Evidence Synthesis Program

Accelerated Diagnostic Protocols Using High-sensitivity Troponin Assays to "Rule In" or "Rule Out" Myocardial Infarction in the Emergency Department: A Systematic Review

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The findings and conclusions in this document are those of the author(s) who are responsible for its contents and do not necessarily represent the views of the Department of Veterans Affairs or the United States government. Therefore, no statement in this article should be construed as an official position of the Department of Veterans Affairs. No investigators have any affiliations or financial involvement (*eg*, employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties) that conflict with material presented in the report.

PREFACE

The VA Evidence Synthesis Program (ESP) was established in 2007 to provide timely and accurate syntheses of targeted health care topics of importance to clinicians, managers, and policymakers as they work to improve the health and health care of Veterans. These reports help:

- Develop clinical policies informed by evidence;
- Implement effective services to improve patient outcomes and to support VA clinical practice guidelines and performance measures; and
- Set the direction for future research to address gaps in clinical knowledge.

The program comprises four ESP Centers across the US and a Coordinating Center located in Portland, Oregon. Center Directors are VA clinicians and recognized leaders in the field of evidence synthesis with close ties to the AHRQ Evidence-based Practice Center Program. The Coordinating Center was created to manage program operations, ensure methodological consistency and quality of products, interface with stakeholders, and address urgent evidence needs. To ensure responsiveness to the needs of decision-makers, the program is governed by a Steering Committee composed of health system leadership and researchers. The program solicits nominations for review topics several times a year via the program website.

The present report was developed in response to a request from the VA Office of Emergency Medicine. The scope was further developed with input from Operational Partners (below), the ESP Coordinating Center, the review team, and the technical expert panel (TEP). The ESP consulted several technical and content experts in designing the research questions and review methodology. In seeking broad expertise and perspectives, divergent and conflicting opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Ultimately, however, research questions, design, methodologic approaches, and/or conclusions of the review may not necessarily represent the views of individual technical and content experts.

ACKNOWLEDGMENTS

The authors are grateful to Gaelen Adam, MLIS for literature searching and the following individuals for their contributions to this project:

Operational Partners

Operational partners are system-level stakeholders who help ensure relevance of the review topic to the VA, contribute to the development of and approve final project scope and timeframe for completion, provide feedback on the draft report, and provide consultation on strategies for dissemination of the report to the field and relevant groups.

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Technical Expert Panel

To ensure robust, scientifically relevant work, the TEP guides topic refinement; provides input on key questions and eligibility criteria, advising on substantive issues or possibly overlooked areas of research; assures VA relevance; and provides feedback on work in progress. TEP members are listed below:

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Peer Reviewers

The Coordinating Center sought input from external peer reviewers to review the draft report and provide feedback on the objectives, scope, methods used, perception of bias, and omitted evidence (see Appendix D for disposition of comments). Peer reviewers must disclose any relevant financial or non-financial conflicts of interest. Because of their unique clinical or content expertise, individuals with potential conflicts may be retained. The Coordinating Center works to balance, manage, or mitigate any potential nonfinancial conflicts of interest identified.

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ABBREVIATIONS TABLE

Abbreviation	Definition
ACC/AHA	American College of Cardiology/American Heart Association
ACS	Acute coronary syndrome
ADP	Accelerated diagnostic protocols
BMI	Body mass index
CABG	Coronary artery bypass graft
CI	Confidence interval
CoE	Certainty of evidence
CP	Chest pain
cTn	Cardiac troponins
CVD	Cardiovascular disease
ECG	Electrocardiogram
ED	Emergency Department
EDACS	Emergency Department Assessment of Chest Pain Score
ESC	European Society of Cardiology
ESP	Evidence Synthesis Program
FDA	Food and Drug Administration
FHx	Family history
GRACE	Global Registry of Acute Coronary Events
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HEART	History, Electrocardiogram, Age, Risk Factors, Troponin
hs-cTn	High-sensitivity cardiac troponins
IQR	Interquartile range
KQ	Key Questions
MACE	Major adverse cardiovascular event
MeSH	Medical Subject Heading
MI	Myocardial infarction
Mo	Month(s)
N	Sample size
NA	Not applicable
NR	Not reported
NRCS	Nonrandomized comparative study
NSTEMI	Non-ST-elevation myocardial infarction
OR	Odds ratio
PAD	Peripheral arterial disease
PCI	Percutaneous coronary intervention
PMID	PubMed identifier
RCT	Randomized controlled trial
RD	Risk difference

Abbreviation	Definition
RF	Risk factor
SD	Standard deviation
STEMI	ST-elevation myocardial infarction
TEP	Technical Expert Panel
TIA	Transient ischemic attack
TIMI	Thrombolysis In Myocardial Infarction (study)
US	United States
VA	Veterans Affairs
wk	Week(s)
yo	Years old

EVIDENCE REPORT

INTRODUCTION

PURPOSE

The VA Evidence Synthesis Program (ESP) was asked by the VA Office of Emergency Medicine for an evidence review on accelerated diagnostic protocols (ADPs) that use high-sensitivity cardiac troponins (hs-cTn) to rule in or rule out myocardial infarction (MI) in the emergency department (ED). The Greater Los Angeles VA ED is an early adopter of hs-cTn and is in the process of developing an ADP. The VA Office of Emergency Medicine indicates that most VA EDs still use conventional troponins, but the Office anticipates more VA EDs will transition to hs-cTn and will need guidance on how to interpret test results for this biomarker within the context of an ADP. This evidence review will be used by the VA Office of Emergency Medicine to provide guidance to local VA EDs that seek to implement hs-cTn with ADPs.

BACKGROUND

In the United States (US), 7 million people annually visit the ED for chest pain, but only 4% of these patients are diagnosed with MI.[1] MI is diagnosed when there is clinical evidence of myocardial ischemia, based on any combination of symptoms, history, and electrocardiogram (ECG) findings, together with either a rise or fall in laboratory biomarkers indicative of infarction.[2] For patients with chest pain or symptoms suggestive of acute coronary syndrome (ACS, which also includes unstable angina without infarction), the 2014 American College of Cardiology/American Heart Association (ACC/AHA) guidelines recommend observation, the use of a 12-lead ECG, and serial cardiac troponin testing using conventional troponins over a 3- to 6-hour period.[3] The evaluation of acute chest pain in the ED can be challenging and carries risks of over- and under-diagnosis of MI; it commonly requires a significant amount of hospital time and resources.[4,5] Rapid rule out and rule in of MI should reduce time to correct patient diagnosis and can reduce clinician, staff, and other hospital resource needs, along with ED overcrowding, unnecessary testing, and unnecessary hospitalizations. However, the clinical implications of missing an MI may include mortality as well as medicolegal risk.[6] In addition, incorrectly diagnosing an MI may put patients through unnecessary testing and treatment and may delay accurate diagnosis of their symptoms.

Cardiac troponin I and T are the primary diagnostic biomarkers used to diagnosis MI.[3] Cardiac troponins have several features that make them useful for this purpose: they are highly concentrated in the myocardium, are not present in non-myocardial tissue, are released into the blood stream only in the presence of myocardial injury, and are relatively easy to quantify in routine clinical practice. In the appropriate clinical context, troponin concentrations in the blood above the 99th percentile of the upper reference level identify myocardial injury.[7] During an MI, troponin levels typically rise within 2 to 3 hours of symptom onset, peak within 18 to 24 hours, and then stay elevated for several days.[8] While the 99th percentile of the upper reference level is used to distinguish between normal and elevated troponin levels, the actual cut-off values vary by assay manufacturer and patient characteristics.

The newer hs-cTn assays entered the global market in 2010. Compared with conventional cardiac troponin assays, hs-cTn is 10 to 100 times more sensitive and provides more consistent

results, which can shorten the time between assessments.[9] The US Food and Drug Administration (FDA) first approved hs-cTn for clinical use in 2017.[10,11] Subsequently, clinical guidelines, including the 2021 ACC/AHA Joint Committee on Clinical Practice Guidelines, have recommended hs-cTn as the preferred troponin biomarker for diagnosing MI.[12]

Despite regulatory and guideline support, there are challenges to implementing hs-cTn in clinical practice.[11] Among these are the following: there are multiple assay manufacturers measuring different types of troponins (I and T) with unique performance characteristics, they are intended to be used in tandem with other clinical information, hs-cTn can be measured at different time points (*eg*, only on arrival or serially every 1, 2, 3, and/or 6 hours), and very rapid protocols (*eg*, within 1 hour of ED presentation) may be difficult to implement in low-resource EDs.[12]

Multiple ADPs that incorporate hs-cTn have been devised to help ED providers (*eg*, physicians and physician assistants) quickly rule out MI.[12,13] In addition to hs-cTn, ADPs can incorporate risk scores and other clinical criteria (*eg*, patient history or ECG findings) to stratify patients into risk categories that inform clinical management. ADPs may include an intermediate or grey zone for patients who cannot be readily ruled out or ruled in, which can create uncertainty and challenges for clinical management. For example, the 2020 European Society of Cardiology (ESC) guidelines recommend the use of a 0/1-hour hs-cTn ADP,[14] in which clinical history is combined with hs-cTn measurement at presentation to the ED and 1 hour later. Baseline hs-cTn values and 1-hour change in hs-cTn (assay-specific cut-offs are applied) are used to rule out, rule in, or place patients in the intermediate zone, which requires additional observation, repeat hs-cTn measurement(s), and echocardiography.[14]

Decision rules for most ADPs using hs-cTn were validated in large and well-described observational studies.[13,15-18] These validation studies have demonstrated that various ADPs with hs-cTn likely rule out MI without increasing the risk of adverse events. Health systems, including the VA, now aim to implement ADPs with hs-cTn into routine clinical practice.

In ED settings, however, the effects of ADPs on clinical and health service utilization outcomes (*eg*, MI diagnoses, time to discharge) remain unclear. The aim of this systematic review was to identify and synthesize available evidence on VA-priority clinical and hospital resource utilization outcomes of ADPs using hs-cTn to rule in or rule out MI in ED settings.

METHODS

TOPIC DEVELOPMENT

We worked with representatives from the VA Office of Emergency Medicine and our Technical Expert Panel (TEP) to refine the review scope and develop the key questions (KQ). In this review, we focus on studies that report on the real-world use of ADPs that incorporate a hs-cTn to rule in or rule out MI. We did not include studies that modeled ADPs using retrospective medical record data (*ie,* classifications made from medical record data that were not implemented while the patients were in the ED). We define ADPs as clinical decision-making tools that at a minimum include a clinical metric (*eg,* time since symptom onset) and incorporate hs-cTn to inform the diagnosis of MI. We evaluated the impact that use of the ADP(s) had on clinical outcomes (*eg,* MI diagnosis, mortality, and major adverse cardiac events) and health service use outcomes (*eg,* duration of emergency department stay, hospitalizations, and use of diagnostic testing such as echocardiography). We also evaluated whether patient sex and baseline clinical features may affect the performance of ADPs with hs-cTn and clinical and health service use outcomes.

