) are measured in three studies whilst two studies solely evaluate the clinical performance/diagnostic accuracy. The reader is referred to Table A9 in the appendix for more information on relevant ongoing trials.

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

9 CONCLUSION

Before such tests are implemented or their use extended, further research on specific point of care tests (quantitative, with certain pre-defined analytical characteristics) in specific settings in Austria and Romania is needed. Here a health services research approach might be more appropriate than traditional evidence-based medicine, to assess potential benefits in different settings from a systems approach.

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APPENDIX 1: SEARCH STRATEGIES

METHODS AND DESCRIPTION OF THE EVIDENCE USED

DOCUMENTATION OF THE SEARCH STRATEGIES TN-POCT

Documentation of systematic search for clinical practice guidelines for Tn-POCT

Embase

Session Results	
.....	
No. Query Results	Results Date
#18. (#13 OR #15) AND [2009-2019]/py AND ([english]/lim OR [german]/lim)	42 24 May 2019
#17. (#13 OR #15) AND [2009-2019]/py	43 24 May 2019
#16. #13 OR #15	50 24 May 2019
#15. #12 AND #14	12 24 May 2019
#14. guideline*:ti	93,994 24 May 2019
#13. #12 AND 'practice guideline'/de	47 24 May 2019
#12. #5 AND #11	796 24 May 2019
#11. #6 OR #7 OR #8 OR #9 OR #10	31,186 24 May 2019
#10. 'poc':ti,ab	5,777 24 May 2019
#9. 'poct':ti,ab	2,118 24 May 2019
#8. 'point of care':ti,ab,de	28,499 24 May 2019
#7. 'point of care testing'/exp	11,535 24 May 2019
#6. 'point of care system'/exp	1,534 24 May 2019
#5. #1 OR #2 OR #3 OR #4	74,087 24 May 2019
#4. tn:ti,ab	17,171 24 May 2019
#3. troponin*:ti,ab,de	57,719 24 May 2019
#2. 'troponin'/exp	53,782 24 May 2019
#1. 'troponin test kit'/exp	14 24 May 2019
.....	

Medline

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily - without Revisions <2015 to May 21, 2019>, Ovid MEDLINE(R) <1946 to May Week 3 2019>
Search Strategy:
---
1 exp Point-of-Care Systems/ (17048)
2 exp Point-of-Care Testing/ (2307)
3 point* of care.mp. (30367)
4 POCT.ti,ab. (1792)
5 POC.ti,ab. (5281)

6 1 or 2 or 3 or 4 or 5 (33117)
7 exp Troponin/ (19439)
8 troponin*.mp. (31624)
9 Tn.ti,ab. (14756)
10 7 or 8 or 9 (45815)
11 limit 10 to (guideline or practice guideline) (57)
12 6 and 10 (552)
13 guideline*.ti,pt. (93031)
14 practice guideline.pt. (29264)
15 13 or 14 (103823)
16 12 and 15 (5)
17 11 or 16 (62)
18 limit 17 to yr="2009 - 2019" (39)
19 limit 18 to (english or german) (35)
20 remove duplicates from 19 (25)
****
23.05.2019

Documentation of systematic search for systematic reviews and meta analyses (Tn-POCT)

Cochrane

Search Name: POCT_Troponin (SRs)
Last Saved: 31/05/2019 17:20:07
Comment: LS/GG/JE
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* test*") (Word variations have been searched)
#7 #1 OR #2 OR #3 OR #4 OR #5 OR #6 (Word variations have been searched)
#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 #8 OR #9 OR #10 OR #11 (Word variations have been searched)

#13 #7 AND #12
#14 troponin* NEAR/5 test*
#15 #13 OR #14 with Cochrane Library publication date Between Jan 2009 and Dec 2019, in Cochrane Reviews, Cochrane Protocols (Word variations have been searched)
14 Hits

CRD

POCT_Troponin HTAs (LS/GG/JE)
1 MeSH DESCRIPTOR Troponin EXPLODE ALL TREES
2 (troponin*)
3 (tn)
4 (cTn)
5 #1 OR #2 OR #3 OR #4
6 * IN HTA
7 #5 AND #6
8 * IN HTA FROM 2009 TO 2019
9 #7 AND #8
14 Hits
28.05.2019

Embase

Session Results ..... No. Query Results Results Date	
#25. #16 OR #17 OR #19 OR #24	127 31 May 2019
#24. #15 AND #23	7 31 May 2019
#23. #20 OR #21 OR #22	23,232 31 May 2019
#22. hta*:ti,ab,de	7,274 31 May 2019
#21. 'technolog* assessment*':ti,ab,de	18,752 31 May 2019
#20. 'biomedical technology assessment'/exp	13,726 31 May 2019
#19. #15 AND #18	112 31 May 2019
#18. ('meta analysis'/exp OR 'systematic review'/exp OR ((meta NEAR/3 analy*):ab,ti) OR metaanaly*:ab,ti OR review*:ti OR overview*:ti OR ((synthes* NEAR/3 (literature* OR research* OR studies OR data)):ab,ti) OR (pooled AND analys*:ab,ti) OR (((data NEAR/2 pool*):ab,ti) AND studies:ab,ti) OR medline:ab,ti OR medlars:ab,ti OR embase:ab,ti OR cinahl:ab,ti OR scisearch:ab,ti OR psychinfo:ab,ti OR psycinfo:ab,ti OR psychlit:ab,ti OR psyclit:ab,ti	1,092,239 31 May 2019

OR cinhal:ab,ti OR cancerlit:ab,ti OR cochrane:ab,ti OR bids:ab,ti OR pubmed:ab,ti OR ovid:ab,ti OR (((hand OR manual OR database* OR computer*) NEAR/2 search*):ab,ti) OR ((electronic NEAR/2 (database* OR 'data base' OR 'data bases')):ab,ti) OR bibliograph*:ab OR 'relevant journals':ab OR (((review* OR overview*) NEAR/10	
(systematic* OR methodologic* OR quantitativ* OR research* OR literature* OR studies OR trial* OR effective*)):ab)) NOT ((((retrospective* OR record* OR case* OR patient*) NEAR/2 review*):ab,ti) OR (((patient* OR review*) NEAR/2 chart*):ab,ti) OR rat:ab,ti OR rats:ab,ti OR mouse:ab,ti OR mice:ab,ti OR hamster:ab,ti OR hamsters:ab,ti OR animal:ab,ti OR animals:ab,ti OR dog:ab,ti OR dogs:ab,ti OR cat:ab,ti OR cats:ab,ti OR bovine:ab,ti OR sheep:ab,ti) NOT ('editorial'/exp OR 'erratum'/de OR 'letter'/exp) NOT (('animal'/exp OR 'nonhuman'/exp) NOT (('animal'/exp OR 'nonhuman'/exp) AND 'human'/exp))	
research* OR literature* OR studies OR trial* OR effective*)):ab)) NOT ((((retrospective* OR record* OR case* OR patient*) NEAR/2 review*):ab,ti) OR (((patient* OR review*) NEAR/2 chart*):ab,ti) OR rat:ab,ti OR rats:ab,ti OR mouse:ab,ti OR mice:ab,ti OR hamster:ab,ti OR hamsters:ab,ti OR animal:ab,ti OR animals:ab,ti OR dog:ab,ti OR dogs:ab,ti OR cat:ab,ti OR cats:ab,ti OR bovine:ab,ti OR sheep:ab,ti) NOT ('editorial'/exp OR 'erratum'/de OR 'letter'/exp) NOT (('animal'/exp OR 'nonhuman'/exp) NOT (('animal'/exp OR 'nonhuman'/exp) AND 'human'/exp))	
#17. #15 AND ([cochrane review]/lim OR [systematic review]/lim OR [meta analysis]/lim)	50 31 May 2019
#16. #15 AND ('meta analysis'/de OR 'meta analysis (topic)'/de OR 'systematic review'/de OR 'systematic review (topic)'/de)	58 31 May 2019
#15. #13 OR #14	2,222 31 May 2019
#14. (troponin* NEAR/4 test*):ti,ab,de	1,574 31 May 2019
#13. #5 AND #12	802 31 May 2019
#12. #6 OR #7 OR #8 OR #9 OR #10 OR #11	31,626 31 May 2019
#11. 'near patient* test*':ti,ab,de	462 31 May 2019
#10. 'poc':ti,ab	5,790 31 May 2019
#9. 'poct':ti,ab	2,120 31 May 2019
#8. 'point of care':ti,ab,de	28,585 31 May 2019
#7. 'point of care testing'/exp	11,574 31 May 2019
#6. 'point of care system'/exp	1,546 31 May 2019
#5. #1 OR #2 OR #3 OR #4	74,210 31 May 2019
#4. tn:ti,ab	17,208 31 May 2019
#3. troponin*:ti,ab,de	57,805 31 May 2019
#2. 'troponin'/exp	53,863 31 May 2019
#1. 'troponin test kit'/exp	15 31 May 2019

Medline

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily - without Revisions <2015 to May 24, 2019>, Ovid MEDLINE(R) <1946 to May Week 3 2019>
Search Strategy:
----
1 exp Point-of-Care Systems/ (17055)
2 exp Point-of-Care Testing/ (2307)
3 point* of care.mp. (30385)
4 POCT.ti,ab. (1792)
5 POC.ti,ab. (5274)
6 near patient* test*.mp. (340)
7 1 or 2 or 3 or 4 or 5 or 6 (33332)
8 exp Troponin/ (19445)
9 troponin*.mp. (31635)
10 Tn.ti,ab. (14774)
11 cTn*.ti,ab. (11725)
12 8 or 9 or 10 or 11 (50895)
13 7 and 12 (559)
14 ((troponin* or tn or cTnI or cTnT) adj5 test*).mp. (1677)
15 13 or 14 (2083)
16 limit 15 to (meta analysis or "systematic review" or systematic reviews as topic) (31)
17 (((comprehensive* or integrative or systematic*) adj3 (bibliographic* or review* or literature)) or (meta-analy* or metaanaly* or "research synthesis" or ((information or data) adj3 synthesis) or (data adj2 extract*))).ti,ab. or (cinahl or (cochrane adj3 trial*) or embase or medline or psyclit or (psycinfo not "psycinfo database") or pubmed or scopus or "sociological abstracts" or "web of science").ab. or ("cochrane database of systematic reviews" or evidence report technology assessment or evidence report technology assessment summary).jn. or Evidence Report: Technology Assessment*.jn. or ((review* adj5 (rationale or evidence or study or studies)).ti,ab. and review.pt.) or meta-analysis as topic/ or Meta-Analysis.pt. (575103)
18 15 and 17 (77)
19 technology assessment*.mp. (15521)
20 exp Technology Assessment, Biomedical/ (11858)
21 HTA.ti,ab. (3320)
22 19 or 20 or 21 (17946)
23 15 and 22 (11)
24 16 or 18 or 23 (85)
25 limit 24 to yr="2009 - 2019" (77)
26 limit 25 to (english or german) (77)
27 remove duplicates from 26 (55)
****
27.05.2019

Documentation of systematic search for primary studies (Tn-POCT)

Cochrane

Search Name: Troponin primary lit
Last Saved: 07/07/2019 22:25:08
Comment: Update CADTH/Schols (GG070719)
ID Search
#1 MeSH descriptor: [Point-of-Care Systems] explode all trees
#2 ("point* of care"):ti,ab,kw (Word variations have been searched)
#3 (office*):ti,ab,kw
#4 (bedside*):ti,ab,kw (Word variations have been searched)
#5 (bed-side*):ti,ab,kw
#6 ("near patient*"):ti,ab,kw (Word variations have been searched)
#7 POC:ti,ab
#8 (on-site):ti,ab,kw (Word variations have been searched)
#9 (rapid):ti,ab,kw
#10 (ultra-rapid):ti,ab,kw (Word variations have been searched)
#11 (portable):ti,ab,kw
#12 (hand-held):ti,ab,kw (Word variations have been searched)
#13 (hand-held):ti,ab,kw
#14 (ambulatory):ti,ab,kw
#15 (transportable):ti,ab,kw
#16 (quick):ti,ab,kw
#17 (remote*):ti,ab,kw
#18 (immediate):ti,ab,kw
#19 (mobile):ti,ab,kw
#20 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19
#21 (test*):ti,ab,kw
#22 (assay*):ti,ab,kw
#23 (immunoassay*):ti,ab,kw (Word variations have been searched)
#24 (immuno-assay*):ti,ab,kw
#25 MeSH descriptor: [Point-of-Care Testing] explode all trees
#26 POCT:ti,ab
#27 #21 OR #22 OR #23 OR #24 OR #25 OR #26
#28 #20 AND #27
#29 MeSH descriptor: [Troponin] explode all trees
#30 (troponin*):ti,ab,kw
#31 TnI*:ti,ab
#32 TnT*:ti,ab
#33 cTn*:ti,ab
#34 hsTn*:ti,ab

#35	hs-Tn*:ti,ab
#36	#29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35
#37	#28 AND #36
#38	#37 with Cochrane Library publication date Between Oct 2014 and Jul 2019
#39	#37 with Publication Year from 2014 to 2019, in Trials
#40	#38 OR #39
208 Hits	

CINAHL

#	Query	Limiters/Expanders	Last Run Via
S18	S8 AND S16	Limiters - Published Date: 20141001-20190731 Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Basic Search Database - CINAHL
S17	S8 AND S16	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Basic Search Database - CINAHL
S16	S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Basic Search Database - CINAHL
S15	TI hs-Tn* OR AB hs-Tn*	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Basic Search Database - CINAHL
S14	TI hsTn* OR AB hsTn*	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Basic Search Database - CINAHL
S13	TI cTn* OR AB	Search modes -	Interface -

	cTn*	Boolean/Phrase	EBSCOhost Research Databases Search Screen - Basic Search Database - CINAHL
S12	TI TnT* OR AB TnT	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Basic Search Database - CINAHL
S11	TI TnI* OR AB TnI*	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Basic Search Database - CINAHL
S10	troponin*	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Basic Search Database - CINAHL
S9	MH "Troponin+"	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Basic Search Database - CINAHL
S8	S3 AND S7	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Basic Search Database - CINAHL
S7	S4 OR S5 OR S6	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Basic Search Database - CINAHL
S6	TI POCT OR AB POCT	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases

			Search Screen - Basic Search Database - CINAHL
S5	MH "Point-of- Care Testing+"	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Basic Search Database - CINAHL
S4	test* OR assay* OR immunoassay* OR immunoassay*	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Basic Search Database - CINAHL
S3	S1 OR S2	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Basic Search Database - CINAHL
S2	"point* of care" OR point*-ofcare OR office* OR bedside* OR bed-side OR "near patient*" OR POC OR on-site OR rapid OR ultrarapid OR portable OR hand-held OR handheld OR ambulatory OR transportable OR quick OR remote* OR immediate OR mobile	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Basic Search Database - CINAHL
S1	MH "Point-of- Care Systems+"	Search modes - SmartText Searching	Interface - EBSCOhost Research Databases Search Screen - Basic Search Database - CINAHL

184 hits

Embase

Session Results	
No. Query	Results Date
#14. #13 AND [1-10-2014]/sd NOT [8-7-2019]/sd	689 7 Jul 2019
#13. #11 NOT #12	1,722 7 Jul 2019
#12. #10 AND 'human'/de AND 'Conference Abstract'/it	1,159 7 Jul 2019
#11. #10 AND 'human'/de	2,881 7 Jul 2019
#10. #1 AND #9	3,632 7 Jul 2019
#9. #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8	114,079 7 Jul 2019
#8. 'hs-tn*':ti,ab	47,467 7 Jul 2019
#7. hstn*:ti,ab	1,153 7 Jul 2019
#6. ctn*:ti,ab	15,632 7 Jul 2019
#5. tnt*:ti,ab	5,912 7 Jul 2019
#4. tni*:ti,ab	3,411 7 Jul 2019
#3. troponin*:ti,ab,de,tn	58,231 7 Jul 2019
#2. 'troponin'/exp	54,281 7 Jul 2019
#1. ('point of care system':de,ti,ab,tn OR 'point* of care':ti,ab,de,tn OR office*:ti,ab,de,tn OR bedside*:ti,ab,de,tn OR 'bed side':ti,ab,de,tn OR 'near patient*':ti,ab,de,tn OR poc:ti,ab,de,tn OR 'on site':ti,ab,de,tn OR rapid:ti,ab,de,tn OR 'ultra rapid':ti,ab,de,tn OR portable:ti,ab,de,tn OR 'hand held':ti,ab,de,tn OR handheld:ti,ab,de,tn OR ambulatory:ti,ab,de,tn OR transportable:ti,ab,de,tn OR quick:ti,ab,de,tn OR remote*:ti,ab,de,tn OR immediate:ti,ab,de,tn OR mobile:ti,ab,de,tn) AND (test*:ti,ab,de,tn OR assay*:ti,ab,de,tn OR immunoassay*:ti,ab,de,tn OR 'immuno assay*':ti,ab,de,tn) OR 'point-of-care testing'/exp OR poct:ti,ab	421,075 7 Jul 2019

Medline

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily - without Revisions <2015 to July 03, 2019>, Ovid MEDLINE(R) <1946 to June Week 5 2019>
Search Strategy:
----
1 ((exp Point-of-Care Systems/ or point* of care or point*-of-care or office* or bedside* or bed-side or near patient* or POC or on-site or rapid or ultra-rapid or portable or hand-held or handheld or ambulatory or transportable or quick or remote* or immediate or mobile) and (test* or assay* or immunoassay* or immuno-assay*)).mp. or exp Point-of-Care Testing/ or POCT.ti,ab. (366755)
2 exp Troponin/ (19655)
3 troponin*.mp. (31988)
4 TnI*.ti,ab. (2360)
5 TnT*.ti,ab. (5046)
6 cTn*.ti,ab. (11921)
7 hsTn*.ti,ab. (555)
8 hs-Tn*.ti,ab. (454)
9 2 or 3 or 4 or 5 or 6 or 7 or 8 (41559)
10 1 and 9 (1640)
11 exp animals/ not humans.sh. (5022795)
12 10 not 11 (1525)
13 limit 12 to ed=20160213-20190705 (541)
14 remove duplicates from 13 (290)
****
05.07.2019

DOCUMENTATION OF THE SEARCH STRATEGIES D-DIMER POCT

Documentation of systematic search for clinical practice guidelines (D-dimer POCT)

Embase

No.	Query	Results	Date
#39.	#27 AND #38	68	23 May 2019
#38.	(#6 OR #35) AND [2009-2019]/py AND ([english]/lim OR [german]/lim)	101	23 May 2019
#37.	(#6 OR #35) AND [2009-2019]/py	108	23 May 2019
#36.	#6 OR #35	148	23 May 2019
#35.	#29 OR #34	8	23 May 2019
#34.	#28 AND #33	8	23 May 2019
#33.	#30 OR #31 OR #32	522826	23 May 2019
#32.	guideline*:ti	93958	23 May 2019
#31.	'guideline'/exp	141	23 May 2019
#30.	'practice guideline'/exp	495957	23 May 2019
#29.	#28 AND 'practice guideline'/de	6	23 May 2019
#28.	#13 AND #27	189	23 May 2019
#27.	#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	1047060	23 May 2019
#26.	stroke*:ti, ab, de	405896	23 May 2019
#25.	'brain ischemia'/exp	170336	23 May 2019
#24.	cerebrovascular accident'/exp	304508	23 May 2019
#23.	vte:ti, ab	18609	23 May 2019
#22.	dvt:ti, ab	18035	23 May 2019
#21.	pe:ti, ab	56694	23 May 2019
#20.	'pulmonary embolism*':ti, ab, de	48368	23 May 2019
#19.	'lung embolism'/exp	91016	23 May 2019
#18.	thrombo embolism*':ti, ab, de	1349	23 May 2019
#17.	thromboembolism*:ti, ab, de	114959	23 May 2019
#16.	'thromboembolism'/exp	482650	23 May 2019
#15.	thrombos*:ti, ab, de	347401	23 May 2019
#14.	'thrombosis'/exp	319904	23 May 2019
#13.	#4 AND #12	296	23 May 2019
#12.	#7 OR #8 OR #9 OR #10 OR #11	31167	23 May 2019
#11.	'poc':ti, ab	5773	23 May 2019
#10.	'poct':ti, ab	2116	23 May 2019
#9.	'point of care':ti, ab, de	28483	23 May 2019
#8.	point of care testing'/exp	11529	23 May 2019
#7.	'point of care system'/exp	1533	23 May 2019

#6.	#4 AND #5	140	23 May 2019
#5.	guideline*:ti	93958	23 May 2019
#4.	#1 OR #2 OR #3	147907	23 May 2019
#3.	dimer*:ti, ab, de	147907	23 May 2019
#2.	'd dimer*':ti, ab, de	21872	23 May 2019
#1.	'd dimer test'/exp	51	23 May 2019

Medline

No.	Query	Results	Date
1	exp Point-of-Care Systems/	17010	22 May 2019
2	exp Point-of-Care Testing/	2296	22 May 2019
3	point* of care.mp.	30319	22 May 2019
4	POCT.ti ab.	1781	22 May 2019
5	POC.ti ab.	5259	22 May 2019
6	1 or 2 or 3 or 4 or 5	33051	22 May 2019
7	d-dimer*.mp.	11396	22 May 2019
8	dimer*.mp.	147086	22 May 2019
9	7 or 8	147086	22 May 2019
10	limit 9 to (guideline or practice guideline)	30	22 May 2019
11	exp Guideline/	36540	22 May 2019
12	exp Practice Guideline/	29235	22 May 2019
13	exp Practice Guidelines as Topic/	131734	22 May 2019
14	guideline*.mp.	508405	22 May 2019
15	11 or 12 or 13 or 14	508405	22 May 2019
16	6 and 9	172	22 May 2019
17	limit 16 to (guideline or practice guideline)	0	22 May 2019
18	15 and 16	6	22 May 2019
19	10 or 18	36	22 May 2019
20	limit 19 to yr="2009 - 2019"	23	22 May 2019
21	limit 20 to (english or german)	19	22 May 2019
22	remove duplicates from 21	13	22 May 2019

Documentation of systematic search for systematic reviews and meta analyses (D-dimer POCT)

Cochrane

Last Saved: 31/05/2019 18:44:05

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* test*") (Word variations have been searched)
#7	#1 OR #2 OR #3 OR #4 OR #5 OR #6 (Word variations have been searched)
#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	#8 OR #9 OR #10 (Word variations have been searched)
#12	#7 AND #11
#13	(D-Dimer* OR dimer*) NEAR test* (Word variations have been searched)
#14	#12 OR #13 with Cochrane Library publication date Between Jan 2009 and Dec 2019, in Cochrane Reviews, Cochrane Protocols (Word variations have been searched)
21 Hits Last Saved: 31/05/2019 18:44:05	

CRD

1 (D-Dimer*)
2 (dimer*)
3 MeSH DESCRIPTOR Fibrin Fibrinogen Degradation Products EXPLODE ALL TREES
4 #1 OR #2 OR #3
5 * FROM 2009 TO 2019
6 #4 AND #5
7 (#6) IN HTA
2 Hits
31.05.2019

Embase

Session Results		
.....		
No. Query Results	Results	Date
#27. (#16 OR #17 OR #19 OR #24) AND [2009-2019]/py AND	127	31 May 2019
([english]/lim OR [german]/lim)		
#26. (#16 OR #17 OR #19 OR #24) AND [2009-2019]/py 2019	133	31 May
#25. #16 OR #17 OR #19 OR #24 2019	183	31 May
#24. #15 AND #23 2019	4	31 May
#23. #20 OR #21 OR #22 2019	23,232	31 May
#22. hta*:ti,ab,de 2019	7,274	31 May
#21. 'technolog* assessment*':ti,ab,de 2019	18,752	31 May
#20. 'biomedical technology assessment'/exp 2019	13,726	31 May
#19. #15 AND #18 2019	172	31 May
#18. ('meta analysis'/exp OR 'systematic review'/exp 2019	1,092,239	31 May
OR ((meta NEAR/3 analy*):ab,ti) OR		
metaanaly*:ab,ti OR review*:ti OR overview*:ti OR		
((synthes* NEAR/3 (literature* OR research* OR		
studies OR data)):ab,ti) OR (pooled AND		
analys*:ab,ti) OR (((data NEAR/2 pool*):ab,ti)		
AND studies:ab,ti) OR medline:ab,ti OR		
medlars:ab,ti OR embase:ab,ti OR cinahl:ab,ti OR		
scisearch:ab,ti OR psychinfo:ab,ti OR		
psycinfo:ab,ti OR psychlit:ab,ti OR psyclit:ab,ti		
OR cinhal:ab,ti OR cancerlit:ab,ti OR		
cochrane:ab,ti OR bids:ab,ti OR pubmed:ab,ti OR		
ovid:ab,ti OR (((hand OR manual OR database* OR		
computer*) NEAR/2 search*):ab,ti) OR ((electronic		
NEAR/2 (database* OR 'data base' OR 'data		
bases')):ab,ti) OR bibliograph*:ab OR 'relevant		
journals':ab OR (((review* OR overview*) NEAR/10		
(systematic* OR methodologic* OR quantitativ* OR		
research* OR literature* OR studies OR trial* OR		

effective*)):ab)) NOT ((((retrospective* OR		
record* OR case* OR patient*) NEAR/2		
review*):ab,ti) OR (((patient* OR review*) NEAR/2		
chart*):ab,ti) OR rat:ab,ti OR rats:ab,ti OR		
mouse:ab,ti OR mice:ab,ti OR hamster:ab,ti OR		
hamsters:ab,ti OR animal:ab,ti OR animals:ab,ti		
OR dog:ab,ti OR dogs:ab,ti OR cat:ab,ti OR		
cats:ab,ti OR bovine:ab,ti OR sheep:ab,ti) NOT		
('editorial'/exp OR 'erratum'/de OR 'letter'/exp)		
NOT (('animal'/exp OR 'nonhuman'/exp) NOT		
(('animal'/exp OR 'nonhuman'/exp) AND		
'human'/exp))		
#17. #15 AND ([cochrane review]/lim OR [systematic 2019	90	31 May
review]/lim OR [meta analysis]/lim)		
#16. #15 AND ('meta analysis'/de OR 'meta analysis 2019	95	31 May
(topic)'/de OR 'systematic review'/de OR		
'systematic review (topic)'/de)		
#15. #13 OR #14 2019	2,796	31 May
#14. (('d dimer*' OR dimer*) NEAR/4 test*):ti,ab,de 2019	2,590	31 May
#13. #5 AND #12 2019	297	31 May
#12. #6 OR #7 OR #8 OR #9 OR #10 OR #11 2019	31,626	31 May
#11. 'near patient* test*':ti,ab,de 2019	462	31 May
#10. 'poc':ti,ab 2019	5,790	31 May
#9. 'poct':ti,ab 2019	2,120	31 May
#8. 'point of care':ti,ab,de 2019	28,585	31 May
#7. 'point of care testing'/exp 2019	11,574	31 May
#6. 'point of care system'/exp 2019	1,546	31 May
#5. #1 OR #2 OR #3 OR #4 2019	148,048	31 May
#4. 'd dimer'/exp 2019	18,475	31 May
#3. dimer*:ti,ab,de 2019	148,048	31 May

#2. 'd dimer*':ti,ab,de 2019	21,904	31 May
#1. 'd dimer test'/exp 2019	51	31 May
.....		

Medline

Search Strategy:
---
1 exp Point-of-Care Systems/ (17093)
2 exp Point-of-Care Testing/ (2316)
3 point* of care.mp. (30466)
4 POCT.ti,ab. (1797)
5 POC.ti,ab. (5302)
6 near patient* test*.mp. (340)
7 1 or 2 or 3 or 4 or 5 or 6 (33430)
8 D-dimer*.mp. (11433)
9 dimer*.mp. (147344)
10 exp Fibrin Fibrinogen Degradation Products/ (9252)
11 8 or 9 or 10 (151007)
12 7 and 11 (188)
13 ((D-Dimer or dimer*) adj5 test*).mp. (2018)
14 12 or 13 (2135)
15 limit 14 to (meta analysis or "systematic review" or systematic reviews as topic) (55)
16 (((comprehensive* or integrative or systematic*) adj3 (bibliographic* or review* or literature)) or (meta-analy* or metaanaly* or "research synthesis" or ((information or data) adj3 synthesis) or (data adj2 extract*))).ti,ab. or (cinahl or (cochrane adj3 trial*) or embase or medline or psyclit or (psycinfo not "psycinfo database") or pubmed or scopus or "sociological abstracts" or "web of science").ab. or ("cochrane database of systematic reviews" or evidence report technology assessment or evidence report technology assessment summary).jn. or Evidence Report: Technology Assessment*.jn. or ((review* adj5 (rationale or evidence or study or studies)).ti,ab. and review.pt.) or meta-analysis as topic/ or Meta-Analysis.pt. (576745)
17 14 and 16 (98)
18 technology assessment*.mp. (15538)
19 exp Technology Assessment, Biomedical/ (11869)
20 HTA*.ti,ab. (4685)
21 18 or 19 or 20 (19256)
22 14 and 21 (0)
23 15 or 17 or 22 (98)
24 limit 23 to yr="2009 - 2019" (69)
25 limit 24 to (english or german) (68)
26 remove duplicates from 25 (47)
****
31.05.2019

Documentation of systematic search for primary studies: DVT in primary care settings (D-dimer POCT)

Cochrane

Search Name: D-Dimer primary lit
Last Saved: 01/07/2019 12:19:00
Comment: LS 01.07.2019
ID Search
#1 ("point of care" OR point-of-care OR office OR bedside OR "near patient" OR POC OR on-site OR rapid OR ultra-rapid) (Word variations have been searched)
#2 test* OR assay* OR immunoassay* OR immuno-assay* OR [mh "'Point-of-Care Systems'"] OR [mh "Point-of-Care Systems"] OR [mh "Point-of-Care Testing"] OR POCT:ti,ab,kw OR D-dimer* OR dimer* OR [mh "Fibrin Fibrinogen Degradation Products"] (Word variations have been searched)
#3 #1 AND #2 (Word variations have been searched)
#4 "primary care" OR "primary health care" OR "general practice*" OR "family practice*" OR "general practitioner*" OR GP:ti,ab,kw OR "family doctor*" OR "family physician*" OR [mh "'Primary Health Care'"] OR [mh "'Physicians, Primary Care'"] OR [mh "'Family Practice'"] OR [mh "'General Practitioners'"] OR [mh "'Physicians, Family'"] (Word variations have been searched)
#5 #3 AND #4 (Word variations have been searched)
#6 MeSH descriptor: [Venous Thrombosis] explode all trees
#7 (vein* OR ven* OR deep*) NEAR thrombo* (Word variations have been searched)
#8 (VTE):ti,ab,kw
#9 (DVT):ti,ab,kw
#10 (leg* NEAR (pain OR cramp*)) (Word variations have been searched)
#11 MeSH descriptor: [Muscle Cramp] explode all trees
#12 MeSH descriptor: [Leg] explode all trees
#13 #11 AND #12 (Word variations have been searched)
#14 #6 OR #7 OR #8 OR #9 OR #10 OR #12 (Word variations have been searched)
#15 #5 AND #14 (Word variations have been searched)
#16 #15 with Cochrane Library publication date Between Oct 2014 and Jun 2019 (Word variations have been searched)
#17 #15 with Publication Year from 2014 to 2019, in Trials (Word variations have been searched)
#18 #16 OR #17 (Word variations have been searched)
63 Hits

CINAHL

#	Query	Limiters/Expanders	Last Run Via
S12	S1 AND S10	Limiters - Erscheinungsdatum: 20141001-20190631 Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Basic Search Database -

			CINAHL
S11	S1 AND S10	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Basic Search Database - CINAHL
S10	S2 OR S3 OR S4 OR S5 OR S6 OR S9	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Basic Search Database - CINAHL
S9	S7 AND S8	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Basic Search Database - CINAHL
S8	(MH "Leg+")	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Basic Search Database - CINAHL
S7	(MH "Muscle Cramp+")	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Basic Search Database - CINAHL
S6	(leg* N3 (pain OR cramp*))	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Basic Search Database - CINAHL
S5	TI DVT OR AB DVT	Search modes - Boolean/Phrase	Interface - EBSCOhost

			Research Databases Search Screen - Basic Search Database -
S4	TI VTE OR AB VTE	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Basic Search Database - CINAHL
S3	((vein* OR ven* OR deep*) N5 thrombo*)	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Basic Search Database - CINAHL
S2	(MH "Venous Thrombosis+")	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Basic Search Database - CINAHL
S1	("point of care" OR point-ofcare OR office OR bedside OR "near patient" OR POC OR onsite OR rapid OR ultra-rapid) AND (test* OR assay* OR immunoassay* OR immuneassays* OR (MH "'Point-of-Care Systems'+") OR (MH "Point-of-Care Testing+") OR POCT OR D-dimer* OR dimer* OR (MH "Fibrin Fibrinogen Degradation	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Basic Search Database - CINAHL

88 Hits

Embase

No. Query Results	Results Date
#20. #19 AND [1-10-2014]/sd NOT [29-6-2019]/sd	101 28 Jun 2019
#19. #10 AND #18	389 28 Jun 2019
#18. #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17	244,361 28 Jun 2019
#17. 'leg cramp'/exp	2,111 28 Jun 2019
#16. 'leg pain'/exp	45,848 28 Jun 2019
#15. (leg* NEAR/2 (pain OR cramp*)):ti,ab,de	23,871 28 Jun 2019
#14. dvt:ti,ab	18,148 28 Jun 2019
#13. vte:ti,ab	18,770 28 Jun 2019
#12. ((vein* OR ven* OR deep*) NEAR/4 thrombo*):ti,ab,de	175,204 28 Jun 2019
#11. 'vein thrombosis'/exp	127,891 28 Jun 2019
#10. #1 AND #9	1,809 28 Jun 2019
#9. #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8	151,142 28 Jun 2019
#8. 'fibrin degradation product'/exp	3,897 28 Jun 2019
#7. dimer*:ti,ab,de,tn	148,769 28 Jun 2019
#6. 'd-dimer*':ti,ab,de,tn	22,030 28 Jun 2019
#5. 'd dimer assay'/exp	15 28 Jun 2019
#4. 'd dimer blood level'/exp	19 28 Jun 2019
#3. 'd dimer test'/exp	51 28 Jun 2019
#2. 'd dimer'/exp	18,590 28 Jun 2019
#1. (('point* of care':ti,ab,de OR office*:ti,ab,de OR bedside*:ti,ab,de OR 'near patient*':ti,ab,de OR poc:ti,ab,de OR 'on site':ti,ab,de OR rapid:ti,ab,de OR 'ultra rapid':ti,ab,de) AND (test*:ti,ab,de OR assay*:ti,ab,de OR immunoassay*:ti,ab,de OR 'immuno assay*':ti,ab,de OR 'point-of-care systems'/exp) OR 'point-of-care testing'/exp OR poct:ti,ab,de) AND ('primary care':ti,ab,de OR 'primary health care':ti,ab,de OR 'general practice*':ti,ab,de OR 'family practice*':ti,ab,de OR 'general practitioner*':ti,ab,de OR gp*:ti,ab,de OR 'family doctor*':ti,ab,de OR 'family physician*':ti,ab,de OR 'primary health care'/exp OR 'physicians, primary care'/exp OR 'family practice'/exp OR 'general practitioners'/exp OR 'physicians, family'/exp)	276,985 28 Jun 2019

Medline

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily - without Revisions <2015 to June 27, 2019>, Ovid MEDLINE(R) <1946 to June Week 4 2019>
Search Strategy:
----
1 (((point* of care or point*-of-care or office* or bedside* or near patient* or POC or on-site or rapid or ultra-rapid).mp. and ((test* or assay* or immunoassay* or immuno-assay*).mp. or exp Point-of-Care Systems/)) or exp Point-of-Care Testing/ or POCT.mp. or D-dimer*.mp. or dimer*.mp. or exp Fibrin Fibrinogen Degradation Products/) and ((primary care or primary health care or general practice* or family practice* or general practitioner* or GP* or family doctor* or family physician*).mp. or exp Primary Health Care/ or exp Physicians, Primary Care/ or exp Family Practice/ or exp General Practitioners/ or exp Physicians, Family/) (10357)
2 exp Venous Thrombosis/ (59129)
3 ((vein* or ven* or deep*) adj5 thrombo*).mp. (99640)
4 VTE.ti,ab. (12377)
5 DVT.ti,ab. (11089)
6 (leg* adj3 (pain* or cramp*)).mp. (9011)
7 exp Muscle Cramp/ (2295)
8 exp Leg/ (65791)
9 7 and 8 (253)
10 2 or 3 or 4 or 5 or 6 or 9 (127405)
11 1 and 10 (127)
12 limit 11 to ed=20160301-20190628 (29)
13 remove duplicates from 12 (16)
****
28.06.2019

Documentation of systematic search for primary studies in emergency care settings (D-dimer POCT)

Cochrane

ID Search
#1 ("point* of care" OR point-of-care OR office* OR bedside OR "near Patient*" OR POC:ti,ab,kw OR [mh "'Point-of-Care Systems'"] OR on-site OR rapid OR ultra-rapid) OR D-dimer* OR dimer* OR [mh "Fibrin Fibrinogen Degradation Products"] (Word variations have been searched)
#2 test* OR assay* OR immunoassay* OR immuno-assay* OR [mh "Point-of-Care Testing"] OR POCT:ti,ab,kw (Word variations have been searched)
#3 #1 AND #2 (Word variations have been searched)
#4 MeSH descriptor: [Emergency Service, Hospital] explode all trees
#5 (Emergency department*):ti,ab,kw (Word variations have been searched)
#6 (Accident* & Emergenc*):ti,ab,kw (Word variations have been searched)
#7 ((Accident* and Emergenc*)):ti,ab,kw (Word variations have been searched)