KEY QUESTIONS

KQ1: Among adults presenting to the emergency department with suspected acute coronary syndrome, what are the effectiveness and comparative effectiveness of accelerated diagnostic protocols that use high sensitivity cardiac troponin assays on:

> i) clinical outcomes (*eg*, myocardial infarction, mortality, and major adverse cardiac events) within 6 weeks?
>
> ii) health service use (*eg*, duration of emergency department stay, duration of hospitalization, readmission) within 6 weeks?

KQ1a: Does effectiveness differ as a function of patient characteristics (*eg*, gender, chest pain duration, clinical risk score)?

KQ1b: What is the performance of accelerated diagnostic protocols that use 1-hour delta troponin compared to accelerated diagnostic protocols that use 2-hour delta troponin?

KQ2: What are the clinical and health service use outcomes among adults presenting to the emergency department with suspected acute coronary syndrome who have indeterminant (“grey” or “observational” zone) results of accelerated diagnostic protocols that use high sensitivity cardiac troponin assays?

KQ2a: Do clinical and health service outcomes differ as a function of patient characteristics (*eg*, gender, chest pain duration, clinical risk score)?

PROTOCOL

A preregistered protocol for this review can be found on the PROSPERO international prospective register of systematic reviews (http://www.crd.york.ac.uk/PROSPERO/; registration number CRD42022343247).

DATA SOURCES AND SEARCHES

We conducted a preliminary search in PubMed which was focused on Medical Subject Headings (MeSH) terms for *acute coronary syndrome* and related terms, *troponins*, and *emergency services*, together with a list of known relevant publications. As described next, these were screened, after which we expanded our searches and continued screening.

To identify articles relevant to the KQs for our final searches, we searched for peer-reviewed articles from January 2008 to May 2022 in Medline (via PubMed), Embase, ClinicalTrials.gov, and the Cochrane Database of Systematic Reviews. We used MeSH and title/abstract terms related to *chest pain*, *accelerated diagnostic protocols*, *high-sensitivity cardiac troponin*, and *emergency department* (see Appendix A for complete search strategies). Additional citations were identified from hand-searching reference lists of relevant systematic reviews and consultation with content experts.

STUDY SELECTION

Citations were uploaded into the online abstract screening software Abstrackr (http://abstrackr.cebm.brown.edu) and duplicates were removed.[19] To begin screening of the focused search, we used pilot rounds to train the research team during which all team members screened the same sets of abstracts and conflicts were discussed in conference. Subsequently, 2 independent reviewers screened titles and abstracts using the prespecified inclusion and exclusion criteria (Table1). Conflicts between screeners were resolved by a third senior researcher.

Abstrackr uses machine learning algorithms to predict the likelihood that unscreened abstracts are relevant. Based on empirical evidence, we stopped screening when all remaining unscreened abstracts had a prediction value of <0.40 (on a 0–1 scale) and subsequently 400 abstracts in a row were rejected.[19] The initial focused search enabled quicker training of the team and quicker predictions by the machine learning algorithms.

Accepted abstracts underwent full-text review. During full-text review, 2 reviewers decided on inclusion and, when necessary, they consulted a third senior researcher. A list of studies excluded at full-text review, with rejection reasons, is provided in Appendix B.

Eligible populations were ≥18 years of age presenting to the ED with suspected acute coronary syndrome (excluding studies of patients with ST-elevation MI or drug-related ED admissions). Eligible articles addressed ADPs that were clinically applied (*ie,* the clinical team in the ED used the evaluated ADP(s) to manage patients). Studies were excluded if the ADP was not clinically applied in an ED (*eg,* observational studies that derived or validated decision rules without furnishing results to the ED clinical team for use in real time). Our focus was on evaluation ADPs when used with hs-cTn; we thus excluded studies of ADPs used with standard (non-hs) cTn. Studies had to report clinical or heath service use outcomes within 6 weeks of ED admission, as listed in Table 1. Comparative studies of interest had to compare alternative ADPs (both with hs-cTn) or ADP with hs-cTn versus no use of ADP. We did not include comparisons of an ADP with versus without hs-cTn. For studies that compared an ADP with hs-cTn versus a protocol that did not meet our criteria (*eg,* ADP with standard hs-cTn), we included the eligible study group as a single group cohort and omitted (ignored) the ineligible study group. For single group studies (including comparative studies with only a single eligible group), in which all

patients were evaluated in the ED with a single defined ADP with hs-cTn, we analyzed only ED length of stay (or time to discharge/admission) and those outcomes that were reported by rule-in/rule-out category.

Table 1. Inclusion and Exclusion Criteria

	Inclusion Criteria	Exclusion Criteria
Population	Adults ≥18 years of age presenting to the emergency department with suspected acute coronary syndrome.	• People who present with ST-elevation myocardial infarction (STEMI) • Chest pain related to cocaine or other illicit drug use
Intervention	ADPs that use hs-cTn. ADP must at a minimum incorporate clinical history to risk stratify patients. ADP must have been applied in real time during care of the patient in the ED.	• hs-cTn not within an ADP framework (*eg,* lab test alone) • ADP that included standard cTn • ADP that included copeptin + hs-cTn • ADP and/or hs-cTn that was derived based on medical record and was not available to the ED team for clinical care
Comparator	Alterative ADP, no use of ADP, no comparator	• Not alternative lab measures (*eg,* copeptin) • ADP with conventional troponin
Outcomes	• Clinical Outcomes – MI ▪ MI delayed or missed diagnosis ▪ MI correct diagnosis – Mortality ▪ Cardiac ▪ All-cause – MACE (any definition) • Health Service Use Outcomes – Cardiac revascularization – Delayed intervention (*eg,* revascularization) – Duration of emergency department stay – Hospitalizations (full admission as opposed to emergency department observation) – Duration of hospitalization – Emergency department or hospital readmission – Further cardiac testing (*eg,* stress test, heart CT, heart MRI, echocardiography, coronary angiography)	• Components of MACE other than MI and mortality • Chest X-ray • Chest CT
Timing	• Upon arrival to the emergency department • Follow-up within 6 weeks	
Setting	ED or prior to arrival in ED (*ie,* by emergency medical technicians)	Inpatient and outpatient (non-ED) settings

	Inclusion Criteria	Exclusion Criteria
Study Design	• RCT • NRCS, prospective or retrospective • Single group studies, prospective or retrospective • N ≥ 30 per group	• Observational studies not evaluating the real-world use of an ADP • Study protocols (without results) • Case reports and series • Cross-sectional (no follow-up) • Qualitative research studies • Conference abstracts • Reviews, editorials, opinion
Other	No language restriction, no country restrictions	• Unable to translate within Center

Abbreviations. ADPs=accelerated diagnostic protocols; CT=a computerized tomography scan; cTn=cardiac troponin; ED=emergency department; hs-cTn=high sensitivity cardiac troponin; MACE=major adverse cardiac events; MI=myocardial infarction; MRI=magnetic resonance imaging; N=number of participants; NRCS=nonrandomized comparative studies; RCT=randomized controlled trials; STEMI=ST-elevation myocardial infarction.

DATA EXTRACTION AND ASSESSMENT

We created a data extraction form in the Systematic Review Data Repository-Plus (SRDR+) online system (https://srdrplus.ahrq.gov). We extracted the following data from eligible studies: study design, setting, baseline population characteristics, ADP and hs-cTn characteristics, and clinical and health service use outcomes. All data extraction was first completed by 1 reviewer and then checked by a second reviewer. Disagreements were resolved by consensus or discussion with a third reviewer.

Study risk of bias was independently assessed by 2 reviewers using questions derived from the Cochrane Risk of Bias and the ROBINS-I tools (Appendix C).[20,21] We assessed risk of bias separately for clinical and health service use outcomes. For comparative studies, we identified risks of bias that could influence the observed effect of an ADP on an eligible outcome. Single group studies were assessed for risks to the measurement of outcomes only.

RCTs had high risk of bias if there was 1) inadequate randomization method, 2) inadequate allocation concealment, or 3) not explicitly blinding outcome assessors (only a concern for clinical measures) and high attrition. RCTs with no concerns had low risk of bias. NRCSs had high risk of bias if they did not adjust for potential confounders (*ie*, conducted crude analyses). Medium risk of bias NRCSs adjusted for confounders but had at least 1 other concern. NRCS with no concerns had low risk of bias. Single group studies had high risk of bias if they had ≥2 concerns. Studies with only 1 concern had medium risk of bias. Single group studies with no concerns were rated as having low risk of bias.

Discrepancies were resolved by consensus between reviewers. Ratings for eligible studies are in Appendix D.

SYNTHESIS AND CERTAINTY OF EVIDENCE

We conducted a narrative synthesis of the evidence. We aimed to meta-analyze quantitative data, but this was not feasible. We synthesized the certainty of evidence (CoE) following the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach.[22] We compiled key study findings in Evidence Profiles, which provide the basis for determination of CoE and summarize conclusions for prioritized outcomes. Within each evaluated study

comparison (*eg*, ADP vs no ADP) and priority outcome, we considered the study design, the number of studies (and participants), methodological limitations (*ie*, risk of bias), directness of the evidence, precision of the findings, consistency across studies, and other issues. Based on these, we determined CoE, which could be high, moderate, low, or very low. Where we found very low CoE, there is insufficient evidence to draw conclusions. For each outcome, we also provide a summary of the findings.

RESULTS

LITERATURE FLOW

Of 6,591 unique titles and abstracts screened, 377 articles underwent full-text review, and ultimately 17 primary studies (reported in 18 articles) were eligible and included (Figure 1). The 17 primary studies evaluated 23 ADPs. Studies excluded at full-text review are available in Appendix B. The most common reasons for exclusion of articles were the ADP was not clinically applied in an ED (128 articles) and the study did not evaluate an ADP (122 articles). In the next sections, we describe the evidence base and 23 ADPs; evaluate the evidence of ADP use versus no ADP followed by comparisons of different ADPs; and conclude by summarizing evidence about how well ADPs stratify patients by risk of cardiovascular events.