#8 ("A and E"):ti,ab,kw (Word variations have been searched)
#9 A&E
#10 "A & E"
#11 (casualty):ti,ab,kw
#12 ((casualty OR emergenc*) NEAR (department* OR ward* OR station* OR unit* OR room*)):ti,ab,kw (Word variations have been searched)
#13 (walk-in centre*):ti,ab,kw (Word variations have been searched)
#14 (walk-in center*):ti,ab,kw (Word variations have been searched)
#15 #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 (Word variations have been searched)
#16 #3 AND #15 (Word variations have been searched)
#17 MeSH descriptor: [Venous Thrombosis] explode all trees
#18 (vein* OR ven* OR deep*) NEAR thrombo* (Word variations have been searched)
#19 (VTE):ti,ab,kw
#20 (DVT):ti,ab,kw
#21 (leg* NEXT (pain* OR cramp*)):ti,ab,kw (Word variations have been searched)
#22 MeSH descriptor: [Muscle Cramp] explode all trees
#23 MeSH descriptor: [Leg] explode all trees
#24 #22 AND #23 (Word variations have been searched)
#25 #17 OR #18 OR #19 OR #20 OR #21 OR #24 (Word variations have been searched)
#26 ("cardio-pulmonary disease*" OR "cardiopulmonary disease*" OR "pulmonary disease*" OR "thromboembolic event*" OR dyspnoea OR "pulmonary embolism*" OR "lung embolism*" OR pneumonia* OR "lower respiratory infect*" OR cough* OR bronchit* OR asthma* OR COPD OR pleuritis):ti,ab,kw OR [mh "Pulmonary Heart Disease"] OR [mh "Lung Diseases"] OR [mh "Lung Diseases, Obstructive"] OR [mh Thromboembolism] OR [mh Dyspnea] OR [mh "Pulmonary Embolism"] OR [mh Pneumonia] OR [mh "Pneumonia, Bacterial"] OR [mh "Pneumonia, Viral"] OR [mh Cough] OR [mh Bronchitis] OR [mh Asthma] OR [mh "Pulmonary Disease, Chronic Obstructive"] OR [mh Pleurisy] (Word variations have been searched)
#27 #25 OR #26 (Word variations have been searched)
#28 #16 AND #27 (Word variations have been searched)
#29 #28 with Cochrane Library publication date Between Oct 2014 and Jun 2019 (Word variations have been searched)
#30 #28 with Publication Year from 2014 to 2019, in Trials (Word variations have been searched)
#31 #29 OR #30 (Word variations have been searched)
131 Hits

CINAHL

#	Query	Limiters/Expanders	Last Run via
S28	(S1 AND S12) AND (S25 AND S26)	Limiters - Published Date: 20141001-20190731 Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL
S27	(S1 AND S12) AND (S25 AND S26)	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL
S26	S1 AND S12	Search modes - Boolean/Phrase	Interface - EBSCOhost
S25	S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL
S24	("walk-in center*")	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL
S23	("walk-in centre*")	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL
S22	(casualty OR emergenc*) N3 (department* OR ward* OR station* OR unit* OR room*)	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced

			Search Database - CINAHL
S21	(casualty)	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL
S20	"casualty department"	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL
S19	("A & E")	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL
S18	A&E	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL
S17	"A and E"	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL
S16	"Accident* and Emergenc*"	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL
S15	"Accident* &	Search modes -	Interface -

	Emergenc*"	Boolean/Phrase	EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL
S14	"Emergency department*"	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL
S13	(MH "Emergency Service, Hospital+")	Expanders - Apply related words; Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL
S12	S10 OR S11	Search modes - Boolean/Phrase	Interface - EBSCOhost Research
S11	("cardio-pulmonary disease*" OR "cardiopulmonary disease*" OR "pulmonary disease*" OR "thromboembolic event*" OR dyspnoea OR "pulmonary embolism*" OR "lung embolism*" OR pneumonia* OR "lower respiratory infect*" OR cough* OR bronchit* OR asthma* OR COPD OR pleuritis) OR (MH "Pulmonary Heart Disease+") OR (MH "Lung Diseases+") OR (MH "Lung Diseases, Obstructive+") OR (MH "Thromboembolism+") OR (MH "Dyspnea+") OR (MH "Pulmonary Embolism+") OR (MH "Pneumonia+") OR (MH "Pneumonia, Bacterial+") OR (MH "Pneumonia, Viral+") OR (MH "Cough+") OR (MH "Bronchitis+") OR	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL

	(MH "Asthma+") OR (MH "Pulmonary Disease, Chronic Obstructive+") OR (MH "Pleurisy+")		
S10	S2 OR S3 OR S4 OR S5 OR S6 OR S9	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Basic Search Database - CINAHL
S9	S7 AND S8	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Basic Search Database - CINAHL
S8	(MH "Leg+")	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Basic Search Database - CINAHL
S7	(MH "Muscle Cramp+")	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Basic Search Database - CINAHL
S6	(leg* N3 (pain OR cramp*))	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Basic Search Database - CINAHL
S5	TI DVT OR AB DVT	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Basic Search

			Database - CINAHL
S4	TI VTE OR AB VTE	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Basic Search Database - CINAHL
S3	((vein* OR ven* OR deep*) N5 thrombo*)	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Basic Search Database - CINAHL
S2	(MH "Venous Thrombosis+")	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Basic Search Database - CINAHL
S1	("point of care" OR point-of-care OR office OR bedside OR "near patient" OR POC OR on-site OR rapid OR ultra-rapid) AND (test* OR assay*	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced

137 hits

Embase

Session Results	
No. Query Results	Results Date
#33. #32 AND [1-10-2014]/sd NOT [3-7-2019]/sd	590 2 Jul 2019
#32. #23 AND #31	1,224 2 Jul 2019
#31. #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30	151,197 2 Jul 2019
#30. 'fibrin degradation product'/exp	3,898 2 Jul 2019
#29. dimer*:ti,ab,de,tn	148,823 2 Jul 2019
#28. 'd-dimer*':ti,ab,de,tn	22,042 2 Jul 2019
#27. 'd dimer assay'/exp	15 2 Jul 2019
#26. 'd dimer blood level'/exp	19 2 Jul 2019
#25. 'd dimer test'/exp	51 2 Jul 2019
#24. 'd dimer'/exp	18,602 2 Jul 2019
#23. #13 AND #22	2,544 2 Jul 2019
#22. #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21	2,339,841 2 Jul 2019
#21. 'leg cramp'/exp	2,111 2 Jul 2019
#20. 'leg pain'/exp	45,870 2 Jul 2019
#19. (leg* NEAR/2 (pain OR cramp*)):ti,ab,de	23,879 2 Jul 2019
#18. dvt:ti,ab	18,160 2 Jul 2019
#17. vte:ti,ab	18,781 2 Jul 2019
#16. ((vein* OR ven* OR deep*) NEAR/4 thrombo*):ti,ab,de	175,271 2 Jul 2019
#15. 'vein thrombosis'/exp	127,935 2 Jul 2019
#14. 'cardio-pulmonary disease*':ti,ab,de OR 'cardiopulmonary disease*':ti,ab,de OR 'pulmonary disease*':ti,ab,de OR 'thromboembolic event*':ti,ab,de OR dyspnoea:ti,ab,de OR 'pulmonary embolism*':ti,ab,de OR 'lung embolism*':ti,ab,de OR pneumonia*:ti,ab,de OR 'lower respiratory infect*':ti,ab,de OR cough*:ti,ab,de OR bronchit*:ti,ab,de OR asthma*:ti,ab,de OR copd:ti,ab,de OR pleuritis:ti,ab,de OR 'pulmonary heart disease'/exp OR 'lung diseases'/exp OR 'lung diseases, obstructive'/exp OR 'thromboembolism'/exp OR 'dyspnea'/exp OR 'pulmonary embolism'/exp OR 'pneumonia'/exp OR 'pneumonia, bacterial'/exp OR 'pneumonia, viral'/exp OR 'cough'/exp OR 'bronchitis'/exp OR 'asthma'/exp OR 'pulmonary disease, chronic obstructive'/exp OR 'pleurisy'/exp	2,278,833 2 Jul 2019
#13. #1 AND #12	8,606 2 Jul 2019
#12. #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11	210,161 2 Jul 2019
#11. 'walk-in center*':ti,ab,de	21 2 Jul 2019

#10. 'walk-in centre*':ti,ab,de	162 2 Jul 2019
#9. ((casualty OR emergenc*) NEAR/2 (department* OR ward* OR station* OR unit* OR room*)):ti,ab,de	190,015 2 Jul 2019
#8. casualty:ti,ab,de	6,347 2 Jul 2019
#7. 'a & e':ti,ab,de	11,471 2 Jul 2019
#6. a&e:ti,ab	11,401 2 Jul 2019
#5. 'a and e':ti,ab,de	4,046 2 Jul 2019
#4. 'accident* and emergenc*':ti,ab,de	5,382 2 Jul 2019
#3. 'accident* & emergenc*':ti,ab,de	472 2 Jul 2019
#2. 'emergency ward'/exp	127,928 2 Jul 2019
#1. ('point* of care':ti,ab,de OR office*:ti,ab,de OR bedside*:ti,ab,de OR 'near patient*':ti,ab,de OR poc:ti,ab,de OR 'on site':ti,ab,de OR rapid:ti,ab,de OR 'ultra rapid':ti,ab,de) AND (test*:ti,ab,de OR assay*:ti,ab,de OR immunoassay*:ti,ab,de OR 'immuno assay*':ti,ab,de OR 'point-of-care systems'/exp) OR 'point-of-care testing'/exp OR 'fibrin fibrinogen degradation products'/exp OR poct:ti,ab,de OR 'd dimer*':ti,ab,de OR dimer*:ti,ab,de	426,365 2 Jul 2019

Medline

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily - without Revisions <2015 to June 27, 2019>, Ovid MEDLINE(R) <1946 to June Week 4 2019>
Search Strategy:
---
1 ((point* of care or point*-of-care or office* or bedside* or near patient* or POC or on-site or rapid or ultra-rapid) and (test* or assay* or immunoassay* or immuno-assay*)).mp. or exp Point-of-Care Systems/ or exp Point-of-Care Testing/ or exp Fibrin Fibrinogen Degradation Products/ or (POCT or D-dimer* or dimer*).mp. (391653)
2 exp Emergency Service, Hospital/ (88709)
3 Emergency department*.mp. (101775)
4 Accident* & Emergenc*.mp. (813)
5 "Accident* and Emergenc*".mp. (5006)
6 "A and E".mp. (28830)
7 A&E.mp. (25331)
8 A & E.mp. (9368)
9 casualty.mp. (7705)
10 ((casualty or emergenc*) adj3 (department* or ward* or station* or unit* or room*)).mp. (128129)
11 walk-in centre*.mp. (156)
12 walk-in center*.mp. (15)
13 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 (223712)
14 1 and 13 (7050)
15 exp Venous Thrombosis/ (59129)
16 ((vein* or ven* or deep*) adj5 thrombo*).mp. (99640)

17 VTE.ti,ab. (12377)
18 DVT.ti,ab. (11089)
19 (leg* adj3 (pain* or cramp*)).mp. (9011)
20 exp Muscle Cramp/ (2295)
21 exp Leg/ (65791)
22 20 and 21 (253)
23 (cardio-pulmonary disease* or cardiopulmonary disease* or pulmonary disease* or thromboembolic event* or dyspnoea or pulmonary embolism* or lung embolism* or pneumonia* or lower respiratory infect* or cough* or bronchit* or asthma* or COPD or pleuritis).mp. or exp Pulmonary Heart Disease/ or exp Lung Diseases/ or exp Lung Diseases, Obstructive/ or exp Thromboembolism/ or exp Dyspnea/ or exp Pulmonary Embolism/ or exp Pneumonia/ or exp Pneumonia, Bacterial/ or exp Pneumonia, Viral/ or exp Cough/ or exp Bronchitis/ or exp Asthma/ or exp Pulmonary Disease, Chronic Obstructive/ or exp Pleurisy/ (1265615)
24 15 or 16 or 17 or 18 or 19 or 22 or 23 (1350232)
25 14 and 24 (1202)
26 limit 25 to ed=20160301-20190702 (444)
27 remove duplicates from 26 (234)
****
02.07.2019

APPENDIX 2: REGULATORY AND REIMBURSEMENT STATUS

Table A1: Summary of (reimbursement) recommendations in European countries for the technology

Country	Summary of (reimbursement) recommendations and restrictions on D-dimer POCT	Summary (reimbursement) recommendations and restrictions on Tn-POCT
England[1]	Positive recommendation. The technology is reimbursed. https://www.nice.org.uk/guidance/cg144/chapter/Recommendations	Positive recommendation. The technology is reimbursed. https://www.nice.org.uk/guidance/dg15/chapter/1-Recommendations
Italy[1,2]	No details are available about the status of recommendation. The technology is reimbursed only in hospital use and part of DRG.	No details are available about the status of recommendation. The technology is reimbursed only in hospital use and part of DRG.
Germany[1,2]	The technology has not been assessed. It is reimbursed.	The technology has not been assessed. It is reimbursed.
Norway[1]	The technology has not been assessed. It is reimbursed.	The technology has not been assessed. It is reimbursed.
Austria[1]	The technology has not been assessed. Reimbursement differs between the social security institutions	The technology has not been assessed. Reimbursement differs between the social security institutions
Switzerland[1,2]	No details are available about the status of recommendation. It is reimbursed.	No details are available about the status of recommendation. It is reimbursed.
Belgium[2]	No details are available about the status of recommendation. It is reimbursed.	No details are available about the status of recommendation. It is reimbursed.
The Netherlands[2]	No details are available about the status of recommendation. It is reimbursed.	No details are available about the status of recommendation. It is reimbursed.
France[2]	No details are available about the status of recommendation. It is reimbursed.	No details are available about the status of recommendation. It is reimbursed.
Czech Republic[2]	No details are available about the status of recommendation. It is reimbursed.	No details are available about the status of recommendation. It is reimbursed.

Abbreviations: DRG

[1] EUnetHTA partners from the respective countries provided the information.

[2] Radiometer Medical ApS provided this information regarding their products.

APPENDIX 3: DESCRIPTION OF THE EVIDENCE USED

DESCRIPTION OF THE EVIDENCE USED

Guidelines for diagnosis and management

Table A2: Overview of guidelines on the use of Tn-POCT

Name of society/organisation issuing guidance	Date of issue	Country/ies to which applicable	Setting in which applicable	Summary of recommendation	Level of evidence (A,B,C)/ class of recommendation (I, IIa, IIb, III)
AHA/ACC [11]	2014	U.S.	ED and outpatient facilities	Point-of-care troponin values may provide initial diagnostic information, although their sensitivity is substantially below that of central laboratory methods. In addition, the rigorous quantitative assay standardization needed for routine diagnosis favours central laboratory testing.	NA
SIGN [28]	2016	UK	ED, pre-hospital, ambulance, specialist offices	Troponin point-of-care testing assays currently licensed in the UK are equivalent in sensitivity to 12-hour laboratory-based standard troponin assays.	Good practice recommendation
ANZCOR [16]	2016	Australia and New Zealand	Chest pain observation units	There has been a lack of evidence of supporting the routine use of point of care troponin testing in isolation as the primary test in a pre-hospital setting to evaluate patients with ACS.	NA
ESC [14]	2016	Europe	NA	It is recommended to measure cardiac troponins with sensitive or high-sensitivity assays and obtain the results within 60 min.	Level A, Class I
DEGAM [15]	2011	Germany	Primary care	In primary care area there are various qualitative and quantitative tests as a point-of-care tests	Level A, DI (strong recommendation,

Name of society/organisation issuing guidance	Date of issue	Country/ies to which applicable	Setting in which applicable	Summary of recommendation	Level of evidence (A,B,C)/ class of recommendation (I, IIa, IIb, III)
				available, which allows for the determination of various biomarkers, partly also in combination. The routine use of a qualitative troponin tests or other biomarker tests to exclude an acute myocardial infarction is not recommended in primary care. A troponin test is appropriate to exclude myocardial infarction only in clinically ambiguous cases (intermediate clinical probability of an ACS) when the onset of symptoms is >12 hours and the ECG is unremarkable.	highest level of evidence)
Oman Heart Association [27]	2012	Oman	Applicable for all cardiac caregivers.	Blood has to be drawn promptly for troponin (cardiac Tn T or I) measurement. The result should be available within 60 minutes. If the local laboratory cannot provide Tn results within 60 minutes, point-of-care testing should be performed.	NA
Japanese Circulation Society [29]	2016	Japan	Disaster medicine	ECG and whole-blood rapid cardiac troponin T assay or a human fatty acid-binding protein (H-FABP) ELISA kit should be used to enable early diagnosis of ACS.	Level C
NACB [30]	2007	U.S.	Outpatient facilities	The laboratory should perform cardiac marker testing with a TAT of 1 h, optimally 30 min, or less. Institutions that cannot consistently deliver cardiac marker TATs of approximately 1 h	Level A, Class II Level B, Class II

Name of society/organisation issuing guidance	Date of issue	Country/ies to which applicable	Setting in which applicable	Summary of recommendation	Level of evidence (A,B,C)/ class of recommendation (I, IIa, IIb, III)
				should implement POCT devices.	
				Performance specifications and characteristics for central laboratory and POC platforms should not differ.	Level A, Class III
				It is recommended that POC systems provide quantitative results, not only qualitative information.	Level C, Class II
				Manufacturers and professional organizations should collaborate to develop committees for the standardization of new analytes. Implementation of new tests is more easily integrated into the laboratory when these markers are available on a wide spectrum of analyzers.	Level A, Class III

Abbreviations: DEGAM Deutsche Gesellschaft für Allgemeinmedizin und Familienmedizin, AHA/ACC American Heart Association/American College of Cardiology, SIGN Scottish Intercollegiate Guidelines Network, ANZCOR Australian and New Zealand Resuscitation Council, ESC European Society of Cardiology, ACS Acute Coronary Syndrome, NA Not available, U.S. United States, UK United Kingdom, Tn Troponin, ECG Electrocardiograph, AWMF Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften, POC point-of-care, POCT point-of-care test, TAT turnaround time, ELISA enzyme-linked immunosorbent assay, NACB National Academy of Clinical Biochemistry