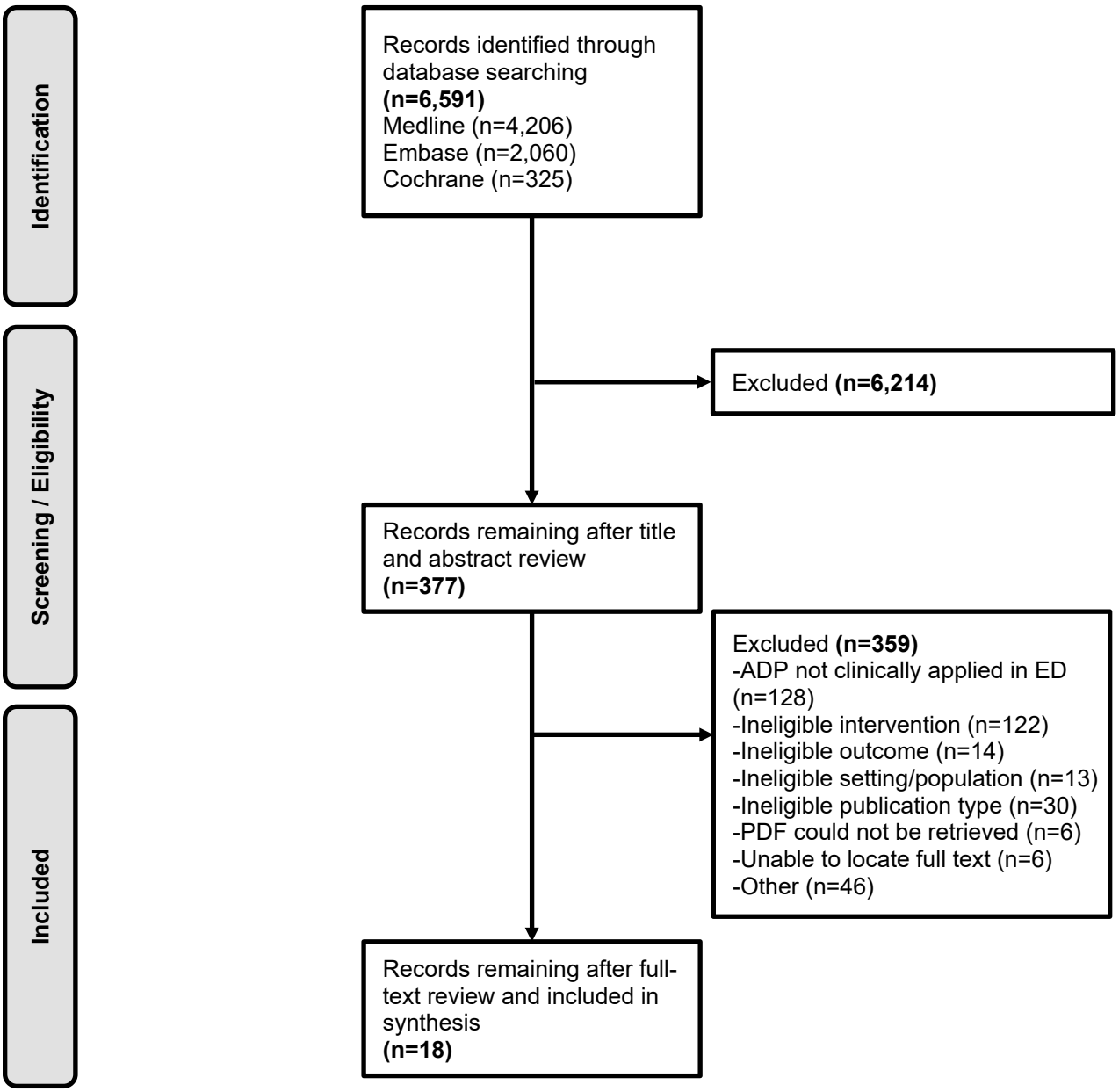
LITERATURE OVERVIEW

Seventeen studies (in 18 publications) reported 23 ADPs with hs-cTn. Table 2 shows the characteristics of the eligible studies. Study designs varied and included 2 RCTs,[23,24] 5 NRCSs[25-29] and 10 single group designs[30-39] (these include 8[30-39] comparative studies from which we evaluated only a single eligible study group). Six of the 7 comparative studies included an ADP as a comparator;[23-25,27-29] in contrast only 1 study compared an ADP with hs-cTn to hs-cTn without an ADP.[26] Of the 10 single group studies, 1 was a RCT evaluated as a single group design[30] and 7 were NRCSs evaluated as a single group design.[30-39] We analyzed these 8 studies as single group designs since the comparator employed a standard troponin, which did not meet our inclusion criteria.

Appendix F shows the study design details including study-level eligibility criteria. One RCT conducted in Scotland was large ($N = 31,492$)[23] and the second RCT conducted in New Zealand included 558 patients.[24] Both RCTs had independent outcome assessors for the clinical measures and overall low risk of bias for clinical and health service measures. Five NRCSs included 18,377 participants total and all used a pre-post design, which consisted of evaluating a hospital or health systems change in ADP.[25-29] For example, Sandeman et al compared a "pre" period during which patients received a local ED's standard 0/6/12 GRACE ADP and a "post" period when the ED introduced a new 0/3/6 ADP.[27] One of the NRCSs had blinded or independent outcome adjudicators for the clinical measures,[28] and the remaining 4 either relied on record linkage (*eg*, electronic medical record) or did not describe how clinical outcomes were determined.[25-27,29] Four of the NRCSs analyzed at least some outcomes using multivariate regression to control for possible confounders.[25-28] One NRCS conducted only crude (unadjusted) analyses.[29] The 10 single group studies included 44,016 patients. Six of the single group studies either did not describe how they assessed clinical outcomes or relied on record linkage (all medium risk of bias for measurement of clinical measures).[30-39]

Study eligibility criteria were consistent across studies. All studies included patients with either chest pain or symptoms suggestive of acute coronary syndrome. Fourteen studies explicitly excluded patients with STEMI.[23-32,34,35,37,39] As presented in summary tables below and discussed in various design-specific sections, the outcomes evaluated across studies varied and included ED length of stay ($N = 15$), 30-day mortality ($N = 12$), discharge to the community ($N = 11$), 30-day MI ($N = 10$), revascularization ($N = 10$), return to ED or hospital ($N = 9$), cardiac testing ($N = 8$), and 30-day MACE ($N = 5$).

Figure 1. Literature Flowchart



Abbreviations. ADP=accelerated diagnostic protocol.

Table 2. Summary Characteristics of Eligible Studies

Characteristics	RCT (n=2)	NRCS (n=5)	Single Group (n=10)[a]
Risk of Bias for Clinical Measures			
Low	2	-	5[b]
Medium	-	4	4
High	-	1	-
Risk of Bias for Health Service Use Measures			
Low	2	4	10
Medium	-	-	-
High	-	1	-
Funding			
Industry	-	1	-
Non-industry	2	1	2
Both industry and non-industry	-	1	3
Not reported	-	2	5
Countries			
United States	-	1	3
Canada	-	-	1
Europe (multiple countries)	1	2	1[c]
Australia	-	1	1
New Zealand	1	1	
Argentina	-	-	2
Sweden	-	-	1
United Kingdom	-	-	1
Centers			
Single emergency department	1	5	5
Multiple emergency departments	1	-	5
High-sensitivity Troponin Manufacturer[d]			
Roche	-	3	6
Abbott	2	2	2
Siemens	-	-	-
Not reported	-	-	3
Risk Score[d]			
HEART	-	2	4
TIMI	1	1	1
EDACS	1	2	-
GRACE	-	1	1
Maximum Serial Troponin Timing[d]			
1 hr	-	-	4
2 hr	1	1	1
3 hr	1	1	5
6 hr	1	6	-
12 hr	1	1	-

Characteristics	RCT (n=2)	NRCS (n=5)	Single Group (n=10)[a]
Clinical and Health Service Use Outcomes			
MACE	2	1	3
MI	2	3	5
Death	1	4	7
Cardiac testing	-	2	6
Revascularization	1	2	7
ED length of stay	1	4	10
Discharge to community	1	3	7
Return to ED or hospital	-	2	7

Notes. [a] One RCT and seven NRCS were analyzed as a single group study; [b] One single group study did not report clinical measures; [c] Conducted in Switzerland and Argentina; [d] Some studies include multiple risk scores, assays or troponin timings.
Abbreviations. ED=emergency department; EDACS=(Emergency Department Assessment of Chest Pain Score); GRACE=(Global Registry of Acute Coronary Events); h=hour; HEART=(History, Electrocardiogram, Age, Risk factors, Troponin); MACE=major adverse cardiac events; MI=myocardial infarction; n=number; NRCS=non-randomized comparative studies; RCT=randomized clinical trial; TIMI=(Thrombolysis in Myocardial Infarction).

DESCRIPTION OF ADPs AND hs-cTn

As displayed in Table 3, we describe the ADPs evaluated in each of the 23 studies based on use of risk score (*eg*, HEART), additional features of the ADP (*eg*, chest pain duration), hs-cTn timing, earliest time patients were eligible for discharge, and whether the final disposition includes a grey or observation zone. Appendix G shows the characteristics of common risk scores and Appendix H shows the characteristics (*eg*, manufacturer and limit of detection) of the hs-cTn used in each ADP.

Most ADPs ($N = 13$) included an explicit risk score.[24-27,29,33-36,38] Six ADPs included HEART or a modification of HEART,[25,26,33-35,38] 3 ADPs included EDACS,[24,29] 2 ADPs include TIMI,[24,25] 1 ADP included GRACE and TIMI,[36] and 1 ADP included GRACE.[27] Seventeen ADPs included chest pain duration as a factor in the ADP.[23,25,27-33,35-39] Five ADPs included 0/1 serial hs-cTn,[28,30,34,35,37] 6 ADPs included 0/3 serial hs-cTn,[23,26,28,31,36,39] 2 ADPs included 0/1/3 serial hs-cTn,[33,38] and the remaining ADPs used other combinations of serial hs-cTn up to 12 hours. In 18 ADPs, the earliest time patients were eligible for discharge was after the first troponin.[23,25-33,35-39] Finally, 2 ADPs included a grey or observation zone as a final disposition, and 3 included a “medium risk category” not described as grey zone or observation, or rule in or rule out.

ADPs varied in complexity. Relatively simple ADPs such as the ESC 0/1 protocol described by Twerenbold et al used time from symptom onset and hs-cTn at presentation to immediately rule out patients or, if needed, obtaining a second sample 1 hour after.[37] Barnes et al describes the ADP 0/(2 or 3)/6 TIMI, which is relatively complex and involves multiple decision pathways based on hs-cTn, TIMI, and ECG changes.[25]

Table 3. Description of Accelerated Diagnostic Protocol

Author, Year, PMID	Arm, ADP Name	Risk Score	Additional Features of ADP (Yes / No)						hs-cTn Timing (hr from ED Admission)	Earliest Time Eligible for Discharge[a]	Grey Zone / Observation Inclusion
			Age	Sex	RF	History of MI	ECG	CP Duration			
Anand 2021 33752439	High-STEACS ADP 0/3							Y	0/3	0	N
	ADP 0/6/12							Y	0/6/12	0	N
Barnes 202133436490	STAT ADP 0/2/6 HEART	HEART	Y			Y	Y	Y	0/2/6	0	N
	ADP 0/(2 or 3)/6 TIMI	TIMI	Y			Y	Y		0/2/3/6	2	
Chew 2019 31478763 Lambrakis 2021 33998255	ADP 0/1							Y	0/1	0	Y
Conde 2013 23810070	ADP 0/3		Y		Y	Y	Y	Y	0/3	0	N
Costable 2014	ADP 0/3		Y		Y	Y	Y	Y	0/3	0	N
Crowder 2015 26387473	ADP 0/2-4							Y	0/2-4	0	N[b]
Ford 2021 33662739	ADP 0/1/3 HEART	HEART						Y	0/1/3	0	N
Hyams 2018 29478861	ADP 0/3 HEART	HEART							0/3	0	N
Ljung 2019 30661856	ADP 0/1 HEART	HEART		Y					0/1	1	N[b]
Sandeman 2021 34824100	ADP 0/3/6							Y	0/3/6	0	N
	ADP 0/6/12 GRACE	GRACE							0/6/12	6	N
Stoyanov 2020 31298551	ADP ESC 0/1							Y	0/1	0	N
	ADP ESC 0/3							Y	0/3	0	N
Suh 2022 35571147	ADP 0/1 mHEART	Modified HEART		Y				Y	0/1	0	N[b]
Sweeney 2020 32104767	ADP 0/3 TIMI & GRACE	TIMI & GRACE					Y	Y	0/3	0	N
Than 2021 33753972	COVID-ADP 0/2 EDACS	EDACS		Y			Y	Y	0/2	0	N
	ADP 0/2/6 EDACS	EDACS		Y			Y	Y	0/2/6	0	N
Than 2016 26947800	ADP 0/2 EDACS	EDACS		Y			Y		0/2	2	N
	ADAPT ADP 0/2 TIMI	TIMI		Y			Y		0/2	2	N
Twerenbold 2019 31345421	ADP ESC 0/1							Y	0/1	0	Y
Vigen 2020 32320036	ADP 0/1/3 mHEART	Modified HEART						Y	0/1/3	0	N

Notes. [a] Hours from first measurement: 0 indicates patients are eligible for discharge after the first hs-cTn measurement; [b] Includes a medium risk category that is not described as grey zone or observation, or rule in or rule out.

Abbreviations. ADP=accelerated diagnostic protocol; CP=chest pain, ECG=electrocardiogram; ED=emergency department; EDACS=Emergency Department Assessment of Chest Pain Score; ESC=European Society of Cardiology; GRACE=Global Registry of Acute Coronary Events; HEART=(History, Electrocardiogram, Age, Risk factors, Troponin); High-STEACS=High-Sensitivity Troponin in the Evaluation of Patients With Suspected Acute Coronary Syndrome; hr= hours; mHEART=Modified HEART; MI=myocardial infarction; N=no; PMID=PubMed Identifier; RF=risk factor; STAT=single troponin accelerated triage; TIMI=Thrombolysis in Myocardial Infarction; Y=yes.

EFFECT OF USING ADPS IN THE ED (ADP vs NO ADP)

Only 1 eligible study addressed the effect of using ADPs in the ED by comparing an ADP with hs-cTn without ADP.[26] The pre-post study of 866 patients in a single US ED compared the ADP 0/3 HEART to a period during which the ED used only the hs-cTn value. The study had moderate risk of bias; they did not adjust for possible confounders for outcomes of interest to this review (they did a multivariate regression for hospital admission) and clinical outcomes were not independently adjudicated. Appendix I presents the baseline characteristics of the sample. Half of the patients were male, they were on average 55 years of age, and 12% had a prior MI.

This study found risks of 30-day MACE, MI, death, and any revascularization did not differ between an ADP with hs-cTn (0/3 HEART) and use of hs-cTn without an ADP. Discharges from the ED to the community (vs hospital admission) were higher for patients in the ADP group compared to the no-ADP group. We have low confidence in these findings primarily because they are based on evidence from a single observational study, with some methodological concerns (Table 4). The study did not report on ED length of stay, 30-day return to the hospital, cardiac testing, or hospital length of stay.

MACE was defined as mortality, nonfatal MI or revascularization within 6 weeks post discharge. There was no significant difference in 30-day MACE among patients who received the ADP 0/3 HEART or hs-cTn without ADP (risk difference [RD] = -1.8%, 95% CI [-5.1, 1.5]; Appendix Table J-1). No patients with a HEART score ≤3 (*ie*, low risk) in either cohort had MACE.

ED length of stay was not reported (Appendix K). However, patients who received the ADP 0/3 HEART were much more likely to be discharged to the community compared with those who received hs-cTn without an ADP (RD = 15.2%, 95% CI [8.7, 21.7]; Appendix Table L-1). No data were reported on 30-day return to ED (Appendix M).

The proportion of patients who had an MI (RD = -0.1%, 95% CI [-2.9, 2.7]; Appendix Table N-1), death (RD = -0.8%, 95% CI [-1.8, 0.2]; Appendix Table O-1), or any revascularization (RD = -1.7%, 95% CI [-4.6, 1.1]; Appendix Table P-1) within 6 weeks were similar in both cohorts. No data were reported for cardiac testing (Appendix Q) or hospital length of stay (Appendix R).

Table 4. Summary of Findings for ADP Compared to hs-cTn without ADP

Outcome	Studies (Patients); Design	Methodological Limitations	Indirectness	Imprecision	Inconsistency	Other Issues	Overall Confidence	Summary of Findings
MACE	1 (866); NRCS[26]	Some limitations[a,b]	Direct	Precise	NA	Single study	Low	No evidence of a difference RD = -1.8%, 95% CI (-5.1 to 1.5)
ED length of stay	0 (0)							(none)
Discharge to the community	1 (866); NRCS[26]	Some limitations[a]	Direct	Precise	NA	Single study	Low	ADP associated with higher proportion of patients discharge to community, vs hs-cTn alone RD = 15.2%, 95% CI (8.7, 21.8)
Return to ED or hospital	0 (0)							(none)
MI	1 (866); NRCS[26]	Some limitations[a,b]	Direct	Precise	NA	Single study	Low	No evidence of a difference RD = -0.1, 95% CI (-2.9, 2.7)
Death	1 (866); NRCS[26]	Some limitations[a,b]	Direct	Precise	NA	Single study	Low	No evidence of a difference RD = -0.8, 95% CI (-1.8, 0.2)
Cardiac testing	0 (0)							(none)
Revascularization	1 (866); NRCS[26]	Some limitations[a]	Direct	Precise	NA	Single study	Low	No evidence of a difference RD = -1.7, 95% CI (-4.6, 1.1)
Hospital length of stay	0 (0)							(none)

Notes. [a] Used crude unadjusted analysis to evaluate this outcome; [b] Outcome assessors were not blinded.
Abbreviations. ADP=accelerated diagnostic protocol; CI=confidence interval; ED=emergency department; hs-cTn=high-sensitivity cardiac troponin; MACE=major adverse cardiovascular event; MI=myocardial infarction; NA=not applicable; NRCS=nonrandomized comparative study; RD=risk difference.

COMPARISONS OF DIFFERENT ADPS

Six studies (2 RCTs[23,24] and 4 NRCSs[25,27-29]) compared ADPs, which are summarized in Table 5. The 6 studies included 12 unique ADPs; thus, comparisons within each study were unique. The 2 RCTs had low risk of bias for the clinical and health service use measures.[23,24] Three NRCSs relied on record linkage for the clinical outcomes (moderate risk of bias) and had no concerns for the health service outcomes (low risk of bias health service measures).[25,27,28] One NRCS had high risk of bias for both the clinical and health service use measures.[29] This study did not provide a description of the method for adjudicating clinical outcomes, did not provide data on the characteristics of patients by cohort, and used crude unadjusted analyses to evaluate all outcomes.

All 6 comparator studies included 49,561 patients (RCT $N = 32,050$;[23,24] NRCS $N = 17,511$[25,27-29]). Table 2 shows the characteristics of the studies. Only 1 study was conducted in multiple EDs.[23] Three studies were conducted in Europe,[23,27,28] 2 in New Zealand,[24,29] and 1 in Australia.[25] All studies explicitly excluded patients with STEMI. Appendix I shows the baseline characteristics of patients in the 6 studies. Race/ethnicity data were reported in 2 studies, both of which were conducted by the same author in New Zealand.[24,29] Across the studies, the mean age range was 54 to 64 years and men were in the majority (range 53%–62%). There was variation in the proportion of patients who had a prior MI (range 8%–23%), with 1 study not reporting these data.[29] In all studies, the assay manufacturer did not change between comparisons.

Table 5. Comparisons of Accelerated Diagnostic Protocols

Author, Year, PMID	Arm, ADP Name	Additional Features of ADP (Yes / No)						hs-cTn Timing (hr from ED Admission)	Final Disposition Includes Grey Zone / Observation
		Age	Sex	RF	History of MI	ECG	CP Duration		
Shorter vs Longer ADP									
Anand 2021 33752439	High-STEACS ADP 0/3						Y	0	N
	ADP 0/6/12						Y	0	N
Sandeman 2021 34824100	ADP 0/3/6						Y	0	N
	ADP 0/6/12 GRACE							6	N
Stoyanov 2020 31298551	ADP ESC 0/1						Y	0	N
	ADP ESC 0/3						Y	0	N
Than 2021 33753972	COVID-ADP 0/2 EDACS		Y			Y	Y	0	N
	ADP 0/2/6 EDACS		Y			Y	Y	0	N
Comparison of Risk Scores									
Barnes 202133436490	STAT ADP 0/2/6 HEART	Y			Y	Y	Y	0	N
	ADP 0/(2 or 3)/6 TIMI	Y			Y	Y		2	N
Than 2016 26947800	ADP 0/2 EDACS		Y			Y		2	N
	ADAPT ADP 0/2 TIMI		Y			Y		2	N

Abbreviations. ADP=accelerated diagnostic protocol; CP=chest pain; ECG=electrocardiogram; ED=emergency department; EDACS=Emergency Department Assessment of Chest Pain Score; ESC=European Society of Cardiology; GRACE=Global Registry of Acute Coronary Events; HEART=History, Electrocardiogram, Age, Risk factors, Troponin; High-STEACS=High-sensitivity Troponin in the Evaluation of Patients with Suspected Acute

Coronary Syndrome; MI=myocardial infarction; N=no; PMID=PubMed identifier; RF=Risk factor(s); TIMI=Thrombolysis in Myocardial Infarction; Y=yes.