Table A3: Overview of guidelines on the use of D-dimer POCT

Name of society/ organi-sation issuing guidance	Date of issue	Country/ ies to which applic-able	Setting in which applicable	Summary of recommendation	Level of evidence (A,B,C)/ class of recommen dation (I, IIa, IIb, III)
SIGN [19]	2014	Scotland	Primary care (GPs, nurses, pharmacists)	In patients with a first episode of VTE, the combination of a low probability clinical decision rule or 'DVT or PE unlikely' and a negative D-dimer test can be used to safely exclude a diagnosis of VTE. A variety of D-dimer tests, including POCTs can be used in the exclusion of suspected VTE in low probability patients.	Level B
ESC [43]	2019	Europe	In- and outpatient	In community or primary care medicine, POC D-dimer testing may have advantages over referring a patient to a central laboratory. This may particularly apply to remote areas where access to healthcare is limited. How-ever, POC assays have a lower sensitivity and negative predictive value compared with laboratory-based D-dimer tests. POC D-dimer assays should only be used in patients with a low pre-test probability.	NA
NCGC [18]	2012	UK	Primary, secondary and tertiary care	There are various D-dimer tests available, including POCTs which can be done in the community, for example by a GP. The sensitivity of the assays chosen is very important as different tests have varying sensitivities.	NA
NICE [42]	2012	UK	NA	A laboratory or POC test can be done to assess the concentration of D-dimer in a person's blood. The threshold for a positive result varies with the type of D-dimer test used and is determined locally. The result of the D-dimer test can be used as part of probability assessment when DVT or PE is suspected.	NA
AWMF [38]	2015	Germany	Ambulatory care, inpatient (e.g., inpatient, day clinics)	In low-risk patients, a simple qualitative bedside test for D-dimer determination in combination with the clinical probability compared to the more elaborate quantitative ELISA test was comparable in its value.	NA
DEGAM [15]	2011	Germany	Primary care	The diagnostic value depends on the type of test, the comorbidities, the age and the duration of the symptoms. The classic ELI-SA and the rapid ELISA tests are moderate-ly specific and highly sensitive in the inpa-tient setting and therefore recommended to exclude PE. It is not recommended to apply less sensitive tests like manual qualitative or semi-quantitative agglutination tests that are also offered in the GP praxis's.	NA
DGK [39]	2009	Germany	NA	If, in place of the highly sensitive ELISA-D-dimer test, a qualitative "bedside" test is used, this should be done only in patients with low clinical probability (or PE unlikely) to exclude a PE. In hospitalized patients, the diagnostic value of the D-dimer assessment is low.	NA

Name of society/ organi-sation issuing guidance	Date of issue	Country/ ies to which applic-able	Setting in which applicable	Summary of recommendation	Level of evidence (A,B,C)/ class of recommen dation (I, IIa, IIb, III)
Jaeschke [41]	2009	NA	Outpatient or emergency room, i.e., not among hospitalized patients	The guideline concludes that different D-dimer tests have different characteristics and thus require differing recommendations for use. Moderate sensitivity rapid D-dimer assays can effectively rule out DVT in patients with a low pre-test probability. Nevertheless, in patients with moderate or high pre-test probability, the initial use of the moderately sensitive D-dimer assay to exclude DVT is not recommended.	NA
Fesmire [40]	2001	US	ED	The guideline committee decided not to assess the evidence for qualitative D-dimer tests used as point-of-care tests because of the problems with variability in their interpretation and lower sensitivity reported in many studies. The guideline also highlights that the only RCT directly assessing the impact of a D-dimer strategy used POCT (SimpliRED).	Level A
Japanese Circula-tion Soci-ety [29]	2016	Japan	Disaster medicine	Upper leg venous ultrasound imaging is not necessary for people in whom D-dimer levels may be determined with POCT.	Level B

Abbreviations: SIGN Scottish Intercollegiate Guidelines Network, ED emergency department, ESC European Society of Cardiology, NA Not available, U.S. United States, UK United Kingdom, AWMF Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften, POCT point of care test, DVT deep vein thrombosis, VTE venous thromboembolism, GP general practicioner, PE pulmonary embolism, NICE National Institute for Health and Care Excellence, NCGC National Clinical Guideline Centre, DGK Deutsche Gesellschaft für Kardiologie – Herz und Kreislaufforschung e.V., ELISA enzyme-linked immunosorbent assay

Evidence tables of individual studies included for clinical effectiveness and safety

Table A4: Characteristics of eligible systematic reviews for Tn-POCT

Author or Institution/ country, year	CADTH/CA, 2016 [25]	Schols/NE, 2018 [26]
Number and type of included studies	41 primary studies, 5 companion reports, 2 evidence based guidelines Overall: 7 RCTs 22 prospective observational studies 10 retrospective observational studies 2 surveys 2 evidence based guidelines DTA: 9 studies (+1 companion report) Clinical utility: 30 studies (+3 companion reports) 2 guidelines 2 further studies that looked at both DTA and clinical utility	7 studies in total of which 2 studies contained Tn- POCT 2 prospective comparative cohort studies Planer 2006 Nillsson 2013
Setting	No filter: incl. ED & primary care	Primary care
Search period	14/01/2015, regular alerts until 12/02/2016	To October 2014
Databases/ sources searched	MEDLINE (updates via Ovid), Embase (updates via Ovid), The Cochrane Library, PubMed Additional handsearch for grey literature	PubMed, EMBASE, CINAHL, Cochrane Library
Funding/ sponsor of SR Funding/ sponsor of included studies	"CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec". Industry or author COI: 22 studies NR: 16 studies No funding from industry and no author CoI: 3 studies	Netherlands Organisation for Health Research and Development (ZonMw) NR
Inclusion and exclusion criteria	DTA: Setting: Medical centres where central laboratory testing is available (such as hospital emergency departments) Population: Adults presenting with chest pain or other symptoms suggestive of ACS Intervention: Tn-POCT approved for use in Canada by Health Canada that use the 99th percentile cut-off threshold Central laboratory methods for measuring cTn Comparator: Clinical adjudication Outcomes: Clinical validity of Tn-POCT, including: sensitivity, specificity, positive predictive value, negative predictive value, positive-likelihood ratio, and negative-likelihood ratio of Tn-POCT in the detection of AMI Study design: RCTs, cohort studies, case-control studies Clinical utility: Setting:	Population: Included: patients with acute cardiopulmonary conditions/symptoms in primary care. Excluded: non-chest related conditions like DVT. Intervention: POCT Comparator: care as usual, no POCT Outcomes: included studies on clinical effectiveness and clinical diagnostic accuracy; excluded test accuracy studies

Author or Institution/ country, year	CADTH/CA, 2016 [25]	Schols/NE, 2018 [26]
	• Medical centres where central laboratory testing is available (such as hospital emergency departments) • Medical centres or settings where central laboratory testing is not available (such as pre-hospital settings, rural health care centres or remote locations) Population: Adults presenting with chest pain or other symptoms suggestive of ACS Intervention: Any Tn-POCT Comparator: • For settings where a central laboratory is available: central laboratory methods either alone or in addition to Tn-POCT • For settings where central laboratory is not available: standard care (e.g., transfer to facility with testing capabilities) Outcomes: • Benefits and risks of Tn-POCT such as: turnaround time, time to clinical decision-making, time to discharge or transfer (length of hospital stay, length of emergency department stay), number of hospital admissions, adverse events rate, mortality rate, repeat emergency department visit • Behaviour/treatment patterns of health care professionals • Availability of the test, acceptability of and interest in the test for patients • Ethical, legal, social implications of Tn-POCT • Recommendations from evidence-based guidelines Study design: RCTs, cohort studies, evidence-based guidelines, surveys (for outcomes related to behaviour/treatment patterns, and availability and acceptability of tests)	
Quantitative synthesis (yes/no)	No	No
Total number of patients across all included studies	NR	545
Countries of included studies	United States (n=12), Australia (n=5), Sweden (n=4), Italy (n=4), Denmark (n=3), United Kingdom (n=3), Netherlands (n=2), Canada (n=1), New Zealand (n=1), Germany (n=1), Finland (n=1), Slovenia (n=1), France (n=1), China (n=1) multiple countries (n=1): Spain, the UK, Germany, Austria, Ireland, and Sweden	NR
Type of index tests in the included studies	16 different POCT devices: Stratus CS, i-STAT, AQT90 FLEX, Cardiac Reader, PATHFAST, Triage, Cobas h232, Triage Cardiac Panel, Triage Profiler SOB, Triage Cardio3, Triage Meter Pro, Spectra Status, GEM Immuno, TropT, Cardiac T, and Cardio3 99th percentile: 0.014-0.08 mcg/L	Brand name: NR Planer 2006: Troponin T POCT (0.08ug/l) Nillsson 2013: Troponin T POCT (0.03ug/l)
Type of reference test of the included studies	Clinical adjudication was heterogeneous across studies and included but was not limited to the following: • Roche Modular E170 hs-cTnT + coronary angiography • Independent adjudication by a cardiologist and cardiology	Planer 2006: Common practice, including follow up only Nilsson 2013: Evaluation of hospital

Author or Institution/ country, year	CADTH/CA, 2016 [25]	Schols/NE, 2018 [26]
	research clinician • final diagnosis of AMI using the ESC/ACC diagnostic criteria by cardiologists • determination of final diagnosis using the laboratory data • ECG results and clinical findings[22]	records, ECG and GP's clinical evaluation or telephone interviews
Selected endpoints in the SR	DTA, clinical utility	Accuracy of clinical diagnosis and impact on patient management
Results/Outcomes		
DTA		
DTA (SEN, SPEC, NPV, PPV)	DTA at admission: range of POCT vs. range of CL SEN: 26%-88% vs. 68%-100% SPEC: 84.0%-98.0% vs. 75%-94% PPV: 31.0%-85.0% vs. 10%-82% NPV: 90%-99% vs. 95%-100%	SEN (MI, MI+unstable angina): Planer et al.: 83%, 21% Nilsson et al.: 67%, 29% SPEC (MI, MI+unstable angina): Planer et al.: 100%, 100% Nilsson et al.: 98%, 98% PPV (MI, MI+unstable angina): Planer et al.: 100%, 100% Nilsson et al.: 40%, 40% NPV (MI, MI+unstable angina): Planer et al.: 99.7%, 94% Nilsson et al.: 99%, 96%
Effectiveness /clinical utility		
No. of hospital admissions	ED: NR Hospitalisation in pre-hospital setting with no access to central laboratory testing (ambulance; evidence base: 1 RCT, 601 enrolled pts) • No difference between Tn-POCT and usual care (no further information provided)	NR
Treatment initiation	NR	NR
Referral rates	Referral rate from GP to ED (1 cohort study, cTnT testing, 196 enrolled pts): • Reduction in 1/1 study: 32/128 pts (25%) vs. 29/68 pts (43%), p value not reported[23]	Referral rate from GP to ED (1 cohort study, cTnT testing, 196 enrolled pts): Reduction in 1/1 study: 32/128 pts (25%) vs. 29/68 pts (43%), p value not reported[23]
Door-to-needle time (DNT)	NR	NR
Turnaround time (TAT)	TAT in ED (2 RCTs, 11 observational studies using a variety of different definitions of TAT[24]) RCTs (2 studies, cTnI or cTnT testing, 2,134 and 833	NR

[22] It appeared that numerous studies did not adequately report on the reference standard as well.

[23] Yet, it is mentioned in the review that the authors of the primary study noted that there were some two patients that were not referred and missed cases (one AMI and one unstable angina respectively). It is therefore concluded that the use of Tn-POCT in pts with chest pain "may reduce emergency referrals, but probably at the cost of an increased risk to miss patients with an acute myocardial infarction or unstable angina".

[24] E.g., time from blood draw to result.

Author or Institution/ country, year	CADTH/CA, 2016 [25]	Schols/NE, 2018 [26]
	enrolled patients respectively): • Reduction in 2/2 studies: 43 min (median; p value not available) in one study, and 71 and 147 min in the other study[25] (median; s. s., with p<0.001) Observational studies (5 prospective, 1 retrospective and 5 pre-post studies respectively, cTnI or cTnT testing, 31 to 2,386 enrolled pts) • Reduction in 11/11 studies: 18-93 min (p values available for 5/11 studies, with s. s. differences in these studies) TAT in the ambulance (median time from symptom onset to blood sampling; 1 observational study; 928 pts): 83 min (range: 46-167)	
Time to discharge (TTD)	TTD in ED (evidence base: 2 RCTs, 1 observational study): RCTs (2 studies, cTnT or cTnI testing, 487 and 2,134 enrolled pts respectively): • Reduction in 2/2 studies: 5 and 7 min (mean and median; s. s. with p=0.04 and p value not available respectively) Observational studies (1 pre-post study, multiple biomarkers 4,886 enrolled pts): • Reduction in 1/1 study: 26 min (mean; p value not available) TTD in pre-hospital setting with no access to central laboratory testing (ambulance; evidence base: 1 RCT) • Reduction in 1/1 study (median time Tn-POCT vs CL): 8.8 hours (range: 6.2 h to 10.8 h) vs. 9.1 h (range 6.7 hours to 11.2 hours), *P* = 0.05.	NR
Length of stay (LOS)	LoS in ED Emergency room stay (evidence base: 3 RCTs, 2 observational studies): *RCTs* (3 studies, cTnI or cTnT testing, 487-912 enrolled pts): • Reduction in 2/3 studies: 0.2 and 0.8 h (mean and median; diff. n. s. in individual studies) • Increase in 1/3 studies: 0.1 h (median; diff. n. s.) *Observational studies* (2 pre-post studies, cTnI testing, 366 and 671 enrolled pts respectively): • Reduction in 2/2 studies: 1.9 h (mean; p value NR) and 2-2.7 h respectively (median; diff. s. s.) Hospital stay in ED (evidence base: 1 RCT) *RCTs* (1 study, cTnI testing, 2,243 enrolled pts) • Reduction in 1/1 study: 2.2 h (mean; diff. n. s.)	NR
Further diagnostic testing	NR	NR
Time to clinical decision (TCD)	TCD in ED (evidence base: 1 RCT, 1 pre-post study): RCTs (1 study, cTnI testing, 2,134 enrolled pts) • Reduction in 1/1 study: 9 min (median; p value not available) Observational studies (1 pre-post study, multiple biomarker testing, 4,886 enrolled pts): • Reduction in 1/1 study (multiple biomarkers): 26 min (mean; p value not available)	NR

[25] When using the definitions “time from collection to physician notification” and “time from presentation to anti-ischemic therapy” respectively.

Author or Institution/ country, year	CADTH/CA, 2016 [25]	Schols/NE, 2018 [26]
Mortality/ morbidity	Mortality in ED (evidence base: 2 RCTs and 3 further observational studies) RCTs (2 studies; cTnT or cTnI testing, 487 and 2,243 enrolled pts respectively) • POC vs. central lab: 0.5 vs. 0% in one study (p value NR) and 1% vs.0.2% in another study (n. s., with p=0.142) Observational studies (3 prospective studies; cTnI or cTnT testing; 508-1,410 enrolled pts) • None of the studies compared Tn-POCT with CL head-to-head (statistically) Mortality in pre-hospital setting with no access to central laboratory testing (ambulance; evidence base: 1 RCT, 601 enrolled pts) • Death in the next 30 days: no difference between groups (no further information provided) Cardiac events in ED (evidence base: 2 prospective studies, cTnI or cTnT testing) 30 day cardiac event rate (1Iprospective study, 704 enrolled pts; POCT vs. central lab): • Low risk pts: 0% (95%CI: 0-25.9) vs. 0% (95%CI: 0-21.5), p value NR • High risk pts: 24.8% (95%CI: 20.1-30.1) vs. 28.6% (95%CI: 23.4-34.4), p value NR Cardiac events after 1 year (1 prospective study, 1,410 enrolled pts; POCT vs central lab): • 2.1% (95%CI: 1.5-3) vs. 2.2% (95%CI: 1.6-3.1), p value NR Other Adverse events and composite end points in ED (evidence base: 2 RCTs, cTnT or cTnI testing) Major AE after 3 m FU (1 RCT, 2,243 enrolled pts; POCT vs central lab): 3% vs. 2%, diff. n. s., with p=0.313 CEP events[26] at 6 m (1 RCT, 487 enrolled pts; cTnT testing, POCT vs. central lab): 10.4% vs. 5.4%, p value NR	NR
Patient Quality of Life (QoL)	QoL in ED (evidence base: 1 RCT, cTnI testing, 2,243 enrolled pts using the EQ-5D questionnaire): POC vs. central lab: • After 1 m: 0.742 vs. 0.759 (n. s., with p=0.614) • After 3 m: 0.752 vs. 0.759 (n. s., with p=0.638)	NR
Harms (e.g., from false positive and false negative tests, harms from delayed treatment)	NR	The SR identified 1 cohort study that reported a decrease in referrals of TN-POC may increase the risk of missing out patients with an acute myocardial infarction or unstable angina. 2/128 in the TN-POC group needed but did not receive a referral (overall referral rate: 25% and 43% patients managed by physicians using and not using Tn-POCT respectively).
Safety		
Safety outcomes	NR	NR

[26] AMI, coronary revascularization, cardiac arrest, or mortality in patients with a negative first cTn test at 3 m FU

Author or Institution/ country, year	CADTH/CA, 2016 [25]	Schols/NE, 2018 [26]
Conclusion	"Overall, given the limitations with the data and the inconsistency in DTA estimates, the usefulness of [Tn-POCT[27]] in settings with access to central laboratories may be limited. However, in settings with no access to a central laboratory, such as in rural health care centres or remote settings, [Tn-POCT] may be useful due to the potential to help reduce unnecessary transfer of patients to larger centres."	No conclusion made on Tn-POCT: "With regards to the clinical value of Troponin POCT in a secondary care population, the literature is inconclusive"[28]

Abbreviations: ACC – American College of Cardiology; ACS – acute coronary syndrome; ACS – acute coronary syndrome; CA – Canada; CADTH – Canadian Agency of Drugs and Technologies in Health; CL – central laboratory; COI – conflict of interest; cTn – cardiac troponin; DTA – diagnostic test accuracy; DVT – deep vein thrombosis; ECG – electrocardiogram; ED – emergency department; ESC – European Society of Cardiology; FU – follow up; GP – general practitioner; h – hour(s); h – hours; m – month(s); NR – not reported; n. s. – not statistically significant; NE – Netherlands; NPV – negative predictive value; POCT – point of care testing; PPV – positive predictive value; pts – patients; QoL – quality of life; RCT – randomised controlled trial; s. s. – statistically significant; SEN – sensitivity; SPEC – specificity; SR – systematic review.

Table A5: Characteristics of eligible systematic reviews for D-dimer POCT (part 1)

Author/Institution/country, year	Pasha, 2010 [32]	Schols, 2018 [26]
Number and type of included studies	4 studies with D-dimer and Wells rule, 1 of which was POC	7 studies in total of which 2 studies (4 papers) contained D-dimer POCT data; RCTs or non-randomised controlled trials
Setting	only "outpatients" stated in the only relevant study (Rodger) in this review that used a POCT but not defined further (i.e. if primary care or ED)	primary care
Search period	2000 (introduction of Wells score) to 2008	To October 2014 (with PubMed search update from October 2014 to February 2016)
Databases/sources searched	Medline, Embase, Cochrane	PubMed, EMBASE, CINAHL, Cochrane Library, reference lists, contact with authors
Funding/sponsor of SR	NR	Netherlands Organisation for Health Research and Development (ZonMw)
Inclusion and exclusion criteria	Included study type: prospective studies with a minimum 3 month clinical follow up using a diagnostic strategy including a dichotomized clinical decision rule and a D-dimer test to rule out PE. Included population: all patients with an unlikely clinical probability and normal D-dimer who did not undergo radiological imaging	Population: Included: patients with acute cardiopulmonary conditions/symptoms (acute conditions or symptoms of either the heart, lungs or vascular blood supply of these organs at the height of the chest cavity) in primary care in western /developed countries. Excluded: non-chest related conditions like DVT. Intervention: POCT Comparator: care as usual, no POCT Outcomes: included studies on clinical effectiveness and clinical

[27] Note: The synonymous term "POC cTn testing" was used instead of the term Tn-POCT in the report.

[28] It is further stated that: "If a validated cardiac clinical decision rule like the MHS [note: Marburg Heart Score] would be added to a Troponin POCT, this would most likely lead to a more effective and safer exclusion of acute cardiac pathology. More research is necessary to investigate whether the combination of the two leads to a high enough NPV to safely exclude cardiac pathology"

Author/Institution/country, year	Pasha, 2010 [32]	Schols, 2018 [26]
		diagnostic accuracy; excluded analytical test accuracy studies
Quantitative synthesis (yes/no)	Yes	No
Total number of patients across all included studies	4,384 but only 1 study (199 patients) included relevant intervention (POC)	892
Countries of included studies	NR	NR
Type of index tests in the included studies (n of studies)	POC study: Simplired and Acculot Laboratory studies: VIDAS and Tinaquant	NR
Type of reference test of the included studies	N/A	Composite reference standard
Selected endpoints in the SR	Primary endpoints were the recurrence rate of venous thromboembolism (VTE) and PE-related mortality during 3-months follow up.	Accuracy of clinical diagnosis and impact on patient management
Results/Outcomes		
DTA		
DTA rates (SEN, SPEC, NPV, PPV)	Incidence of VTE despite negative testing and unlikely clinical probability: 2% (95% CI: 0.1-10.1%)	SEN: stand alone D-dimer 84%; Wells ≤4 + D-dimer 94- 95%; Wells ≤2 + D-dimer 97%. SPEC: stand-alone D-dimer 62%; Wells ≤4 + D-dimer 38- 51%; Wells ≤2 + D-dimer 32%. PPV: stand alone D-dimer 24%; Wells ≤4 + D-dimer 21- 37%; Wells ≤2 + D-dimer 20%. NPV: stand alone D-dimer 96%; Wells ≤4 + D-dimer 94- 99%; Wells ≤2 + D-dimer 99%.
Effectiveness/clinical utility		
No. of hospital admissions	NR	NR
Treatment initiation	NR	NR
Referral rates	NR	NR
Door-to-needle time (DNT)	NR	NR
Turnaround time	NR	NR
Time to discharge (TTD)	NR	NR
Length of stay (LOS)	NR	NR
Further diagnostic testing	In 49/199 (25%) patients with unlikely clinical probability and normal D-dimer CT scans could be withheld.	NR
Time to clinical decision (TCD)	NR	NR
Failure rate/efficacy/ efficiency	NR	NR
Mortality/morbidity	Mortality: 1 person (2%)	NR
Patient Quality of Life (QoL)	NR	NR
Safety		
Safety outcomes	NR	NR
Conclusion	Overall (across POCT and lab tests) pooled incidence of morbidity was 0.34% (95%CI 0.036-0.96%) and combined incidence of death (across POCT and lab tests) was 0.1% (95% CI 0.0-0.5%). Combined 3-month mortality risk of PE (across POCT and lab tests) was 0.10% (95%CI 0.002-0.46%).	No studies assessed the effects of D-dimer on treatment initiation or referral rates. All studies were considered at high risk of bias. Evidence suggests combining D-dimer with a clinical decision rule

Author/Institution/country, year	Pasha, 2010 [32]	Schols, 2018 [26]
	1 death occurred across all studies (this was in the POCT study). Ruling our PE on basis of unlikely clinical probability and normal D-dimer is very safe.	(e.g. when GP use of a D-dimer POCT is combined with the Wells clinical decision rule) leads to more accurate diagnosis. Further research on clinical effectiveness is necessary.

Abbreviations: CI – confidence interval; CT – computer tomography; ED – emergency department; n – number; No. – number; NPV – negative predictive value; NR – not reported; PE – pulmonary embolism; POCT – point of care testing; PPV – positive predictive value; SEN – sensitivity; SPEC – specificity; SR – systematic review; VTE – venous thromboembolism.

Table A6: Characteristics of eligible systematic reviews for D-dimer POCT (part 2)

Author/Institution/country, year	Lucassen, 2011 [34]	Hendriksen, 2015 [33]
Number and type of included studies	52 prospective studies including consecutive patients suspected of having PE.	10 published prediction models for the diagnosis of PE. 5 models were validated with the primary care dataset (AMUSE-2).
Setting	Hospital setting (emergency department, outpatients or inpatients)	primary care
Search period	1966-2011	January 2010-October 2014 (update of Lucassen systematic review)
Databases/sources searched	MEDLINE and EMBASE	PUBMED and EMBASE
Funding/sponsor of SR	Dutch Heart Foundation	The Netherlands Organization for Scientific Research
Inclusion and exclusion criteria	Included: Patients aged 16 years+ with symptoms suggesting acute PE and use gestalt or a clinical decision rule to estimate the clinical probability of PE. Clinical decision rules had to be based on a multivariate logistic regression model and provide data enabling the construction of a 2x2 table. Diagnosis of PE had to be confirmed with an "appropriate" reference standard.	Diagnostic prediction model development studies with or without external validation in independent data. Primary care patients in whom the diagnosis pulmonary embolism is considered: • Unexplained acute dyspnoea, and/ or • Unexplained cough, and/ or • Pain on inspiration
Quantitative synthesis (yes/no)	Yes	Yes
Total number of patients across all included studies	55,268	NR
Countries of included studies	NR	NR
Type of index tests in the included studies (n of studies)	11 studies using qualitative d-dimer testing as part of the clinical decision rule	Diagnostic prediction models (including point of care d-dimer) for use in primary care
Type of reference test of the included studies	Ventilation-perfusion lung scanning, CT, pulmonary angiography, autopsy	Established reference standard, such as spiral CT scanning, pulmonary angiography, ventilation-perfusion scanning, clinical follow up or a combination.
Selected endpoints in the SR	Failure rate and efficiency	Sensitivity, specificity, efficiency, failure rates
Results/Outcomes		
DTA		
DTA rates (SEN, SPEC, NPV, PPV)	NR specifically for qualitative D-dimer/POCT	Sensitivity*: 88% (78%-94%) for simplified revised Geneva ≤2 model; 90% (81-96%) for original revised Geneva ≤5; 95% (87%-98%) for original Wells ≤4; 95% (87-98%) for modified Wells ≤2; 96% (88%-99%) for simplified Wells ≤1. Specificity*: 48% (44%-53%) for original

Author/Institution/country, year	Lucassen, 2011 [34]	Hendriksen, 2015 [33]
		revised Geneva ≤5; 49% (45-53%) for the simplified Wells ≤1; 50% (46-55%) for the modified Wells ≤2; 51% (47-55%) for the original Wells ≤4; 53% (49%-57%) for simplified revised Geneva ≤2. PPV*: 20% (15%-24%) for original revised Geneva ≤5; 21% (17-26%) for original Wells ≤4; 21% (17-26%) for modified Wells ≤2; 21% (17-25%) for simplified Wells ≤1; 21% (16-26%) for simplified revised Geneva ≤2. NPV*: 97% (95-99%) original revised Geneva ≤5; 97% (94-99%) simplified revised Geneva ≤2; 99% (96-100%) original Wells ≤4; 99% (96-100%) modified Wells ≤2; 99% (97-100%) simplified Wells ≤1. *Data are ordered by values of the test accuracy rate.
Effectiveness/clinical utility		
No. of hospital admissions	NR	NR
Treatment initiation	NR	NR
Referral rates (RR)	NR	NR
Door-to-needle time (DNT)	NR	NR
Turnaround time (TAT)	NR	NR
Time to discharge (TTD)	NR	NR
Length of stay (LOS)	NR	NR
Further diagnostic testing	NR	NR
Time to clinical decision (TCD)	NR	NR
Failure rate/efficacy/efficiency (% & 95% CI)	Failure rate: Across all studies with qualitative D-dimer testing: 1.0% (95%CI 0.8-1.3%); combined with gestalt 0.7% (95%CI 0.4-1.2%); combined with Wells cutoff value ≤4: 1.7% (95%CI 1.0-2.8%); combined with Wells cutoff value <2: 0.9% (95%CI 0.6-1.5%). Efficiency: Across all studies with qualitative d-dimer testing: 45% (95%CI 39-52%); combined with gestalt 52% (95%CI 40-64%); combined with Wells cutoff value ≤4: 42% (95%CI 32-52%); combined with Wells cutoff value <2: 40% (95%CI 33-48%).	Failure rates across all models: 1.2% (95%CI 0.2%-3.3%) for simplified Wells ≤1; 1.5% (95%CI 0.4-3.7%) for original Wells ≤4; 1.5% (95%CI 0.4-3.8%) for modified Wells ≤2; 2.7% (95%CI 1.1-5.4%) for original revised Geneva ≤5; 3.1% (95%CI 1.4%-5.9%) for simplified revised Geneva ≤2. Efficiency across all models: 43% (95%CI 39%-48%) for simplified Wells ≤1; 44% (95%CI 40-48%) for original revised Geneva ≤5; 45% (95%CI 41-49%) for modified Wells ≤2; 46% (95%CI 41-50%) for original Wells ≤4; 48% (95%CI 44%-52%) for simplified revised Geneva ≤2.
Mortality/morbidity	NR	NR
Patient Quality of Life (QoL)	NR	NR
Safety		
Safety outcomes	NR	NR
Conclusion	Combining a decision rule and gestalt can safely exclude PE when combined with sensitive D-dimer testing except when the less sensitive Wells rule (cutoff value ≤4) is combined with qualitative D-dimer POCT	Efficiency was comparable across all models but the Wells rules combined with D-dimer POCT gave the best performance in terms of lower failure rates

Abbreviations: CT – computer tomography; DTA – diagnostic test accuracy; No. – number; NPV – negative predictive value; NR – not reported; PE – pulmonary embolism; POCT – point of care testing; PPV – positive predictive value; SEN – sensitivity; SPEC – specificity; SR – systematic review.

Table A7: Characteristics of eligible systematic reviews for D-dimer POCT (part 3)

Author/Institution/country, year	Geersing, 2009 [31]	Marquardt, 2015 [35]
Number and type of included studies	23 studies on the diagnostic accuracy of D-dimer POCT in outpatients	9 prospective or retrospective studies (7 related to turnaround time and 2 to cost-effectiveness).
Setting	Primary or secondary care	ED
Search period	January 1995-September 2008	Various, widest date range 1980-2015
Databases/sources searched	Medline & Embase, reference lists, expert contact	Embase, Medline, Cochrane, EBM and NHS Economic Evaluation Database, Ovid Nursing Full Text Plus, grey literature and product literature
Funding/sponsor of SR	Netherlands Heart Foundation & Zilveren Kruis Achmea	NR
Inclusion and exclusion criteria	Studies were included if: • Adult study population of consecutive outpatients in primary or secondary care suspected of DVT and/or PE • POC test used (not routine laboratory machine) • Use reference test for DVT • Use follow up reference test • Include calculation of SENS, SPEC, NPV, PPV and prevalence	Studies were excluded if they were not primary studies. Studies were included if they focused on D-dimer POCT and at least one of the following criteria: turnaround time, quality of care, cost-effectiveness, user-friendliness, length of stay, time to diagnosis, time to result.
Quantitative synthesis (yes/no)	Yes	No
Total number of patients across all included studies	13,959	3,279 (turnaround studies)
Countries of included studies	NR	NR
Type of index tests in the included studies (n of studies)	SimpliRED D-dimer (12 studies) Clearview Simplify D-dimer (7 studies) Cardiac D-dimer (4 studies) Triage D-dimer (2 studies)	11 D-dimer POCTs were used across all studies
Type of reference test of the included studies	Reference test for DVT: Compression ultrasonography, venography, impedance plethysmography, or uneventful follow up (no DVT or PE in 3 months). Reference test for PE: computerised tomography pulmonary angiography, ventilation-perfusion lung scanning, pulmonary angiography or uneventful follow up.	NR
Selected endpoints in the SR	Diagnostic accuracy	Turnaround times and time to diagnosis, referral or discharge
Results/Outcomes		
DTA		
DTA rates (SEN, SPEC, NPV, PPV)	SEN: 0.85 (95%CI 0.78-0.90) for SimpliRED D-dimer; 0.87 (0.81-0.91) for Clearview Simplify D-dimer;0.93 (0.88-0.97) for Triage D-dimer; 0.96 (0.91-0.98) for Cardiac D-Dimer. SPEC: 0.48 (95% CI 0.33-0.62) for Triage D-dimer; 0.57 (0.52-0.62) for Cardiac D-dimer; 0.62 (0.54-0.69) for Clearview Simplify D-dimer; 0.74 (95%CI 0.69-0.78) for SimpliRED Likelihood ratio of a negative test result: 0.07 (95%CI 0.04-0.16) for Cardiac D-dimer; 0.18 (95%CI 0.08-0.43) for Triage D-dimer; 0.21 (0.15-0.29) for SimpliRED D-dimer; 0.22 (95% CI 0.15 to 0.29) for Clearview Simplify D-dimer.	NR

Author/Institution/country, year	Geersing, 2009 [31]	Marquardt, 2015 [35]
Effectiveness/Clinical utility		
No. of hospital admissions	NR	No. of hospital admissions (one before-after study, 462 pts) decreased by 13.8%
Treatment initiation	NR	NR
Referral rates	NR	NR
Door-to-needle time (DNT)	NR	NR
Turnaround time (TAT)	NR	TAT in ED (evidence base: 7 observational studies[29], 3,279 pts): • Reduction in 5 studies (comparative; prospective and retrospective): 10-101.5 min (using different measures of central tendency; p-values and information on stat. testing NR) • No comparative data shown in 2 studies[30]
Time to discharge (TTD)	NR	NR
Length of stay (LOS)	NR	LoS in ED (evidence base: 1 before-after study, 462 pts): • Decrease in mean LoS (8.46 to 7.14 hrs; n. s. with p=0.16)
Further diagnostic testing	NR	NR
Time to clinical decision (TCD)	NR	NR
Failure rate/efficacy/ efficiency (% & 95% CI)	NR	NR
Mortality/morbidity	NR	NR
Patient Quality of Life (QoL)	NR	NR
Safety		
Safety outcomes	NR	NR
Conclusion	The two quantitative tests (Cardiac D-dimer and Triage D-dimer) scored most favourably. In outpatients suspected of VTE, D-dimer POCT can contribute important information and guide patient management, especially in low-risk patients (i.e. with low score on a clinical decision rule).	D-dimer POCT can safely improve patient journey times

Abbreviations: DVT – deep vein thrombosis; ED – emergency department; n – number; No. – number; NPV – negative predictive value; NR – not reported; POC – point of care; PPV – positive predictive value; SEN – sensitivity; SPEC; specificity; TAT – turnaround time.

[29] While the review reported initially on seven included studies on TAT, data are only presented for six studies.

[30] Non-comparative data was shown in one study (time to result: 10-38 min) and not reported at all in another study that the review described.

Table A8: Characteristics of eligible primary studies for D-dimer POCT

Author, year [reference number]	Oude Elferink, 2015 [37]	Kingma, 2017 [36]
Study design	Non-randomised controlled trial	Non-randomised controlled trial
Country	Netherlands	Netherlands
Funding/Sponsor	Statement that no direct financial support was received	Netherlands Organization for Health Research & Development (ZonMw)
Intervention (IG) | Product	8 different D-dimer tests, one of which was POCT (Simplify)	Implementation of a guideline consisting of clinical decision rule combined with negative D-dimer test
Comparator (usual care; UC)	DVT diagnosed by compression ultrasonography	Usual care (no guideline implementation strategy)
Number of patients	290 consecutive primary care patients over a period of 23 months divided into 2 groups on the basis of clinical decision criteria (from 305 patients with suspected DVT)	Intervention group : 217 GPs with 619 patients Usual care (UC): 32 GPs with 62 patients
Inclusion/exclusion criteria	Exclusion criteria: age below 18, anticoagulant therapy with vitamin K antagonists and/or low molecular-weight heparin Inclusion criteria: patients with symptoms of pain, swelling and/or redness of leg	NR Patients in the intervention group were included from 10/2013 to 06/2015. Patients in the usual care group were included from 05/2014 to 06/2016.
Selected endpoints in the SR	DTA and turnaround time	Effectiveness, as measured by (i) Proportion of non-referred patients; (ii) proportion of missed DVT cases; (iii) proportion of patients in whom guideline incorrectly applied
Follow up (months)	NR	3 months (to identify potentially missed DVT cases)
Drop-outs (n (%)	None	Intervention group: 6/625 patients (<1%) were lost to follow up Usual care group: 8/70 patients (11%)
Patient characteristics		
Age of patients (yrs.)	CDR≤3: M 56 (R18-88) CDR>3: M 62 (R 19-83) Wells score <2: M 56 (R 18-88) Wells score ≥2: M 60 (R 19-84)	IG: M 62 (R15-96) UC: M 59 (R 17-90)
Sex (% female)	CDR≤3:61% CDR>3: 48% Wells score <2: 60% Wells score ≥2: 62%	IG: 62% Usual care group: 66%
Comorbidity /risk factors		Contraceptive use (female): IG 9%; UC 13% Cancer in last 6 mnths: IG 5%, UC 5% Surgery in last month: IG 6% UC 2%
DTA rates (SEN, SPEC, NPV, PPV)	Results for Simplify: SENS all patients 91.3%, CDR ≤3 95.2%, Wells <2 91.7% SPEC all patients 60.8%, CDR ≤3 62.7%, Wells <2 62.8% NPV all patients 98.7% CDR ≤3 99.3%, Wells <2 99.1%	NR

Author, year [reference number]	Oude Elferink, 2015 [37]	Kingma, 2017 [36]
Clinical utility/effectiveness outcomes		
Mortality/Morbidity	NR	NR
QoL	NR	NR
	NR	NR
No. of hospital admissions	NR	NR
Treatment initiation	NR	NR
Referral rates	NR	Patients referred: IG: 284/619 (46%) UC: 31/62 (50%), p=ns Proportion of VTE in patients referred: IG: 120/284 (42%) UC: 11/31 (36%), p=ns Patients not referred: IG: 335/619 (54%) UC: 31/62 (50%), p=NR Proportion of VTE in patients not referred: IG: 6*/335 (1.8; 95%CI 0.7-0.39) UC: 0 (0.0; 95%CI 0-11.2), p=ns * 3 patients were deliberately not referred due to shared decision making
Door-to-needle time (DNT)	NR	NR
Turnaround time	Simplify had analysis time of 10 minutes. Turnaround time of laboratory tests ranged between <5 minutes (Liatest) and 34 minutes (Vidas)	NR
Time to clinical decision	NR	NR
Time to discharge	NR	NR
Length of stay	NR	NR
Further diagnostic testing	NR	NR
Failure rate/efficacy/ efficiency	NR	NR
Safety		
Safety	NR	NR

Abbreviations: CDR – clinical decision rule; DTA – diagnosic test accuracy; DVT – deep vein thrombosis; IG – intervention group; n – number; No. – number; NPV – negative predictive value; NR – not reported; PPV – positive predictive value; SEN – sensitivity; SPEC – specificity; SR – systematic review; UC – usual care.