Comparisons of ADPs with Different Durations

Four studies directly compared ADPs with shorter versus longer times between first and last hs-cTn (Table 5).[23,27-29] Two of these studies compared ADPs with different hs-cTn timings that did not include risk scores.[23,28] Specifically, 1 RCT[21] compared a novel High-STEACS 0/3 ADP to the standard 0/6/12 ADP, and 1 NRCS[26] compared the ESC 0/1 to the ED standard ESC 0/3 ADP. In Than 2021 et al, the EDACS risk score was used in the novel (COVID-ADP 0/2 EDACS) and standard (0/2/6 EDACS) ADPs.[29] This study was unique in that it compared an ADP developed in response to the COVID-19 pandemic (COVID-ADP 0/2 EDACS) to the ED’s standard ADP. Finally, a NRCS compared a novel shorter ADP that did not include a risk score (0/3/6) to a longer ADP that included GRACE (0/6/12 GRACE).[27] In the longer ADP, patients were not eligible for discharge till 6 hours after the first hs-cTn measurement. As noted above, the Than et al study had high risk of bias for both the clinical and health service use measures.[29]

In summary, there is no evidence of differences between shorter and longer duration ADPs in 30-day MACE or 30-day MI, but shorter ADPs probably increase discharge to the community from the ED (Table 6; moderate confidence). In addition, together with evidence from single group (noncomparative) studies, shorter duration ADPs probably reduce ED length of stay. There is no evidence of differences in 30-day mortality or follow-up cardiac testing (low confidence). The studies provide insufficient evidence (very low confidence) regarding coronary artery revascularization. The studies did not evaluate return to ED or hospital or hospital length of stay.

MACE

One RCT compared the High-STEACS ADP 0/3 to ADP 0/6/12 and evaluated risk of 30-day MACE.[23] As a primary analysis, MACE was defined as MI (type 1/4b/4c) or cardiac death. The study also evaluated a version of MACE that includes MI type 2. Overall, 0.4% of patients had 30-day MACE. With both definitions, there were no significant differences in 30-day MACE between ADPs (RD = -0.1%, 95% CI [-0.2, 0.03] and RD = -0.1%, 95% CI [-0.2, 0.05], respectively; Appendix Table J-1).

Table 6. Summary of Findings for Shorter versus Longer Duration ADPs

Outcome	Studies (Patients); Design	Methodological Limitations	Indirectness	Imprecision	Inconsistency	Other Issues	Overall Confidence	Summary of Findings
MACE, 30-day	1 (31,492); RCT[23]	No limitations	Direct	Precise	NA	Single study	Moderate	Probably no difference RD = -0.1, 95% CI (-0.2, 0.03)
ED length of stay	4 (46,784); 1 RCT[23] and 3 NRCS[27-29]	Some limitations[a]	Direct	Precise	Consistent	None	Moderate	ADPs with shorter hs-cTn probably reduce length of stay.
Discharge to the community	2 (33,908); 1 RCT[23] and 1 NRCS[29]	Some limitations[a]	Direct	Precise	Consistent	None	Moderate	ADPs with shorter hs-cTn probably increase discharge to the community.
Return to ED or hospital, 30-day	0 (0)							(none)
MI, 30-day	1 (31,492); RCT[23]	No limitations	Direct	Precise	NA	Single study	Moderate	Probably no difference RD = -0.1, 95% CI (-0.2, 0.01)
Death, 30-day	1 (10,873); NRCS[27]	No limitations	Direct	Imprecise	NA	Single study	Low	Maybe no difference in all-cause (RD = 0.1, 95% CI [-0.7, 0.9]) or cardiovascular (RD = 0.1, 95% CI [-0.5, 0.7]) death
Cardiac testing	1 (2525); NRCS[28]	Some limitations[c]	Direct	Precise	NA	Single study	Low	Maybe no difference in angiograms RD = -3.2, 95% CI (-6.7, 0.3)
Revascularization	1 (2525); NRCS[28]	Some limitations[c]	Indirect[b]	Precise	NA	Single study	Very low	Insufficient evidence
Hospital length of stay	0 (0)							(none)

Notes. [a] One NRCS did not provide data on the characteristics of patients by cohort and used crude unadjusted analyses to evaluate all outcomes; [b] Report revascularization only among patients who received coronary angiography; [c] Used crude unadjusted analysis to evaluate this outcome.
Abbreviations. ADP=accelerated diagnostic protocol; CI=confidence interval; ED=emergency department; hs-cTn=high-sensitivity cardiac troponin; MACE=major adverse cardiovascular event; MI=myocardial infarction; NA=not applicable; NRCS=nonrandomized comparative study; RCT=randomized controlled trial; RD=risk difference.

ED Length of Stay

In summary, ED length of stay was considerably longer for ADPs with up to 12 hours of hc-Tn compared to ADPs with 6 or less hours of hs-cTn timing. One RCT[23] and 3 NRCSs[27-29] all found that ADPs with shorter serial hs-cTn testing compared to longer hs-cTn testing significantly reduced ED length of stay (Appendix Table K-1). Three of the 4 studies had low risk bias[23,27,28] and 1 had high risk of bias, resulting in some overall methodological limitations.[29] Anand et al and Sandeman et al both compared novel ADPs (High-STEACS 0/3 and 0/3/6) to standard ADPs with up to 12 hours of hs-cTn (0/6/12 and 0/6/12 GRACE). In both studies, a novel ADP was associated with a significantly shorter length of stay (High-STEACS 0/3 vs 0/6/12: mean 6.8 vs 10 hours, $p < 0.001$[23] and 0/3/6 vs 0/6/12 GRACE: median 6.5 vs 8.9 hours, $p < 0.001$; Appendix Table K-1).[23,27] Another study found length of stay was shorter for patients who received ESC 0/1 compared to patients who received ESC 0/3 (median difference -2.1 hours, $p < 0.001$).[28] Finally, Than et al (2021) found a novel COVID-19 0/2 EDACS ADP reduced median length of stay compared to the standard 0/2/6 EDACS ADP (median 3.4 vs 3.8 hours, $p < 0.001$).

Two NRCSs reported subgroup comparisons for ED length of stay.[27,29] Sandeman et al found that among patients with initial hs-cTn <14 ng/L (*ie*, not high risk), a novel ADP 0/3/6 was associated with a shorter length of stay than the standard ADP 0/6/12 GRACE. Than et al (2021) found that among discharged patients, those who received a novel COVID-ADP 0/2 EDACS had a shorter length of stay than patients who received ADP 0/2/6 EDACS (median 3.1 vs 3.7 hours, p-value not reported).

Evaluating the comparative and single group studies together, 15 studies (of 20 ADPs) reported on ED length of stay (Table 7).[23,25,27-29,31-39] Five ADPs included 0/1 hs-cTn timing (length of stay range 2.5–4.8 hours),[28,30,34,35,37] 2 ADPs included 0/2 hs-cTn timing (length of stay range 3.5–6.1 hours),[29,32] 5 ADPs included 0/3 hs-cTn timing (length of stay range 4.1–6.8 hours),[23,28,31,36,39] 2 ADPs included 0/1/3 hs-cTn timing (length of stay range 3.4–6.5 hours),[33,38] 4 ADPs included hs-cTn timing up to 6 hours (length of stay range 3.6–6.5 hours),[25,27,29] and 2 ADPs included 0/6/12 hs-cTn timing (length of stay range 8.9–10 hours)[23,27]

Table 7. Summary of Findings for ED Length of Stay by ADP hs-cTn Timing

Study, Year, PMID	ADP	N	Median (IQR) Length of Stay, Hours
Chew 2019 31478763	ADP 0/1	1646	4.6 (3.4,6.4)
Ljung 2019 30661856	ADP 0/1 HEART	621	4.7 (3.5, 24.7)
Stoyanov 2020 31298551	ADP ESC 0/1	1282	3.2 (2.7,4.4)
Suh 2022 35571147[a]	ADP 0/1 mHEART	821	4.8 (3.1,7.1)
Twerenbold 2019 31345421	ADP ESC 0/1	2296	2.5 (2.2, 3.91)
			0/1 Summary Range: 2.5–4.8
Than 2021 33753972	COVID-ADP 0/2 EDACS	1343	3.4 (2.6,4.6)
Crowder 2015 26387473	ADP 0/2-4	5754	6.1 (4.25, 9.8)
			0/2 Summary Range: 3.4–6.1
Anand 2021 33752439	High-STEACS ADP 0/3	16792	Mean (SD) 6.8 (4.1)
Conde 2013 23810070	ADP 0/3	300	Mean (SD) 4.3 (2.6)
Costable 2014	ADP 0/3	528	Mean (SD) 4.5 (2.6)
Stoyanov 2020 31298551	ADP ESC 0/3	1243	5.3 (4.7,6.5)
Sweeney 2020 32104767	ADP 0/3 TIMI & GRACE	15882	3.8 (0.6, 7)
			0/3 Summary Range: 4.1–6.8
Vigen 2020 32320036	ADP 0/1/3 mHEART	14552	6.5 (4.9, 9.3)
Ford 2021 33662739[b]	ADP 0/1/3 HEART	1616	3.4 (2.2, 4.9)
			0/1/3 Summary Range: 3.4–6.5
Barnes 2021 33436490	ADP 0/(2 or 3)/6 TIMI	1131	4.3 (3.3, 7.1)
Than 2021 33753972	ADP 0/2/6 EDACS	1073	3.8 (2.8,4.9)
Barnes 2021 33436490	STAT ADP 0/2/6 HEART	1124	3.6 (2.6, 5.4)
Sandeman 2021 34824100	ADP 0/3/6	3673	6.5 (3.6, 19.8)
			0/(2 or 3)/6 Summary Range: 3.6–6.5
Anand 2021 33752439	ADP 0/6/12	14700	Mean (SD) 10 (4.1)
Sandeman 2021 34824100	ADP 0/6/12 GRACE	6642	8.9 (3.6, 38)
			0/6/12 Summary Range: 8.9–10

Notes. [a] Provider time to disposition, median (IQR) for total ED LOS 11.5 (7.6, 22.9); [b] Median (IQR) for patient physically entered ED to patient physically left the ED 6.4 (4.3, 9.6).
Abbreviations. ADP=accelerated diagnostic protocol; ED=emergency department; EDACS=Emergency Department Assessment of Chest Pain Score; ESC=European Society of Cardiology; GRACE=Global Registry of Acute Coronary Events; HEART=History, Electrocardiogram, Age, Risk factors, Troponin; High-STEACS=High-sensitivity Troponin in the Evaluation of Patients with Suspected Acute Coronary Syndrome; hs-cTn=high-sensitivity cardiac troponin; mHEART=modified HEART (History, Electrocardiogram, Age, Risk factors, Troponin); IQR=interquartile range; N=sample size; PMID=PubMed identifier; SD=standard deviation; STAT=single troponin accelerated triage; TIMI=Thrombolysis in Myocardial Infarction.