List of ongoing and planned studies

Table A9: List of ongoing studies with Tn-POCT

Study identifier	Study Designs	Status	Setting	Interventions	Outcome Measures	Enrolment	Age	Sponsor/Collaborators	Funded By	Completion Date
NCT03102216	RCT	Completed	ED	Diagnostic Test: iSTAT Diagnostic Test: CBC Diagnostic Test: ECG Diagnostic Test: Lodox	Decrease waiting and disposition times for patients presenting to the Emergency Department| Decrease the costs of special investigations for patients presenting to the Emergency Department	1134	≥18 y. o.	Helen Joseph Hospital Abbott Point of Care University of Johannesburg|Lodox Systems (Ltd)	Other|Industry	June 30, 2017
NCT00222352	NRCT	Completed	ED	Diagnostic Test: Point of Care cTnL testing Traditional central laboratory testing	Time to disposition from the ED| Time to departure	2000	≥18 y. o.	University of Cincinnati Abbott|Jewish Hospital, Cincinnati, Ohio University of Pennsylvania|Stanford University|Mayo Clinic	Other|Industry	March 2007
NCT02972814	NRCT	Recruiting	ED	Device: Laboratory based troponin test Device: Point of care based troponin (Radiometer EQT 90 Flex) Device: Point of care based troponin (Philips Minicare I-20)	Time delay until troponin test results are known	50	≥18 y. o.	Ziekenhuis Oost-Limburg	Other	February 2020
NCT02620397	NRCT	N/A	ED	Subjects will have up to 4 blood samples collected for cTnI testing using the Meritas Troponin I test and Meritas point-of-care (POC) Analyzer. Blood draws and testing will occur at 4 intervals over 24 hours.	Clinical performance of the Meritas Troponin I test| Prognostic capability of sponsor's Meritas Troponin I to predict mortality (all-cause death) and cardiac events (i.e., MI, cardiac death).	1500	≥21 y. o.	Trinity Biotech	Industry	November 2016

Study identifier	Study Designs	Status	Setting	Interventions	Outcome Measures	Enrolment	Age	Sponsor/Collaborators	Funded By	Completion Date
DRKS00000709	RCT	N/A	N/A	Intervention 1: Point-of-care testing group (POCT group): before making a working diagnosis, the physicians can analyse troponin T, NT-proBNP and/or D-dimer with a diagnostic device (Cardiac Reader, Roche Diagnostic). Intervention 2 (Control): conventional diagnostic process	Primary: Diagnostic accuracy: working diagnosis vs. confirmed/Follow up diagnosis (about 3 weeks after working diagnosis) Secondary: Resource utilisation (consultation, transport, hospitalisation) and workdays lost between baseline and follow up	1000	≥18 y. o.	Roche Diagnostic (Schweiz) AG	Roche Diagnostic (Schweiz) AG	N/A

Abbreviations: CBC – complete blood count; ECG – electrocardiography; NRCT – non-randomised controlled trial; ED – emergency department; RCT – randomised controlled trial.

Risk of bias tables Tn-POCT

Table A10: Risk of Bias (Tn-POCT) – study level (systematic reviews and meta analyses)

Author, year	Bruins Slot, 2013 [101]	CADTH, 2016 [25]	Pecoraro, 2014 [102]	Pecoraro, 2017 [103]	Schols, 2018 [26]
1. Did the research questions and inclusion criteria for the review include the components of PICO?	Yes	Yes	Yes	No	Yes
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	No	Yes	No	No	Partial Yes
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Yes	Yes	Yes	Yes	Yes
4. Did the review authors use a comprehensive literature search strategy?	No	Partial Yes	Partial Yes	Partial Yes	Partial Yes
5. Did the review authors perform study selection in duplicate?	Yes	Yes	Yes	No	Yes
6. Did the review authors perform data extraction in duplicate?	Yes	Yes	Yes	Yes	No
7. Did the review authors provide a list of excluded studies and justify the exclusions?	No	Yes	No	No	No

Author, year	Bruins Slot, 2013 [101]	CADTH, 2016 [25]	Pecoraro, 2014 [102]	Pecoraro, 2017 [103]	Schols, 2018 [26]
8. Did the review authors describe the included studies in adequate detail?	Partial Yes	Yes	No	Yes	Yes
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review? RCTs	Yes	Yes	No	No	Yes
10. Did the review authors report on the sources of funding for the studies included in the review?	No	Yes	No	No	No
11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results? RCTs	NA	NA	NA	NA	NA
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	NA	NA	NA	NA	NA
13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	No	Yes	No	No	Yes
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Yes	Yes	No	Yes	Partial Yes
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	NA	NA	NA	NA	NA
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes	Yes	Yes	Yes	Yes
Overall Confidence	**Critically low**[31]	**High**[32]	**Critically low**[33]	**Critically low**[34]	**Moderate**[35]

[31] Critical flaws: Only one database considered for literature search, consideration of RoB when interpreting the results of the review absent.

[32] No critical flaws suspected. Adequacy of "Downs and Black" checklist for clinical utility studies was discussed within the project team but considered as adequate. CADTH also did not search trial/study registries, which was considered as a non-critical weakness.

[33] Critical flaws: RoB assessment unclear (no standardised tool) & incomplete, consideration of RoB when interpreting the results of the review absent.

[34] Critical flaws: RoB assessment unclear (no standardised tool), consideration of RoB when interpreting the results of the review absent.

[35] No critical flaw suspected. Several non-critical flaws: e.g., did not search trial/study registries within their search, data-extraction not in duplicate, etc.

Table A11: AGREE II quality appraisal of guidelines on the use of Tn-POCT

Domain	Item	AGREE II Score							
		DEGAM	AHA/ ACC	SIGN	Oman Heart Ass.	ANZCOR	ESC	Japanese Circ.Soc.	NACB
Scope and purpose	1. The overall objective(s) of the guideline is (are) specifically described.	7	7	7	7	7	7	7	7
	2. The health question(s) covered by the guideline is (are) specifically described.	7	7	7	7	6	7	7	7
	3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.	7	7	7	7	7	7	7	7
Stakeholder involvement	4. The guideline development group includes individuals from all the relevant professional groups.	7	7	7	1	1	7	7	4
	5. The views and preferences of the target population (patients, public, etc.) have been sought.	6	1	7	1	1	5	1	2
	6. The target users of the guideline are clearly defined.	7	7	7	7	7	7	7	3
Rigor of development	7. Systematic methods were used to search for evidence.	7	7	7	1	1	7	7	7
	8. The criteria for selecting the evidence are clearly described.	7	7	7	1	1	7	7	7
	9. The strengths and limitations of the body of evidence are clearly described.	7	7	7	1	1	7	7	7
	10. The methods for formulating the recommendations are clearly described.	7	7	7	1	1	7	7	7
	11. The health benefits, side effects and risks have been considered in formulating the recommendations.	7	7	7	5	4	7	7	7

Domain	Item	AGREE II Score							
		DEGAM	AHA/ ACC	SIGN	Oman Heart Ass.	ANZCOR	ESC	Japanese Circ.Soc.	NACB
	12. There is an explicit link between the recommendations and the supporting evidence.	7	7	7	5	6	7	7	7
	13. The guideline has been externally reviewed by experts prior to its publication.	7	7	7	1	1	7	1	5
	14. A procedure for updating the guideline is provided.	7	7	7	1	1	1	3	1
Clarity of presenta-tion	15. The recommendations are specific and unambiguous.	7	7	7	7	7	7	7	7
	16. The different options for management of the condition or health issue are clearly presented.	7	7	7	7	7	7	7	1
	17. Key recommendations are easily identifiable.	7	7	7	5	7	7	7	7
Applicabil-ity	18. The guideline describes facilitators and barriers to its application.	7	7	7	5	4	7	7	7
	19. The guideline provides advice and/or tools on how the recommendations can be put into practice.	7	7	7	5	4	7	7	7
	20. The potential resource implications of applying the recommendations have been considered.	7	7	7	5	1	1	1	7
	21. The guideline presents monitoring and/ or auditing criteria.	7	7	7	1	1	7	1	7
Editorial independ-ence	22. The views of the funding body have not influenced the content of the guideline.	7	7	7	1	1	7	1	3
	23. Competing interests of guideline development group members have been recorded and addressed.	7	7	7	1	1	7	5	1

Domain	Item	AGREE II Score							
		DEGAM	**AHA/ ACC**	**SIGN**	**Oman Heart Ass.**	**ANZCOR**	**ESC**	**Japanese Circ.Soc.**	**NACB**
Overall Guideline Assess-ment	1. Rate the overall quality of this guideline.	6.96	6.74	7	3.60	3.39	6.39	5.43	5.43
Overall Guideline Assess-ment	2. I would recommend this guideline for use.	*Yes, with modifications* *Note: Excellent methodological quality. How-ever, not up-to-date (update to be published Dec.2019)*	*Yes*	*Yes*	*No* *Note: methodology is not clearly described, editorial independence not described.*	*No* *Note: methodology, editorial independence and applicability are not clearly described.*	*Yes*	*Yes, with modifications* *Note: the guideline is applicable in a special setting i.e. disaster in Japan*	*Yes, with modifications* *Note: this guideline is not up-to-date and there is no recommendation on the update process and timeline, but it is already archived. The guideline is specifically on POCT in various disease areas.*

Risk of bias tables: D-dimer POCT

Table A12: Risk of Bias (D-dimer POCT) – study level (systematic reviews and meta analyses)

Author, year	CADTH, 2016 [104]	Geersing, 2009 [31]	Lucassen, 2011 [34]	Hendrisksen, 2015 [33]	Hendriksen, 2015 [105]	Schols, 2018 [26]	Pasha, 2009 [32]	Florkowski, 2017 [4]	Marquardt, 2015 [35]
1. Did the research questions and inclusion criteria for the review include the components of PICO?	Yes	Yes	Yes	Yes	No	Yes	Partial yes	No	Partial yes
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	No	Partial yes	No	No	No	Partial yes	No	No	No
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Partial yes
4. Did the review authors use a comprehensive literature search strategy?	Partial yes	Partial yes	Partial yes	Partial yes	No	Partial yes	Partial yes	No	Yes
5. Did the review authors perform study selection in duplicate?	No	Partial yes	Yes	Yes	No	Yes	Yes	No	No
6. Did the review authors perform data extraction in duplicate?	No	Yes	Yes	Yes	No	No	No	No	No
7. Did the review authors provide a list of excluded studies and justify the exclusions?	No	No	No	No	No	No	No	No	No
8. Did the review authors describe the included studies in adequate detail?	Partial yes	Partial yes	Yes	Yes	Yes	Yes	Yes	No	Partial yes
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review? RCTs	Partial yes	Yes	Yes	Partial yes	No	Yes	Partial yes	No	Partial yes

Author, year	CADTH, 2016 [104]	Geersing, 2009 [31]	Lucassen, 2011 [34]	Hendrisksen, 2015 [33]	Hendriksen, 2015 [105]	Schols, 2018 [26]	Pasha, 2009 [32]	Florkowski, 2017 [4]	Marquardt, 2015 [35]
10. Did the review authors report on the sources of funding for the studies included in the review?	No	No	No	No	No	No	Yes	No	No
11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results? RCTs	NA	Yes	Yes	Yes	NA	NA	Yes	NA	NA
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	NA	Yes	Partial yes	No	NA	N/A	No	NA	NA
13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	Partial yes	Yes	Partial yes	No	No	Yes	Yes	No	Partial yes
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	No	Yes	Yes	Yes	No	Partial Yes	Yes	No	No
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	NA	Yes	No	No	NA	NA	Yes	NA	NA
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	No	Yes	Yes	Yes	Yes	Yes	Partial yes	NA	Partial yes
Overall Confidence	**Critically low**	**High**	**High**	**High**	**Critically low**	**Moderate**	**Moderate**	**Critically low**	**Moderate**

Table A13: Risk of bias (D-dimer POCT) – outcome level of non randomised studies comparing the use of D-dimer POCT versus usual care

	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
MORTALITY/MORBIDITY, QUALITY OF LIFE, SAFETY								
Oude Elferink, 2015 [37]	Not defined as outcome							
Kingma, 2017 [36]	Not defined as outcome							
PATIENT MANAGEMENT								
Oude Elferink, 2015 [37]	L	L	L	L	L	M Low prevalence of DVT in this sample resulted in small number of events	L	M
Kingma, 2017[36]	L	S Bias possible, particularly in the usual care group, selection of patients (not consecutive)	L	L	M 11% missing data in the usual care group	L	L	S

Abbreviations: L – low; M – moderate; S – severe.

Table A14: AGREE II quality appraisal of the guidelines on the use of D-dimer POCT

Domain	Item	AGREE II Score									
		DEGAM	AWMF	SIGN	Fesmire	Jaeschke	ESC	NCGC	NICE	DGK	Japan Circ.Soc.
Scope and purpose	1. The overall objective(s) of the guideline is (are) specifically described.	7	7	7	7	7	7	7	7	7	7
	2. The health question(s) covered by the guideline is (are) specifically described.	7	7	7	7	7	7	7	7	7	7
	3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.	7	7	7	7	7	7	7	7	7	7
Stakeholder involvement	4. The guideline development group includes individuals from all the relevant professional groups.	7	7	7	7	7	7	7	7	7	7
	5. The views and preferences of the target population (patients, public, etc.) have been sought.	6	6	7	1	1	1	7	7	1	1
	6. The target users of the guideline are clearly defined.	7	7	7	7	7	7	7	7	7	7
Rigor of development	7. Systematic methods were used to search for evidence.	7	3	7	7	7	7	7	7	7	7
	8. The criteria for selecting the evidence are clearly described.	7	3	7	7	7	7	7	7	7	7
	9. The strengths and limitations of the body of evidence are clearly described.	7	3	7	7	7	7	7	7	7	7
	10. The methods for formulating the recommendations are clearly described.	7	7	7	7	7	7	7	7	7	7
	11. The health benefits, side effects and risks have been considered in formulating the recommendations.	7	7	7	7	7	7	7	7	7	7

Domain	Item	AGREE II Score									
		DEGAM	AWMF	SIGN	Fesmire	Jaeschke	ESC	NCGC	NICE	DGK	Japan Circ.Soc.
	12. There is an explicit link between the recommendations and the supporting evidence.	7	7	7	7	7	7	7	7	7	7
	13. The guideline has been externally reviewed by experts prior to its publication.	7	6	7	7	3	7	7	7	7	1
	14. A procedure for updating the guideline is provided.	7	6	7	7	1	7	7	7	7	3
Clarity of presentation	15. The recommendations are specific and unambiguous.	7	7	7	7	7	7	7	7	7	7
	16. The different options for management of the condition or health issue are clearly presented.	7	7	7	7	7	7	7	7	7	7
	17. Key recommendations are easily identifiable.	7	7	7	7	7	7	7	7	7	7
Applicability	18. The guideline describes facilitators and barriers to its application.	7	7	7	6	7	7	7	7	7	7
	19. The guideline provides advice and/or tools on how the recommendations can be put into practice.	7	7	7	6	7	7	7	7	7	7
	20. The potential resource implications of applying the recommendations have been considered.	7	7	7	7	1	7	7	7	7	1
	21. The guideline presents monitoring and/or auditing criteria.	7	7	7	1	1	5	7	7	5	1
Editorial independence	22. The views of the funding body have not influenced the content of the guideline.	7	7	7	7	1	7	7	7	7	1
	23. Competing interests of guideline development group members have been recorded and addressed.	7	6	7	1	1	7	7	7	7	5

Domain	Item	AGREE II Score									
		DEGAM	AWMF	SIGN	Fesmire	Jaeschke	ESC	NCGC	NICE	DGK	Japan Circ.Soc.
Overall Guideline Assess-ment	1. Rate the overall quality of this guideline.	6.96	6.3	7	6.13	5.26	6.65	7	7	6.65	5.43
Overall Guideline Assess-ment	2. I would recommend this guideline for use.	*Yes, with modifica-tions.* *Note: Excellent methodo-logical quality. However, not up-to-date (update to be published Dec.2019) and can, therefore, not be used without caution.*	*Yes* *Note: This is a consen-sus based guideline. Evidence was not reviewed in a sys-tematic way and there was no grading of the evidence.*	*Yes, with modifica-tions.* *Note: The focus of the guide-lines is on pre-vention and man-agement of DVT, the diag-nosis is only a small part of the guideline.*	*Yes, with modifications.* *Note: The main focus is on high sen-sitivityquanti-tative D-dimer tests, however the qualitative tests (often used in point-of-care pan-els) are men-tionedtoo. Evidence was not as-sessed for qualitative tests due to the limitations in terms of their interpre-tation and lower sensi-tivity.*	*Yes, with modifi-cations.* *Note: This is not a classical guide-line but the main objective was to test the GRADE approach on this example. The methods are rigorous, but the Appendix where some further details could have been found is not published.* *Some additional information would be neces-sary to know which D-dimer tests have high and moderate sensitivity.*	*Yes*	*Yes*	*Yes* *Note: this guidance is based on the NCGC full re-port.*	*Yes* *Note: this is the German summary of and state-ment on the ESC guideline*	*Yes, with modifica-tions.* *Note: the guideline is appli-cable in a special setting i.e. dis-aster in Japan*

Table A15: Summary table of the results on the use of Tn-POCT

Effectiveness and diagnostic accuracy of Tn-POCT: Summary of the evidence						
Author, year	**Study design**	**Included studies / included pts**	**Setting**	**Quality**	**Summary of the results**	**Authors' Conclusion**
CADTH, 2016 [25]	SR	41 / NR	Diverse (incl. ED and primary care settings)	High	DTA results (at admission: range of POCT vs. range of CL): SEN: 26%-88% vs. 68%-100% SPEC: 84.0%-98.0% vs. 75%-94% PPV: 31.0%-85.0% vs. 10%-82% NPV: 90%-99% vs. 95%-100% Clinical utility: "In Settings Where a Central Laboratory is Available [Tn-POCT] tended to shorten *turnaround time (TAT)*, *length of hospital stay*, and *time to discharge*. The use of [Tn-POCT] did not statistically change *mortality rates* or severe adverse events compared with a central laboratory in most studies, in up to one year of follow-up. There was no difference in *quality of life among* patients who were tested using POC or central laboratory within up to three months' follow-up. Subgroup analyses of clinical-utility studies based on study design, setting, the level of sensitivity of the central laboratory methods, the types of cTn (I or T), and funding status did not show any differences in findings. (…).	"Overall, given the limitations with the data and the inconsistency in DTA estimates, the usefulness of [Tn-POCT] in settings with access to central laboratories may be limited." "In settings with no access to a central laboratory, such as in rural health care centres or remote settings, [Tn-POCT] may be useful due to the potential to help reduce unnecessary transfer of patients to larger centres."

Effectiveness and diagnostic accuracy of Tn-POCT: Summary of the evidence						
Author, year	**Study design**	**Included studies / included pts**	**Setting**	**Quality**	**Summary of the results**	**Authors' Conclusion**
					In Settings Where No Central Laboratory is Available In pre-hospital or ambulance settings, limited evidence points to the potential use of [Tn-POCT] for the diagnosis and management of patients. [Tn-POCT] testing may *reduce the percentage of patients referred to the emergency department from a primary health care centre.* [Tn-POCT] was shown to be feasible and reliable for patients transported by ambulance, and can s*horten the time from first medical contact to patient disposition* (…)."	
Schols, 2018 [26]	SR	2 / 545	Primary Care	Moderate	DTA results (range of 2 studies, results of MI / MI+unstable angina): SEN: 67%-83% / 21%-29% SPEC: 98-100% / 98-100% PPV: 40%-100% / 40%-100% NPV: 99%-99.7% / 94%-96% Clinical utility: Limited evidence (1 comparative cohort study) was found that Tn-POCT would reduce the referral rate, but the identified cohort study noted that it may be on offset of potentially missing out on patients with an acute myocardial infarction or unstable angina.	No conclusion on Tn-POCT, highlighting the inconclusive available evidence.

Table A16: Summary table of the results on the use of Tn-POCT in the emergency department

The use of Tn-POCT in the emergency department: Summary of the evidence			
Evidence	**Quality**	**Results**	**Conclusion**
		Effect on patient management	
1 SR [25]	High	No. of hospital admission: N/A Treatment initiation: N/A RR: N/A DNT: N/A TAT (evidence base: 2 RCTs, 11 observational studies using a variety of different definitions of TAT[36]): RCTs (2 studies, cTnI or cTnT testing, 2,134 and 833 enrolled patients respectively): • Reduction in 2/2 studies: 43 min (median; p value not available) in one study, and 71 and 147 min in the other study[37] (median; s. s., with p<0.001) Observational studies (5 prospective, 1 retrospective and 5 pre-post studies respectively, cTnI or cTnT testing, 31 to 2,386 enrolled pts) • Reduction in 11/11 studies: 18-93 min (p values available for 5/11 studies, with s. s. differences in these studies) TTD (evidence base: 2 RCTs, 1 observational study): RCTs (2 studies, cTnT or cTnI testing, 487 and 2,134 enrolled pts respectively): • Reduction in 2/2 studies: 5 and 7 min (mean and median respectively; s. s. with p=0.04 and p value not available respectively) Observational studies (1 pre-post study, multiple biomarkers 4,886 enrolled pts): • Reduction in 1/1 study: 26 min (p value not available) LOS: Emergency room stay (evidence base: 3 RCTs, 2 observational studies): *RCTs* (3 studies, cTnI or cTnT testing, 487-912 enrolled pts): • Reduction in 2/3 studies: 0.2 and 0.8 h (mean and median; diff. n. s. in individual studies)	Currently, the evidence is insufficient indicating non-inferiority of using a pathway with Tn-POCT compared to usual care if CL testing is timely available.

[36] E.g., time from blood draw to result.

[37] When using the definitions “time from collection to physician notification” and “time from presentation to anti-ischemic therapy” respectively.

The use of Tn-POCT in the emergency department: Summary of the evidence			
Evidence	**Quality**	**Results**	**Conclusion**
		• Increase in 1/3 studies: 0.1 h (median; diff. n. s.) *Observational studies* (2 pre-post studies, cTnI testing, 366 and 671 enrolled pts respectively): • Reduction in 2/2 studies: 1.9 h (mean; p value NR) and 2-2.7 h respectively (mean; diff. s. s.) Hospital stay in ED (evidence base: 1 RCT) *RCTs* (1 study, cTnI testing, 2,243 enrolled pts) • Reduction in 1/1 study: 2.2 h (mean; diff. n. s.) Further testing: N/A TCD (evidence base: 1 RCT, 1 pre-post study): RCTs (1 study, cTnI testing, 2,134 enrolled pts) • Reduction in 1/1 study: 9 min (median; p value not available) Observational studies (1 pre-post study, multiple biomarker testing, 4,886 enrolled pts): • Reduction in 1/1 study (multiple biomarkers): 26 min (mean; p value not available)	
Effect on mortality/morbidity			
1 SR [25]	High	Mortality (evidence base: 2 RCTs and 3 observational studies) RCTs (2 studies; cTnT or cTnI testing, 487 and 2,243 enrolled pts respectively) POC vs. CL: 0.5 vs. 0% in one study (p value NR) and 1% vs.0.2% in another study (n. s., with p=0.142) Observational studies (3 prospective studies; cTnI or cTnT testing; 508-1,410 enrolled pts) None of the studies compared Tn-POCT with CL head-to-head (using statistical testing) Cardiac events (evidence base: 2 prospective studies, cTnI or cTnT testing) 30 day cardiac event rate (1 prospective study, 704 enrolled pts; POCT vs. CL): • Low risk pts: 0% (95%CI: 0-25.9) vs. 0% (95%CI: 0-21.5), p value NR • High risk pts: 24.8% (95%CI: 20.1-30.1) vs. 28.6% (95%CI: 23.4-34.4), p value NR Cardiac events after 1 year (1 prospective study, 1,410 enrolled pts; POCT vs CL): • 2.1% (95%CI: 1.5-3) vs. 2.2% (95%CI: 1.6-3.1), p value NR	

The use of Tn-POCT in the emergency department: Summary of the evidence			
Evidence	**Quality**	**Results**	**Conclusion**
		Other Adverse events (AE) and composite end points in ED (evidence base: 2 RCTs, cTnT or cTnI testing) Major AE after 3 m FU (1 RCT, 2,243 enrolled pts; POCT vs CL): 3% vs. 2%, diff. n. s., with p=0.313 CEP events[38] at 6 m (1 RCT, 487 enrolled pts; cTnT testing, POCT vs. CL): 10.4% vs. 5.4%, p value NR	
Effect on QoL			
1 SR [25]		QoL (evidence base: 1 RCT, cTnI testing, 2,243 enrolled pts using the EQ-5D questionnaire): POC vs. CL: • After 1 m: 0.742 vs. 0.759 (n. s., with p=0.614) • After 3 m: 0.752 vs. 0.759 (n. s., with p=0.638)	

[38] AMI, coronary revascularization, cardiac arrest, or mortality in patients with a negative first cTn test at 3 m FU

Table A17: Summary table of the results on the use of Tn-POCT in ambulatory (primary or community care)

The use of Tn-POCT in primary care settings: Summary of the evidence			
Evidence base	**Quality**	**Results**	**Conclusion**
Effect on patient management			
2 SRs [25, 26]	Moderate to High	No. of hospital admission: N/A Treatment initiation: N/A RR (evidence base: 1 comparative cohort study identified by both SRs): • Reduction in 1/1 study (TnT testing, 196 enrolled pts): 32/128 pts (25%) vs. 29/68 pts (43%), p value not reported[39] DNT: N/A TAT: N/A TTD: N/A LOS: N/A Further testing: N/A TCD: N/A	Currently, the evidence is insufficient indicating superiority of using a pathway with Tn-POCT compared to usual care in ambulatory care (primary or community care) if CL testing is not timely available.
Effect on mortality/morbidity			
No evidence identified	N/A	-	
Effect on QoL			
No evidence identified	N/A	-	

[39] Yet, it is mentioned in the review that the authors of the primary study noted that there were some two patients that were not referred and missed cases (one AMI and one unstable angina respectively). It is therefore concluded that the use of Tn-POCT in pts with chest pain "may reduce emergency referrals, but probably at the cost of an increased risk to miss patients with an acute myocardial infarction or unstable angina".

Table A18: Summary table of the results on the use of Tn-POCT in pre-hospital emergency medicine (PHEM)

Effectiveness of implementing Tn-POCT in pre-hospital emergency medicine: Summary of the evidence			
Evidence base	**Quality**	**Results**	**Conclusion**
Effect on patient management			
1 SR [25]	High	No. of hospital admission (1 RCT with 601 enrolled pts; pre-hosptial setting with no access to CL methods): • No difference between Tn-POCT and usual care (no further information provided) Treatment initiation: N/A RR: N/A DNT: N/A TAT (ambulance; 1 observational study; 928 pts): 83 min (median, range: 46-167) TTD (ambulance; evidence base: 1 RCT): • Reduction in 1/1 study (median time Tn-POCT vs CL): 8.8 hours (range: 6.2 h to 10.8 h) vs. 9.1 h (range 6.7 hours to 11.2 hours), *P* = 0.05. LOS: N/A Further testing: N/A TCD: N/A	Currently, the evidence is insufficient indicating superiority of using a pathway with Tn-POCT compared to usual care in pre-hospital emergency medicine if CL testing is not timely available.
Effect on mortality/morbidity			
1 SR [25]	High	Mortality: (ambulance; evidence base: 1 RCT, 601 enrolled pts) Death in the next 30 days: no difference between groups (no further information provided)	
Effect on QoL			
No evidence identified	N/A	N/A	

Table A19: Summary table of the results on the use of D-dimer POCT

Effectiveness and diagnostic accuracy of D-dimer-POCT: Summary of the evidence of SRs						
Author, year	**Study design**	**Included studies / included pts**	**Setting**	**Quality**	**Summary of the results**	**Authors' Conclusion**
Schols, 2018 [26]	SR	2 / 892	Primary care	Moderate	DTA: SEN: stand alone D-dimer 84%; Wells ≤4 + D-dimer 94- 95%; Wells ≤2 + D-dimer 97%. SPEC: stand-alone D-dimer 62%; Wells ≤4 + D-dimer 38- 51%; Wells ≤2 + D-dimer 32%. PPV: stand alone D-dimer 24%; Wells ≤4 + D-dimer 21- 37%; Wells ≤2 + D-dimer 20%. NPV: stand alone D-dimer 96%; Wells ≤4 + D-dimer 94- 99%; Wells ≤2 + D-dimer 99%. Effectiveness: NR	No studies assessed the effects of D-dimer on treatment initiation or referral rates. All studies were considered at high risk of bias. Evidence suggests combining D-dimer with a clinical decision rule (e.g. when GP use of a D-dimer POCT is combined with the Wells clinical decision rule) leads to more accurate diagnosis. Further research on clinical effectiveness is necessary.
Geersing, 2009 [31]	SR & meta analysis	23 / 13,959	Primary or secondary care	High	DTA: SEN: 0.85 (95%CI 0.78-0.90) for SimpliRED D-dimer; 0.87 (0.81-0.91) for Clearview Simplify D-dimer; 0.93 (0.88-0.97) for Triage D-dimer; 0.96 (0.91-0.98) for Cardiac D-Dimer. SPEC: 0.48 (95% CI 0.33-0.62) for Triage D-dimer; 0.57 (0.52-0.62) for Cardiac D-dimer; 0.62 (0.54-0.69) for Clearview Simplify D-dimer; 0.74 (95%CI 0.69-0.78) for SimpliRED Likelihood ratio of a negative test result: 0.07 (95%CI 0.04-0.16) for Cardiac D-dimer; 0.18 (95%CI 0.08-0.43) for Triage D-dimer; 0.21 (0.15-0.29) for SimpliRED D-dimer; 0.22 (95% CI 0.15 to 0.29) for Clearview Simplify D-dimer. Effectiveness: NR	The two quantitative tests (Cardiac D-dimer and Triage D-dimer) scored most favourably. In outpatients suspected of VE, D-dimer POCT can contribute important information and guide patient management, especially in low-risk patients (i.e. with low score on a clinical decision rule).

Effectiveness and diagnostic accuracy of D-dimer-POCT: Summary of the evidence of SRs						
Author, year	**Study design**	**Included studies / included pts**	**Setting**	**Quality**	**Summary of the results**	**Authors' Conclusion**
Pasha, 2010 [32]	SR	4 / 199	Not specified[40]	Moderate	DTA: Incidence of VTE despite negative testing and unlikely clinical probability: 2% (95% CI: 0.1-10.1%)? Effectiveness: In 49/199 (25%) patients with unlikely clinical probability and normal D-dimer CT scans could be withheld. Mortality/Morbidtidy: 1 person (2%)	Overall (across POCT and lab tests) pooled incidence of morbidity was 0.34% (95%CI 0.036-0.96%) and combined incidence of death (across POCT and lab tests) was 0.1% (95% CI 0.0-0.5%). Combined 3-month mortality risk of PE (across POCT and lab tests) was 0.10% (95%CI 0.002-0.46%). 1 death occurred across all studies (this was in the POCT study). Ruling our PE on basis of unlikely clinical probability and normal D-dimer is very safe.
Hendriksen, 2015 [33]	SR	10 / 598	Primary care	High	Sensitivity*: 88% (78%-94%) for simplified revised Geneva ≤2 model 90% (81-96%) for original revised Geneva ≤5 95% (87%-98%) for original Wells ≤4; 95% (87-98%) for modified Wells ≤2 96% (88%-99%) for simplified Wells ≤1 Specificity*: 48% (44%-53%) for original revised Geneva ≤5; 49% (45-53%) for the simplified Wells ≤1; 50% (46-55%) for the modified Wells ≤2; 51% (47-55%) for the original Wells ≤4; 53% (49%-57%) for simplified revised Geneva ≤2. PPV*: 20% (15%-24%) for original revised Geneva ≤5; 21% (17-26%) for original Wells ≤4; 21% (17-26%) for modified Wells ≤2; 21% (17-25%) for simplified Wells ≤1; 21% (16-26%) for simplified revised Geneva ≤2. NPV*: 97% (95-99%) original revised Geneva ≤5; 97% (94-99%) simplified revised Geneva ≤2; 99% (96-100%) original Wells ≤4; 99% (96-100%) modified Wells ≤2; 99% (97-100%) simplified Wells ≤1. *Data are ordered by values of the test accuracy rate. Effectiveness: Failure rates across all models: 1.2% (95%CI 0.2%-3.3%) for simplified Wells ≤1	Efficiency was comparable across all models but the Wells rules combined with D-dimer POCT gave the best performance in terms of lower failure rates

[40] Only "outpatients" stated in one study in this review that used a POCT but not defined further (i.e. if primary care or ED)

Effectiveness and diagnostic accuracy of D-dimer-POCT: Summary of the evidence of SRs						
Author, year	**Study design**	**Included studies / included pts**	**Setting**	**Quality**	**Summary of the results**	**Authors' Conclusion**
					1.5% (95%CI 0.4-3.7%) for original Wells ≤4 1.5% (95%CI 0.4-3.8%) for modified Wells ≤2 2.7% (95%CI 1.1-5.4%) for original revised Geneva ≤5 3.1% (95%CI 1.4%-5.9%) for simplified revised Geneva ≤2 Efficiency across all models: 43% (95%CI 39%-48%) for simplified Wells ≤1 44% (95%CI 40-48%) for original revised Geneva ≤5 45% (95%CI 41-49%) for modified Wells ≤2 46% (95%CI 41-50%) for original Wells ≤4 48% (95%CI 44%-52%) for simplified revised Geneva ≤2	
Lucassen, 2011 [34]	SR	52 / 55,268	Hospital setting (emergency department, outpatients or inpatients)	High	DTA: NR for D-dimer POCT Effectiveness: Failure rate (across all studies with qualitative D-dimer testing): 1.0% (95%CI 0.8-1.3%) combined with gestalt 0.7% (95%CI 0.4-1.2%) combined with Wells cutoff value ≤4: 1.7% (95%CI 1.0-2.8%) combined with Wells cutoff value <2: 0.9% (95%CI 0.6-1.5%) Efficiency (across all studies with qualitative D-dimer testing): 45% 95%CI 39-52%); Combined with gestalt: 52% (95%CI 40-64%) Combined with Wells cutoff value ≤4: 42% (95%CI 32-52%) Combined with Wells cutoff value <2: 40% (95%CI 33-48%)	Combining a decision rule and gestalt can safely exclude PE when combined with sensitive D-dimer testing except when the less sensitive Wells rule (cutoff value ≤4) is combined with qualitative D-dimer POCT
Marquardt, 2015 [35]	SR	7 / 3,279	ED	Moderate	DTA: NR Effectiveness: No. of hospital admissions (1 before-after study, 462 pts) decreased by 13.8% TAT in ED (evidence base: 7 observational studies[41], 3,279 pts):	POC D-dimer tests can safely improve patient journey times

[41] While the review reported initially on seven included studies on TAT, data are only presented for six studies.

Effectiveness and diagnostic accuracy of D-dimer-POCT: Summary of the evidence of SRs						
Author, year	**Study design**	**Included studies / included pts**	**Setting**	**Quality**	**Summary of the results**	**Authors' Conclusion**
					Reduction in 5 studies (comparative; prospective and retrospective): 10-101.5 min (using different measures of central tendency; p-values and information on stat. testing not reported) No comparative data shown from 2 studies[42]	

Table A20: Summary table of the results on the use of D-dimer POCT derived from primary studies updating the overview of reviews

Effectiveness of implementing D-dimer-POCT: identified studies updating the evidence from SRs						
Evidence base	**Study design**	**Included pts**	**Setting**	**Risk of Bias**	**Summary of the results**	**Conclusion**
Effect on patient management						
2 studies [36, 37]	NRCT	971	Primary care	Moderate to severe	TAT (1 study): <5min to 34 min RR (1 study): no statistically significant difference in patients referred, not referred between intervention and usual care group	The evidence from updating the evidence found in SRs is insufficient to suggest that implementing D-dimer POCT is non-inferior in comparison to CL testing and superior in comparison to usual care if CL is not (timely) available.
Effect on mortality/morbidity						
No studies identified	-	-	-	-	-	
Effect on QoL						
No studies identified	-	-	-	-	-	

[42] Non-comparative data was shown in one study (time to result: 10-38 min) and not reported at all in another study that the review described.

Applicability tables

Table A21: Summary table characterising the applicability of a body of studies

Domain	Description of applicability of evidence
Population	The identified evidence refers primarily to systematic reviews with limited data on patient characteristics. Nevertheless, no applicability concerns related to the population of interest are raised.
Intervention	For Tn-POCT, the algorithms when troponin is measured may vary. However, the systematic reviews hardly described which algorithm was used in the primary studies. As such, one can only speculate whether this represents a concern of applicability of the identified evidence. Secondly, there are numerous different Tn-POCT devices on the market. While one systematic review [26] controlled for whether there was a systematic pattern of outcomes dependent on specific products, there is still the chance that the diagnostic performance slightly changed within the past years. It may be that the Tn-POCT devices got software updates or changed technologically. For D-dimer POCT, similarly, there are also numerous devices on the market with differences as to whether D-dimers are measured qualitatively or quantitatively and which cut-off values are used. This may represent an intervention-related applicability concern and especially different cut-off values were noted as a factor potentially explaining heterogeneity found in two meta analyses [31, 34].
Comparators	For Tn-POCT, the comparators used were mostly usual care (incl. mostly CL methods as well). Similarly to the intervention-related applicability concerns raised, different algorithms that are in place may have plaid a factor. However, the systematic reviews hardly described which algorithm was used in the primary studies. As such, one can only speculate whether this represents a concern of applicability of the identified evidence. Besides, there were no further suspected applicability concerns in the context of the chosen comparators found for the reviews on Tn-POCT or D-dimer POCT.
Outcomes	For Tn-POCT, no applicability concerns were identified. Evidence was found for most of the outcomes of interest. We have considered DTA studies only if they also considered patient-important outcomes. In so doing, we tried to limit the applicability concern when using surrogate endpoints (diagnostic performance) that can be used to indirectly extrapolate on a potential effect.
Setting	There is no standard global definition of ambulatory care settings or emergency care. The reviews identified studies from all over the world, yet mostly in western countries. For both Tn-POCT and D-dimer POCT, the available evidence stems from studies conducted all over the world. Due to the fact that each health care system – also within the Western world – is structured differently, there may be significant applicability concerns when it comes to the evidence in the ambulatory care setting. Similarly, In Austria, the identified settings may not be identical to the ones to be found in the available evidence. For pre-hospital emergency medicine [106], for instance, voluntary work plays a significant role. Training for becoming a paramedic is relatively short in Austria when compared to international standards and, hence, one needs to reflect as to whether the evidence found in this setting is applicable in the Austrian context. In addition, one systematic review [25] especially reflected on the role of Tn-POCT in settings where no CL is available. Remote settings were, inter alia, listed. These settings may not be identical to the remote areas to be found in Austria or Romania. In addition, for both Tn-POCT and D-dimer POCT, the available evidence is stems from studies conducted all over the world. Due to the fact that each health care system – also within the Western world – is structured differently, there may be significant applicability concerns when it comes to the evidence in the ambulatory care setting.