Discharge from the ED to the Community

One RCT (Annand et al[23]) and 1 NRCS (Than et al 2021[29]) both found that ADPs with shorter hs-cTn timing compared to longer hs-cTn timing discharged more patients to the community (Table 6; Appendix Table L-1). In the RCT, the High-STEACS ADP 0/3 compared to standard 0/6/12 ADP significantly increased discharges to the community (RD = 21%, 95% CI [20.0, 22.0]). The NRCS found that a novel ADP developed in response to COVID-19 (0/2 EDACS) discharged more patients home compared to the standard 0/2/6 EDACS ADP (RD = 3%, 95% CI [0.5, 5.5]). However, the NRCS had high risk of bias because it did not provide data on the

characteristics of patients by cohort and used crude unadjusted analyses to evaluate all outcomes.[29]

In addition, 2 NRCSs reported the proportion of patients discharged from the ED within a pre-defined period of time (*eg*, proportion discharged ≤4 hours; Appendix Table K-2).[27,29] In 1 study, patients were more likely to be discharged from the ED within 4 hours if they received a novel ADP (0/3/6) compared to standard ADP (0/6/12 GRACE; RD = 2.3%, 95% CI [0.4, 4.2]). Similarly, Than et al (2021) found a novel COVID-19 ADP resulted in a greater proportion of patients discharged from the ED within 3 hours compared to the standard ADP (44.2% vs 35.2%; p-value not reported).[29]

Return to ED or Hospital

No study reported data on return to the ED between ADPs with shorter hs-cTn timing compared to ADPs with longer hs-cTn timing.

Myocardial Infarction

One RCT (Annand et al)[23] found no difference in 30-day MI between patients who received the High-STEACS ADP 0/3 compared patients who received the standard 0/6/12 ADP (Table 6). Overall, 30-day MI was low and varied between 0.2% and 0.4% between patients who received each ADP. In a primary analysis, MI was defined as type 1/4b/4c and a secondary analysis evaluated a version of MI that included type 2 (1/2/4b/4c). With both definitions, there were no significant differences in 30-day MI (RD = -0.1, 95% CI [-0.2, 0.1] and RD = -0.1, 95% CI [-0.2, 0.03], respectively; Appendix Table N-1).

Mortality

One NRCS (Sandeman et al) comparing a shorter (0/3/6) to longer (0/6/12 GRACE) ADP found no difference in 30-day all-cause (RD = 0.1%, 95% CI [-0.7, 0.9]) or cardiovascular (RD = 0.01%, 95% CI [-0.5, 0.7]) related death (Table 6 and Appendix Table O-1).[27] In a subanalysis, the same study reported overall more deaths at 30-days among high-risk patients (defined by initial hs-cTn value), but there were no differences in mortality between ADP.

Cardiac Testing

One NRCS (Stoyanov et al) compared the ESC 0/1 to ESC 0/3 and reported cardiac testing outcomes.[28] The study found no difference between ESC 0/1 and ESC 0/3 and the proportion of patients who received an angiogram (RD = -3.2%, 95% CI [-6.7, 0.3]; Appendix Table P-1). In subanalyses and among people ruled out and discharged, there was no difference between patients who received ESC 0/1 and 0/3 and angiogram imaging, or stress testing.

Revascularization

One NRCS found no difference (ADP ESC 0/1 vs ADP ESC 0/3) in the proportion of patients who received a percutaneous coronary intervention among a subgroup who received a coronary angiography (RD = 0.2%, 95% CI [-7.2, 7.6]; Appendix Table Q-1).[28] No other study reported comparative data on revascularization.

Hospital Length of Stay

No study reported compared hospital length of stay between ADPs with shorter and longer hs-cTn timing.

Comparison of ADPs with Different Risk Scores

Two studies compared ADPs with similar hs-cTn timing but different risk scores.[24,25] One NRCS compared a novel STAT 0/2/6 HEART ADP to the ED’s standard 0/(2 or 3)/6 TIMI ADP.[25] The novel STAT ADP and standard ADP both incorporated age, history of MI, and ECG as features.[25] The novel ADP also incorporated the HEART risk score and chest pain duration, and patients were eligible for discharge after the first hs-cTn draw. In contrast, the standard ADP incorporated TIMI, did not include chest pain duration as a feature, and patients where not eligible for discharge until 2 hours after the first hs-cTn. It was unclear whether clinical outcomes were independently adjudicated, so the study had medium risk of bias for clinical outcomes. There were no other concerns and the study was low risk of bias for the health service use measures. One RCT compared a novel 0/2 EDACS ADP to the ADAPT 0/2 TIMI ADP.[24] In both ADPs, patients were not eligible for discharge until 2 hours after first hs-cTn. The novel ADP included the EDACS risk score and the standard ADP included TIMI risk score. The study had no concerns and was rated low risk of bias for the clinical and health service use measures.

In summary, there is no evidence of differences in 30-day MACE, 30-MI, and 30-day death among ADPs with similar hs-cTn timing and different risk scores. We have moderate confidence in these findings due to the large size of available studies and lack of major methodological limitations (Table 8). A HEART-based ADP compared to TIMI-based ADP with similar hs-cTn timing may reduce ED length of stay and increase discharge to the community from the ED. We have moderate confidence in these findings due to the large size of available studies and lack of major methodological limitations. Thirty-day return to the ED is probably similar among patients administered a HEART-based ADP or TIMI-based ADP with similar hs-cTn timing. We have low confidence in these findings because only 1 nonrandomized study was available for this outcome. Studies did not report on revascularization or hospital length of stay.

MACE

One RCT reported 30-day MACE.[24] The authors defined MACE as death, cardiac arrest, emergency revascularization, cardiogenic shock, ventricular arrhythmia needing intervention, high-degree atrioventricular block needing intervention, and MI. There was no significant difference in 30-day MACE between patients who received the 0/2 EDACS ADP and ADAPT 0/2 TIMI ADP (RD = 0.3, 95% CI [-0.9, 1.5]; Appendix Table J-2). All MACE events (0/2 EDACS $N = 2$ [0.7%] vs ADAPT 0/2 TIMI $N = 1$ [0.4%]) occurred in non-low risk patients. No other study reported MACE outcomes.

ED Length of Stay

One RCT found that the proportion of patients discharged from the ED within 6 hours and who did not have 30-day MACE was similar for patients who received a novel 0/2 EDACS ADP or ADAPT 0/2 TIMI ADP (RD = -2.1%, 95% CI [-10.3, 6]; Appendix Table K-2).[24] This finding held in a subanalysis among low risk patients (RD = 3.2%, 95% CI [-4.3, 10.7]). One NRCS reported a consistent finding that a novel HEART-based ADP resulted in a shorter length of stay

than the TIMI-based ADP (median 3.4 vs 3.8 hours; incident rate ratio = 0.71, 95% CI [0.65, 0.77]; Appendix Table K-1).[25]

Discharge from the ED to the Community

One NRCS found the HEART-based ADP compared to TIMI-based ADP was associated with an increase in the proportion of patients discharged home (RD = 25%, 95% CI [21, 29]; Appendix Table L-1).[25]

Return to ED or Hospital

One NRCS found no difference in the proportion of patients who returned to the ED for any reason between people who received the HEART- or TIMI-based ADP (RD = 1.1%, 95% CI [-1.3, 3.4]; Appendix Table M-1).[25] In a secondary analysis, there were no differences in the proportion of patients who returned to the ED for chest pain (RD = -2%, 95% CI [-14.9, 10.9]).

Myocardial Infarction

An NRCS[23] and RCT[24,25] both reported 30-day MI. The NRCS reported no 30-day MI among patients who received either the 0/2/6 HEART ADP or 0/(2 or 3)/6 TIMI ADP (Appendix Table N-1).[25] The RCT found patients who received a novel 0/2 EDACS ADP and ADAPT 0/2 TIMI ADP had similar risk of 30-day non-ST-elevation myocardial infarction (NSTEMI; RD = 0.7%, 95% CI [-2.1, 0.6]) and ST-elevation myocardial infarction (STEMI; RD = -0.4%, 95% CI [-0.7, 1.4]; Appendix Table N-1).[24] The same RCT reported 3 MIs (1 STEMI and 2 NSTEMI) at 30 days all in non-low risk patients.

Mortality

An NRCS[23] and RCT[24,25] reported 30-day mortality. The NRCS reported no patients who received either ADP died within 30 days (Appendix Table O-1).[25] The RCT reported no 30-day all-cause mortality among patients who received a novel 0/2 EDACS ADP and 1 30-day death (0.4%) among a non-low risk patient who received the 0/2 TIMI ADP (RD = -0.4%, 95% CI [-0.7, 1.4]).[24]

Cardiac Testing

One NRCS reported follow-up stress (ECG and imaging) and angiogram (standard and imaging) data (Appendix Table P-1).[25] Patients who received a novel STAT 0/2/6 HEART ADP compared to 0/(2 or 3)/6 ADP had similar use of stress ECG (RD = 1%, 95% CI [-1.2, 3.2]) and CT angiogram (RD = 1.7%, 95% CI [0.1, 3.3]). The novel STAT 0/2/6 HEART ADP compared to 0/(2 or 3)/6 ADP resulted in more myocardial perfusion scans (RD = -2%, 95% CI [-3.4, -0.6]) and CT angiograms (RD = 1.7%, 95% CI [0.1, 3.3]).

Revascularization and Hospital Length of Stay

No study reported data on revascularization or hospital length of stay.

Table 8. Summary of Findings for ADPs with Similar hs-cTn Timing and Different Risk Scores

Outcome	Studies (N); Design	Methodological Limitations	Indirectness	Imprecision	Inconsistency	Other Issues	Overall Confidence	Summary of Findings
MACE, 30-day	1 (558); RCT[24]	No limitations	Direct	Precise	NA	Single study	Moderate	Probably no difference (RD = 0.3, 95% CI [-0.9, 1.5])
ED length of stay	1 (2,255); NRCS[25]	No limitations	Direct	Precise	NA	Single study	Low	ADP 0/2/6 HEART may reduce length of stay compared to ADP 0/(2 or 3)/6 TIMI (IRR = 0.71, 95% CI [0.65, 0.77]; $p < 0.001$)
Discharge to the community	1 (2,255); NRCS[25]	No limitations	Direct	Precise	NA	Single study	Low	ADP 0/2/6 HEART may increase discharge to the community compared to ADP 0/(2 or 3)/6 TIMI (RD = 25, 95% CI [21.0, 29.0]; $p < 0.001$)
Return to ED or hospital	1 (2,255); NRCS[25]	No limitations	Direct	Precise	NA	Single study	Low	No difference between ADP 0/2/6 HEART and ADP 0/(2 or 3)/6 TIMI (RD = 1.1, 95% CI [-1.3, 3.4])
MI, 30-day	2 (2,813); 1 RCT[24] and 1 NRCS[25]	No limitations	Direct	Precise	NA	Sparse data	Moderate	Probably no difference between ADPs with similar hs-cTn but different risk scores
Death, 30-day	2 (2,813); 1 RCT[24] and 1 NRCS[25]	No limitations	Direct	Precise	NA	Sparse data	Moderate	Probably no difference between ADPs with similar hs-cTn but different risk scores
Cardiac testing	1 (2,255); NRCS[25]	Serious limitations[a]	Direct	Precise	Inconsistent[b]	Single study	Very Low	Insufficient evidence
Revascularization	0 (0)							(none)
Hospital length of stay	0 (0)							(none)

Notes. [a] Used crude unadjusted analyses to evaluate this outcome; [b] No difference in stress ECG and CT angiogram but differences in myocardial perfusion scans and CT angiograms.
Abbreviations. ADP=accelerated diagnostic protocol; CI=confidence interval; ED=emergency department; HEART=History, Electrocardiogram, Age, Risk factors, Troponin; hs-cTn=high-sensitivity cardiac troponin; MACE=major adverse cardiovascular event; MI=myocardial infarction; NA=not applicable; NRCS=nonrandomized comparative study; RCT=randomized controlled trial; RD=risk difference; TIMI= Thrombolysis in Myocardial Infarction.