Abbreviations: CL – central laboratory; POCT – point of care testing.

APPENDIX 4: CHECKLIST FOR POTENTIAL ETHICAL, ORGANISATIONAL, PATIENT AND SOCIAL AND LEGAL ASPECTS

1.	**Ethical**	
1.1.	Does the introduction of the new technology and its potential use/non-use instead of the defined, existing comparator(s) give rise to any new ethical issues?	No
1.2.	Does comparing the new technology to the defined, existing comparators point to any differences that may be ethically relevant?	No
2.	**Organisational**	
2.1.	Does the introduction of the new technology and its potential use/non-use instead of the defined, existing comparator(s) require organisational changes?	Yes
	Should the tests show benefits in terms of clinical utility or patient outcomes, it may be necessary to effect organisational changes to be able to realise the potential of the tests.	
2.2.	Does comparing the new technology to the defined, existing comparator(s) point to any differences that may be organisationally relevant?	Yes
	Yes there may be organisationally relevant, contextual factors e.g. in referring practises.	
3.	**Social**	
3.1.	Does the introduction of the new technology and its potential use/non-use instead of the defined, existing comparator(s) give rise to any new social issues?	No
3.2.	Does comparing the new technology to the defined, existing comparator(s) point to any differences that may be socially relevant?	No
4.	**Legal**	
4.1.	Does the introduction of the new technology and its potential use/non-use instead of the defined, existing comparator(s) give rise to any legal issues?	No
4.2.	Does comparing the new technology to the defined, existing comparator(s) point to any differences that may be legally relevant?	No

APPENDIX 5: DOCUMENTATION OF EXPERT INPUT

Pre-defined questions:

1. How are Tn-POCT and D-dimer POCT currently used in the Austrian context? In which setting and by which type of doctors?
2. Where would you see these two diagnostics to be placed within the clinical pathway and do you know of any thresholds that may apply in this context?
3. What is your clinical experience with using these POC tests? Do you use these POCTs in practice?
4. Are there settings where one of these POCTs may be used instead of a central lab test? (e.g., if central lab test is unavailable such as in remote areas). If so, please specify the specific settings and reflect on the potential utility for these two POCT in the respective settings.
5. If a central lab test is available, what clinical benefits do you think might be associated with using POCT in Austria?
6. Do you know of any clinical decision rules in this area (cardiopulmonary symptoms, suspected venous thromboembolism) that are routinely used in practice e.g. Wells rule?

INTERVIEW SUMMARIES (AT)

Interview 1 (primary care):

1. Generally, the clinical expert highlights that he may not be able to answer the first question fully. Nonetheless he is willing to reflect on his thoughts how this may be in Austria: He highlights hereby that he does not think that these POCTs are used regularly in general practice. Potential reasons are hereby mentioned: The GPs might not get paid for them and they are more expensive than the central lab tests. In Austria, the health system is quite focused on hospital care. Patients are referred to the hospital quickly and no POCT is done. The problem with POCT is the lack of sensitivity. These tests are used to rule out diseases, not to prove that the disease is present.
2. Please see drawing. Not aware of any thresholds.
3. The clinical expert has no experience in using them. He used to practice in Germany, where the POCTs are not reimbursed. GPs apply clinical decision rules (e.g. Wells score) and if it is negative the physician can be quite certain that the patient does not have the disease.
4. Not aware of any areas or situations when a central lab would not be available.
5. Especially for the D-dimer POCT the expert does not see the point in using it. The main aim of POCT is to rule out the disease and if the physician has a strong suspect that the patient has the disease, the patient will be sent to the hospital, and no POCT will be done. There is not a high risk of treating DVT later (e.g. 3 hours) if you do not do POCT, the only risk is that the patient will get PE, but it is very unlikely. According to the clinical expert, Tn-POCT makes more sense because coronary artery syndrome is a more severe disease. Nevertheless, it is unlikely that a patient would have ACS and not present symptoms. In ACS, an ECG is done first. If the result is clear it is not necessary to do the Tn test. The clinical expert does not expect a change in the referral practice in Austria.
6. The clinical decision rules are probably not used systematically and routinely used among GPs. There is the Wells score and other scores but as mentioned before, not routinely used.

Interview 2 (primary care):

1. In General practices (randomly – not refunded everywhere: either patient or doctor pays testing), hospital outpatient units (emergency rooms). D-Dimer and Tn are being used, but no quantification possible because the costs are not refunded
2. D-dimer is seen as exclusion test in guidelines, so it is considered most valuable in avoiding further testing and/or hospital admission when negative. Helps reduce uncertainty, and safety-medication (LMWH till results can be obtained – which may, at week-ends, take days). Problem: no funding by social insurance, which in practice limits the use. Troponin: not suitable for exclusion (positive after several hours, does not exclude acute coronary syndrome), but does help somewhat in decision making as to which pathway to choose.
3. D-dimer: yes (s.above; (fear or symptoms of) DVT and PE rather frequent reasons for encounter: highly valuable in daily practice, Troponin: no – no exclusion possible, applicable after hours after symptom onset, so rather infrequent and good chance or expiring unused (no refund either).
4. See above: D-dimer of high value for family practice and any point of first contact. Troponin one helpful tool in a bigger picture, for family practice and outpatient units. Lab test take more than few hours in any extramural setting: patient at risk of DVT/PE or CHD cannot be sent to labs, sending blood samples takes too much time: decisions have to be made within minutes. Unavailable POCT (D-dimer) means: either admission to hospital, or organisation of imaging: venous ultrasound also not generally refunded for outpatients, so mostly angiography is performed (for: refunded): higher potential harm, no higher benefit, invasive, painful.
5. S.above
6. Wells rule, DEGAM algorithm for chest pain available and used – not widely known though. Suspected reasons: CME mostly provided by specialists, for whom those decision rules play a minor role (in-hospital, access to lab test, imaging etc. available and generally preferred), no decision aids integrated in practice software, fast and easy to access point of care tools not routinely used, clinical guidelines to time consuming to search and find. Culture of decision making….

Interview 3 (emergency department):

At the beginning of the interview, the interviewee was asked what he thinks could be an adequate definition of POC and what could be adequate reference standards for the diagnostics under evaluation.

Definition of POC

The definition of POC is ambiguous, which was raised by both the interviewers and the interviewee. According to the expert, there is no standard definition, different experts understand it differently. “Point” in POC can be defined in terms of a time point (i.e. a fast test) or in terms of a geographical point (i.e. bedside of the patients). Many products represent a mix of these two features. According to the expert the location is not as important as the time factor but this is highly dependent on the setting (emergency department, cardiologist office, etc.) and on the type of disease.

So depending on the definition used and the individual perception, some tests may be classified as POC or no POC. The interviewee highlights that this non-standardised definition of POC may also be reflected in the context of marketing: a wider definition may increase the market of some of the available products.

Other problems with POCT are that they are often semi-quantitative and present challenges in proper documentation, it they are not connected to electronic chart systems. Prints on thermal paper turn illegible if they get in contact with disinfectants.

Reference standard

The reference standard was also discussed. In case of the troponin (Tn) POCT it is quite difficult to define the reference standard. Acute coronary syndrome (ACS) is a makeshift-diagnosis, coronary artery occlusion is diagnosed by angiography, and the diagnosis of myocardial infarction or other forms of myocardial injury is even more complex.. Generally, the expert sees the POC test more important for the acute risk stratification than in a definitive diagnosis. Given an appropriate time-frame, a negative Tn is a good prognostic sign. If positive, subsequent diagnostic workup is mandatory. Overall, Tn level is only a part of the diagnostic means.

For D-dimer most frequent diagnosis is pulmonary embolism (PE). PE is diagnosed by CT-scan. Other diagnoses include vascular complications such as aortic dissection, which is likewise diagnosed by CT-scan. However, D-dimer is elevated in several other conditions with a great variety of reference standards. Furthermore D-dimer may be increased during gravidity.

Current use of the tests in Austria

Tn test is important in the diagnosis of ACS. For example in emergency departments Tn test is useful because a negative test result can facilitate an early rule-out diagnosis. Tn test is also useful for specialist clinics and office-based cardiologists, they can also interpret test results in context. However, in the inpatient setting POC Tn test should not be done routinely. Tn test must not be interpreted without at least clinical history, presentation and ECG readings. GPs well-trained in ECG-interpretation who perform acute medicine or emergency medicine or so-called “Gemeinde- and Sprengelärzte” may have access to Troponin if they are far away from hospitals or centres, because early risk stratification can inform decisions e.g. on admission to a hospital.

D-dimer test has a very low specificity. In the diagnosis of PE the pre-test probability is more important than a POC D-dimer test result itself. Only if the d-dimer test is combined with the pre-test probability (for instance via the Wells score) a proper interpretation of the result is possible. However, teaching experience shows that it is unlikely to be the case in Austria that pre-test probability is routinely assessed. Also referrals to emergency department, according to the interviewee’s experience, rarely indicate results of a pre-test probability calculation. One consequences of falsely using and interpreting D-dimer tests are unnecessary CTs. Moreover, PE is a continuum ranging from small or life threatening; probably each person has at least a minor PE in their lives. So if we really look closely, we will increase the detection rate of clinically non-significant PE. An important consequence of a PE diagnosis is therapeutic anticoagulation at least for several months with a particular risk/benefit ratio. However, D-dimer is a very unspecific marker, which may also be positive due to inflammation. Even uncomplicated infections often show positive test results Therefore, POC D-dimer test should have a limited availability and should be used only in selected departments in hospitals, in the EDs and by selected community-based specialists. The expert did not know how frequently the D-dimer test is used currently in office-based practices in Austria. There is potentially an alternative role for d-dimer as a biomarker screening tool as it can rule out many things. There are different cut-off points depending on the product (technical) and population (e.g. pregnant, older persons), which makes interpretation difficult.

Place of the tests in the diagnostic pathway

Tn test: ACS is the most frequent condition for the use of a Tn test. In case of ACS the time is crucial. When patients present with respective acute symptoms, ECG needs to be performed immediately. In case of ST-elevation the therapy does depend on clinical signs and ECG, but not on Tn. There is no established role for a POC Tn test here. In case of non-ST elevation acute coronary syndrome (NSTE-ACS) Tn is a very important diagnosic tool, and will influence therapy and management. This is an area of application for POC Tn.

A proper interpretation the test result requires reflections about misdiagnosis and consequences of subsequent diagnostic and therapeutic interventions.

In Austria the ESC guideline is in use, which describes 2 algorithms, depending on the setting.

D-dimer test: Usual usage for D-dimer POCT is diagnosis of PE. PE diagnosis is less time critical than ACS workup, because usually a delay in diagnosis and treatment of several hours has no

relevant impact on the outcome.. D-dimer tests should be interpreted together with a pre-test probability. In case of increased post-test probability PE is diagnosed or ruled out by CT-scan. PE may be treated in the in-patient or outpatient setting, anticoagulation is usually prescribed for several months. Other diagnoses may be found in the CT-scan, whether relevant or not, which may result in further diagnostic and/ therapeutic actions. In case of low post-test probabilities (D-dimer and clinical factors) alternative diagnoses or no further workup is performed, usually without performing a CT-scan.

Several guidelines, including a 2019 ESC guideline are available and used.

Setting

Settings for these POCT may include hospital units, such as wards, perioperative units, intensive care units, and emergency departments, outpatient departments, specialist offices, GP offices and mobile units, such as ambulance vehicles. These settings itself are heterogeneous, centralised and and decentralised, some very remote. Even some hospital settings do not have a central lab available 24/7.

Clinical decision rules

Clinical decision rules should be used but in practice their application varies greatly

INTERVIEW SUMMARIES (RO)

Interview 1 (cardiologist)

1. Are used by doctors from emergency services and cardiologists. Context: emergency
2. These are diagnostic tests for severe myocardial ischemia and venous thromboembolism (including deep venous thrombosis and pulmonary embolism). The limits are related to the fact that there are no protocols in hospitals (maybe there are, but not respected?) for their interpretation in connection with clinical situations. Other limits - repeating in dynamics can be a problem (kits use), physicians are quick to "resolve" the problem of diagnosis more quickly and send the patient further. Dynamics require patient tracking time. Other limits for Tn: overdose of revascularization in urgency; other causes of increased Tn are not known (by doctors).
3. Yes. Both.
4. There may be screening methods in family doctors' offices and in Permanent Centers to help address emergencies (eg coronary arteries pathology , many do not have ECG) and to decide which patients are sent to the UPU and refer to elective referrals.
5. If the correct instruction is done by those who use them, and if they are being taught what is the normal dynamics of these tests (for example troponin is high and many days after the onset of an MI) and if doctors know that there are false positives too. Not once we were fooled by ambulance staff on the basis of elevated troponin, addmiting patients for the STEMI program (that is revascularization in the first 12 hours after with ST elevation infarction). Patients who sure did not enter in surgery because they were already 2-3 days after their debut but occupied beds in the UTIC and when the STEMI patient actually appeared, it was a problem finding a place for him.
6. Of course. But their use is relative.

Interview 2 (emergency department)

1. *From my knowledge, fast tests for troponin and D dimers are available in all emergency units, and in county and university hospital laboratories. They are used by emergency doctors or other specialists who do triage in emergency rooms.*
2. *These tests are useful in the rapid diagnosis of acute coronary syndrome, especially in the absence of electrocardiographic changes (for troponin), and for confirmation of pulmonary thromboembolism, dimers. There are also false positive results, especially for. D dimers, which have elevated values in sepsis, in neoplasia, but values increased in the clinical context, help a lot in supporting the diagnosis.*
3. *Working in an emergency receiving unit in a university hospital, I use both tests for about 10 years, daily. They are very useful, and for refuting the diagnosis, especially as about 30% of patients coming up accuse chest pain.*
4. *I consider it useful that these tests can be available in small hospitals, which have only an emergency receiving compartment, as well as in permanent centers, an early and accurate diagnosis of acute coronary syndrome, which causes a high mortality rate in Romania*
5. *Consider the widespread use, even in ambulatory cardiology offices, for a more accurate diagnosis of acute coronary artery disease, and especially for not to unnecessarily crowd county and university hospitals with patients coming from the territory without need. Repeating after 6 hours of EKG and troponin at a city hospital, without surprising changes, would be useful in order to avoid unnecessary transfer of patients*
6. *In the diagnostic guidelines of acute coronary artery disease and pulmonary thromboembolism, paraclinical explorations include the dosing of troponin, CK mb, and D dimers respectively. The Institute of Cardiovascular Diseases in Iasi even condition the transfer of patients without EKG changes by the presence of elevated troponin and CK mb values. Widespread use as diagnostic tools would be extremely useful, even with the limits of false positives. It's a useful way of diagnosing in emergency hospital rooms that do not have cardiologists or internists. For example. at Hirlau Town Hospital in Iasi County, triage in emergency room are*

also provided by pediatricians, doctors of infectious diseases, pneumologists who have less clinical experience, in these cases they prove the usefulness of these laboratory parameters.

Interview 3 (family doctor)

1. *In primary medicine, no such tests are used. They are mainly used in EDs and laboratories (public or hospital).*
2. *These tests may fall into the positive or differential diagnosis stage (suspicion of myocardial infarction or thromboembolism), but also in the monitoring of at-risk patients stage (eg, D-dimer thrombophlebitis).*
3. *I did not use it.*
4. *Permanent rural centers, Ambulance substations, all ED services related to hospital units; Being rapid tests, they direct the diagnosis in emergency cases (myocardial infarction, pulmonary embolism, etc.) and consequently the necessary measures can be taken quickly.*
5. *Acute cardiopulmonary symptoms are an emergency that needs to be investigated as quickly as possible. Ideal would be to organize and operate specialized centers on such symptoms (hypotension - collapse / shock, acute chest pain, arrhythmias, etc.), autonomous of what is happening now in ED (all urgency or all patients are seen in that emergency service); to these specialized centers to be directed all acute cases where there is suspicion of major cardiovascular event.*
6. *I do not know protocols applied in practice for such clinical situations. But there are international guidelines on ischemic heart disease or pulmonary thromboembolism, reliable sources for guidance in practice.*

Interview 4 (family doctor)

1. *They are used both in the hospital and outpatient by cardiologists, internists and family doctors.*
2. *D-dimer has negative predictive value for pulmonary embolism and deep vein thrombosis. So if it's normal, the patient does not have these diseases and you can send him home quietly. Troponins can confirm a myocardial infarction in case of acute coronary syndrome without ECG changes (Non-STEMI).*
3. *I use in my ambulatory practice D-dimer in case of clinical suspicion of pulmonary embolism or deep vein thrombosis because I get the result in less than 2 hours. In the case of troponins the response comes after several hours and I do not risk to wait in case of an acute coronary syndrome.*
4. *For isolated rural areas and Medical Permanent Centers, both tests if done quickly can save lives or save unnecessary travel.*
5. *The benefits would be that it is specified if the patient does not have embolism, thrombosis, or stroke, and will not waste any more resources. If the diagnosis is confirmed, the patient would be guided to the appropriate medical service. Clearly, the approach of doctors who will have these tests available will be changed.*
6. *The Romanian Cardiology Society has developed guidelines based on those of the European Society of Cardiology.*

APPENDIX 6: MISCELLANEOUS

Table A22: Documentation of queries to study authors in the assessment report

Study	Content of query	Reply received yes / no	Content of reply
CADTH, 2016 [25]	"In table 26 (p. 128): It appears that there are sensitivity and specificity data inserted in the table dealing with mortality and MAE outcomes (see Venge). Is this a mistake?"	Yes	"You are correct – that is an error in Table 26. The data that should be included from The Venge article is from Table 3 of the original article, but the data from Table 2 has been used in error."
CADTH, 2016 [25]	Evidence of settings where central lab test is not available (ref. 48, 52, 53, 54, 55, 61, 62): We did not see the data in any evidence tables. Is there a supplement document available in which these data are presented? If so, it would be greatly appreciated if you could send it to us.	Yes	"For the settings where central lab is not available, as there was limited data and it's been reported in text, there are no tables for this information."

For the purpose of transparency, a separate document with comments on the 2nd draft assessment from external experts and the manufacturer(s) (fact check), as well as responses from the author, is available on the EUnetHTA website.

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