OUTCOMES BY ADP DISPOSITION

We reviewed comparative and single group studies to summarize the relationship between ADP stratification into disposition groups and outcomes. We first note, though, that the 17 studies did not use a standard system nor set of definitions for how patients were risk stratified. This was in part due to differences in how the various ADPs stratified patients and in part due to differences in language (or classification) across studies. Ultimately, we found 6 partially overlapping categories: rule out, low risk (not described as rule out), discharge (not described as rule out), observation/grey zone, high risk either stated or implied (not described as rule in), and rule in.

In summary, ED length of stay increased and the proportion of patients discharged to the community decreased as risk categorization increased. All ADPs appear to successfully stratify patients based on their risks of 30-day MACE, 30-day MI, and 30-day death. In general, the proportion of patients who returned to the ED, cardiac testing, revascularization, and hospital length of stay increased in risk categorization.

MACE

Five studies that evaluated 6 ADPs reported 30-day MACE by ADP disposition.[24,26,30,35,37] Examples of the various MACE definitions used across studies included MI or cardiac death,[37] MI or all-cause death,[30] and MI, revascularization, ventricular arrhythmia, high degree atrioventricular block requiring intervention, cardiogenic shock requiring mechanical support, cardiac arrest with return of spontaneous circulation, and death.[35] The proportion of patients with 30-day MACE mostly ranged from 0.4% to 5.8%, with an outlier study (Twernbold et al) reporting 10.1%.[37]

In general, the risk of 30-day MACE increased with increase in risk categorization. Three ADPs included 0/1 hs-cTn timing,[30,35,37] 2 included 0/2 hs-cTn timing,[24] and 1 included 0/3 hs-cTn timing.[26] In 2 studies that used a 0/1 ADP, 30-day MACE defined as death (cardiovascular or all-cause) and MI was between 0.2% and 0.5% for **ruled-out** patients (Appendix Table J-2).[30,37] In a second definition of MACE, Chew et al added unstable angina to the composite that resulted in 0.8% 30-day MACE for ruled-out patients. In 3 ADPs (ADP 0/2 EDACS, ADP 0/2 TIMI, and ADP 0/3 HEART), no occurrences of 30-day MACE were reported among **low-risk** patients (not described as rule out).[24,26] In 2 0/1 based ADPs, 30-day MACE among **discharged** patients was ≤1%, and among patients in an **observation** or **grey zone**, 2.3% and 5.3%.[30,37] The same 2 studies reported 30-day MACE of 3.7% and 66.8% among **ruled-in** patients.[30,37] Three studies representing 4 ADPs reported outcomes for **high-risk** patients (not described as rule in).[24,35,37] Twerenbold et al (high risk defined as patients admitted during index visit) reported 34% of patients had MACE at 30 days.[37] A second study reported 8.9% (ADP 0/1 mHEART) of patients experienced 30-day MACE,[35] and a third study reported 0.4% (ADP 0/2 TIMI) and 0.7% (ADP 0/2 EDACS) 30-day MACE among non-low risk patients.[24]

ED Length of Stay

Six studies evaluating 8 ADPs reported ED length of stay by ADP disposition.[27,29,30,34,37,39] All 6 studies reported ED length of stay for patients either **ruled out, low risk** (not described as rule out), or **discharged**. Among these studies, 3 ADPs incorporated 0/1 hs-cTn timing,[30,34,37] 1 incorporated 0/3 timing,[39] 1 incorporated 0/3/6 timing,[27] and 1 incorporated 0/6/12 timing.[27] There was no discernable pattern between hs-cTn timing and ED length of stay among **ruled-out**

patients (range 2.5–4.6 hours),[30,37] **low-risk** patients (range 2.9–4.05 hours),[27,34,39] or **discharged** patients (range 2.5–3.8 hours; Appendix Table K-3).[29,30,34,37] There was a wide range in median length of stay (2.5–12 hours) reported in 2 0/1 ADPs for patients in the **observation** or **grey zone**.[30,37] The same 2 studies reported median length of stay for **ruled-in** patients of 51 hours (Chew et al)[30] and 2.5 hours (Twerenbold et al).[37] Finally, 3 studies evaluating 4 ADPs (ADP 0/1 HEART, ADP ESC 0/1, ADP 0/3/6, and ADP 0/6/12 GRACE) reported median ED length of stay for **high-risk** (not described as rule in) patients between 3 and 46.7 hours.[27,34,37] ED length of stay was sensitive to the definition of high risk.

Two studies evaluating 4 ADPs (ADAPT ADP 0/2 TIMI, ADP 0/2 EDAC, ADP 0/3/6, and ADP 0/6/12 GRACE) reported the **proportion of patients discharged** from the ED within 4 or 6 hours by ADP disposition.[24,27] As noted in the comparative ADP section, Than et al (2016) defined their outcome as proportion discharged within 6 hours and no 30-day MACE. The study reported 26.2% (ADP 0/2 EDACS) and 22.9% (ADAPT ADP 0/2 TIMI) of **low-risk** patients were discharged within 6 hours without 30-day MACE.[24] Sandeman et al compared 2 ADPs (0/3/6 and 0/6/12 GRACE) and reported the proportion of **low-risk** patients discharged ≤4 hours was between 53% and 64% (Appendix Table K-4).[27] The same study also reported ~13% of **high-risk** (not defined as rule in) patients (defined as first hs-cTn >14 ng/L) were discharged within 4 hours in both ADPs. No other study reported these discharge data by ADP disposition.

Discharge from the ED to the Community

Three studies evaluating 3 ADPs (ADP ESC 0/1 and ADP 0/1 HEART) reported data on the proportion of patients discharged from the ED to the community by ADP disposition (Appendix Table L-2).[30,34,37] One ESC 0/1 study reported 45.1% of patients were discharged to the community.[30] In 2 other studies, 67.5% (ADP 0/1 HEART)[34] and 71% (ESC 0/1)[37] were discharged to the community. In 2 ESC 0/1 studies, 49.6%[30] and 88%[37] of **ruled-out** patients were discharged from the ED to the community. Similarly, the 0/1 HEART ADP was associated with 87.3% of **low risk** (not described as rule out) patients being discharged.[34] The 2 ESC 0/1 studies reported 27.3%[30] and 61%[37] of **observed group** patients were discharged home.[30,37] The same 2 studies reported 8% of **ruled-in** patients were discharged home. Finally, the ADP 0/1 HEART study reported 62.6% (HEART score ≥4) and 31.5% (initial hs-cTn >14) **high-risk** (not described as rule in) patients were discharged home.[34]

Return to ED or Hospital

Two studies evaluating 2 ADPs (ADP ESC 0/1 and ADP 0/1 HEART) reported 30-day return to the ED by ADP disposition (Appendix Table M-2).[30,34] Thirty-day return to the ED was low for patients **ruled out** (3.5%),[30] **low risk** not described as rule out (5.2%),[34] or **discharged** (10.7%).[34] One study (ADP ESC 0/1) reported 3.6% and 7.1% of **observe/grey zone** patients returned to the ED for myocardial injury and chest pain, respectively.[30] The same study reported 5.1% of **ruled-in** patients returned to the ED. Another study (ADP 0/1 HEART) reported return to ED among **high-risk** patients with proportions between 17.8% and 22.3% based on the definition of high risk.[34]

Myocardial Infarction

Five studies evaluating 6 ADPs (ADP ESC 0/1,[30,37] ADP 0/1 HEART,[34]ADP 0/2 EDACS,[24]ADAPT ADP 0/2 TIMI, [24] and ADP 0/3[39]) reported MI by ADP disposition

(Appendix Table N-2). Thirty-day MI for patients **ruled out**, **low risk**, or **discharged** was between 0% and 0.8%. Thirty-day MI among patients in the **observe** or **grey zone** was reported for 2 0/1 ADPs (1.9%[30] and 5.2%[37]). Among patients **ruled in or high risk**, 30-day MI varied between 0% and 67%.

Mortality

Six studies evaluating 6 ADPs (ADP ESC 0/1,[30,37] ADP 0/1 HEART,[34] ADP 0/3,[39] ADP 0/3/6,[27] and ADP 0/6/12 GRACE[27]) reported mortality by ADP disposition (Appendix Table O-2). For patients **ruled out**, **low risk** (not described as rule out), or **discharged,** 30-day mortality was between 0% to 0.3%.[27,30,34,37,39] Two ESC 0/1 studies reported 30-day morality for **ruled-in** patients from 0%[30] to 1.7%.[37] One study evaluating 2 ADPs reported 5.4% **high-risk** (not described as rule in) patients had 30-day cardiovascular mortality.[27] The same study found ~9% of high-risk patients had 30-day all-cause mortality. Three studies evaluating 3 ADPs reported 0% to 1% of high-risk patients died within 30 days.[34,37,39]

Cardiac Testing

Three studies evaluating 3 ADPs (ESC 0/1[30,37] and ADP 0/1 HEART)[34] reported any stress testing by ADP disposition (Appendix Table P-2). The proportion of patients who received any stress testing generally increased by risk categorization: **rule out** (5.1% and 8.8%),[30,37] **low risk** not described as rule out (10.1%),[34] **observe/grey zone** (10% and 13%),[30,37] **rule in** (14%),[30,37] and **high risk** not described as rule in (9.2% and 15.1%).[34] Similar findings were reported among 3 studies evalauting 3 ADPs (ESC 0/1[28,30,37] and ESC 0/3[28]) for stress ECG tests and angiograms and 2 studies evalauting ESC 0/1 ADPs[28,30] for stress imaging. Limited angiogram imaging data were reported for studies evaluating ESC 0/1[30] and ESC 0/3.[28]

Revascularization

Two studies both evaluating ESC 0/1 ADPs reported revascularization by ADP disposition.[30,37] In general, the proportion of patients who received any revascularization within 30 days increased by risk categorization. Between 0.6% and 4.4% of **ruled-out** or **discharged** patients received any revascularization (Appendix Table Q-2). Among patients in the **observation zone**, 5.8%[30] and 11%[37] received any revascularization, and 24%[30] and 51%[37] of **ruled-in** patients received any revascularization. Finally, in 1 study 40% of **high-risk** (not described as rule-in) patients received any revascularization.[40]

Hospital Length of Stay

Only 1 study (ADP ESC 0/1) reported hospital length of stay (Appendix Table R-1).[37] Patients in the **observe**, **rule in**, and **high risk** (not described as rule in) groups spent a median (IRQ) of 1 (0, 5), 5 (3, 9), and 5 (2, 8) nights in the hospital, respectively.

DISCUSSION

We identified 17 primary studies that reported 23 ADPs. Only a single study compared an ADP to hs-cTn without an ADP. Six studies compared different ADPs and 10 single group studies evaluated a single ADP. Two comparative studies were RCTs and 4 were NRCSs. Four studies compared ADPs with different hs-cTn timings and 2 studies compared ADPs with similar hs-cTn timing but different risk scores. The most frequently evaluated outcome was ED length of stay. We evaluated overall certainty of evidence for all comparative studies. No studies were conducted in the VA system. Key findings include the following:

- ADPs with hs-cTn may increase discharges to the community but may not impact clinical outcomes.
- Use of ADP with hs-cTn compared to no ADP may be associated with reduced ED resource use.
    - Use of an ADP with hs-cTn is associated with more discharges from the ED to the community and no difference in 30-day MACE, MI, death, and cardiac testing (low confidence for all findings).
    - It is unknown if use of an ADP with hs-cTn is associated with differences in revascularization (very low confidence). No study reported ED length of stay, 30-day return to the ED or hospital, cardiac testing, or hospital length of stay for an ADP with hs-cTn compared to no ADP.
- Use of ADPs with shorter compared to longer hs-cTn timing is probably associated with reduced ED use, but not associated with cardiovascular events.
    - Shorter ADP protocols are probably associated with shorter ED length of stay and more discharges to the community (moderate confidence).
    - Shorter ADP protocols are probably not associated with the proportion of patients who experience 30-day MACE or MI (moderate confidence) and, maybe, death rates (low confidence).
- Use of ADPs with different risk scores (but with similar hs-cTn timing) probably does not affect cardiovascular events, but ADPs that use the HEART rather than the TIMI risk score may decrease ED length of stay and increase discharge to the community form ED (low confidence for all findings).
- No study compared ADPs with 1-hour versus 2-hour (or other time) delta troponins.
- There was sparse reporting of data on the effectiveness of ADPs in patients triaged to a grey or observation zone, and on differences in outcomes based on patient characteristics like gender and chest pain duration.
- All ADPs appear to successfully stratify patients based on their risks of 30-day MACE, MI, and death.

Rapid rule in or rule out of MI has the potential to reduce ED overcrowding and health care costs.[41,42] To facilitate rapid triage, ED providers and administrators can choose from multiple described ADPs, which may have to be tailored to fit local structural needs. We identified 23

ADPs that varied in complexity, hs-cTn variation (I or T), hs-cTn timing, use of risk score, and other features. Unfortunately, heterogeneity across studies in ADPs, how patients were stratified and analyzed, and study design make comparisons challenging. No 2 studies compared the same ADPs. Studies stratified patients into multiple (often poorly defined) overlapping risk categories (*eg*, rule out, low risk, discharge).

Most comparative studies used a pre-post design. That is, they evaluated the effect of an ED’s implementation of a new ADP on clinical and health service use outcomes, compared with their prior ADP. This is a pragmatic approach with strong internal validity to understand the effects of an ADP on outcomes. However, findings from these studies may not generalize to an average ED, because the EDs reporting these studies likely implemented ADPs that they believed would be successful in their health system. There are many factors that may impact the ability to implement an ADP and quickly diagnose patients. For example, the ability to execute a specific hs-cTn timing (*eg*, 0/1) depends on resources for rapid serial blood draws and labs being able to process specimens within a defined time. Fast lab turnaround times may not be feasible in low resource hospitals.[43-45] Successful implementation also depends on support across service lines from the ED, lab, and inpatient units.[11] For example, the HEART score was the most commonly employed risk score. HEART was developed for implementation in the ED, is relatively easy to administer/calculate, and many ED providers are familiar with the tool,[46] although other providers may be less familiar with HEART. TIMI and GRACE, also employed in several ADPs, were initially developed to determine whether patients need invasive therapy and not for the evaluation of chest pain, and ED staff may be less comfortable with using them.[47,48] These measures are more relevant for risk stratifying and managing those with MI. One eligible study found a HEART-based ADP was associated with shorter length of stay and ED discharge compared with TIMI ADP, but the effect cannot be solely attributed to the use of HEART.[25] The ADPs differed on several factors, including use of chest pain duration as a feature and employing different times patients were eligible for discharge from first hs-cTn. In general, across studies, multiple points of variation between ADPs makes it challenging to know whether a specific risk score-based ADP would be effective in an average ED.

One would not expect ADPs to substantively change the rate of within-ED MI or MACE, but they may affect the timing of final diagnosis (rule in or rule out MI), which help (or hinder) more rapid appropriate management (of MI or alternative diagnosis). When hs-cTn was introduced, there was concern that that more rapid (or delayed) diagnoses could impact both clinical outcomes and health system resources (*eg*, more downstream testing).[49,50] However, limited data from the included comparative studies did not find differences between ADPs and outcomes other than ED length of stay. Limited data by ADP disposition (*eg*, rule out or low risk versus rule in or high risk) demonstrate that the use of ADPs enabled appropriate patient triage. Most patients where triaged to rule out, low risk, or a discharge group. As expected, patients triaged to rule in or higher risk generally had more clinical events than patients triaged to low risk or rule out. In the latter group, poor clinical outcomes were rare. Even among high-risk patients, 30-day MACE, MI, and mortality are relatively rare events, and many of the studies may have been underpowered to detect differences between ADPs. In comparative studies, ADPs with shorter compared to longer hs-cTn timing were able to meaningfully reduce ED length of stay. These between ADP studies are supported by single group data that show ADPs with up to 12 hours of hs-cTn have considerably longer ED length of stay than ADPs with up to 6 hours of hs-cTn timing. These findings imply ADPs with 12 hour hs-cTn timing may increase ED congestion without clinical benefit.

Variation across studies in analytic comparisons and definitions presented substantial challenges for interpretation and synthesis of results. The ADPs are complex and with varying structures that at times were poorly reported. Relatedly, the studies applied different terminology to describe similar concepts for ADP disposition. Some studies used terms such as rule in or rule out, while others described populations as being high risk or low risk. The description of a grey or observation zone and associated follow-up care was also inconsistently reported. Studies also varied in the reporting of outcomes by ADP disposition and not all studies reported outcomes by disposition. This presented a major challenge when interpreting single group design studies. ED length of stay was reported in nearly all studies; however, there was sparse reporting of clinical data. As expected, the definition of MACE varied between studies. Most studies that reported clinical data relied on electronic medical records or other administrative data and did not use independent outcome adjudicators. Thus, it is generally difficult to determine with high certainty the effect of any single ADP on clinical and health service use outcomes.

IMPLICATIONS FOR VA POLICY

No study was conducted in the VA. Furthermore, only 1 comparative study[26] and 3 single group studies were conducted in the US.[33,35,38] Although most studies included a majority of men (range 46%–64%), the VA population is 89% male. hs-cTn assays can be interpreted with a general or sex-specific cutoff and the selection of threshold may impact ADP disposition.[11] Only 1 eligible study reported outcomes within an ADP between males and females, and it found no difference in 30-day MACE.[37]

Most studies were conducted in countries with integrated health systems, which may influence how an ADP is implemented and the consequences of mis-stratification (*eg*, inappropriate discharge or admission). For example, health systems with well-coordinated outpatient care may be positioned to discharge more patients knowing they will receive timely follow-up care. Unfortunately, most of the studies only reported on the structure of the ADP and provided minimal detail on protocols to ensure timely follow-up. As a large integrated health system, VA Medical Centers may be well positioned to implement ADPs, as long as they have established protocols to ensure outpatient follow-up.

As the VA moves to include hs-cTn in ED clinical pathways,[45] there are clear opportunities for system-level implementation. The VA can leverage its system and purchasing capacity to identify a single hs-cTn manufacturer, develop timing and measurement standards, and build the necessary normative ranges for the Veteran population. Supporting a common ADP would allow infrastructure developments in the electronic medical record, universal data collection, process measure construction, and outcome development necessary to create a high-reliability system for chest pain management. The ADPs typically incorporated features (*eg*, clinical history) that are already captured in the medical record, but often unstandardized in collection. As a high-reliability organization, the VA could automate a standard ADP that pulls relevant data from the medical record to generate a disposition suggestion (*eg*, rule in). Finally, the VA could create a system for routing Veterans who were at high risk but ruled out into important prevention programs such as preventive cardiology and cardiac rehabilitation.

This review summarizes evidence regarding the effect of hs-cTn ADPs on clinical and health care utilization outcomes. Most comparative studies were conducted in health systems that already had experience implementing an ADP. The relative complexity of hs-cTn and ADPs may

hamper their implementation; however, we did not evaluate implementation outcomes as part of this review. Importantly, any system adopting an ADP should be aware of the natural variation between troponin I and T. The ADPs in the included studies used both variants, but the 2 troponin markers are not interchangeable, which may pose challenges to standardizing an ADP across sites. Other barriers to implementation of ADPs with hs-cTn within the VA may be cost and availability of the hs-cTn laboratory test. Costs may be magnified by protocols that require serial hs-cTn.[11] Other challenges to implementation include updating clinical workflows and obtaining buy in from providers across service lines including ED, pathology, laboratory, and cardiology.[11] Many VA EDs are staffed by part-time providers who have limited familiarity with local protocols or may not have the resources/training to perform additional point-of care testing such as echocardiography. Finally, 1 large academic-affiliated VA Medical Center’s transition from cTn to hs-cTn (without an ADP) may provide helpful lessons.[45,51] The process of implementing hs-cTn took 6 months, required a multidisciplinary team, and a series of educational interventions. Even after implementation and the educational interventions, providers initially reported challenges interpreting hs-cTn. Furthermore, hs-cTn alone was perceived as providing limited additional benefit.[45] Implementing an ADP with complex decision rules would likely take more time and resources.

RESEARCH GAPS/FUTURE RESEARCH

A number of observational studies have computationally derived and evaluated the performance of proposed hs-cTn ADPs.[18] However, we found only a few studies that evaluated hs-cTn ADPs implemented in routine practice and even fewer that compared ADPs implemented in practice. Heterogeneity in ADPs and comparative data presents challenges to determine the causal effect of a specific ADP on outcomes. In addition, ADP complexity makes it challenging to determine the effect of specific ADPs features (*eg*, risk score) on outcomes. To address this gap, there is a need for repeat comparative studies of already-studied ADPs, with an eye toward comparisons of ADP duration and, separately, ADP complexity. There is also a need for comparisons of ADP implementation in different hospital and geographic settings (*eg*, urban/rural and low-resource/high-resource communities). It is also important to understand whether hs-cTn ADPs can be successfully and safely implemented in US EDs that may not be part of large integrated health systems. Very few included studies reported outcomes by subgroups. There is an opportunity to conduct secondary database analyses to identify effects of ADPs in different subgroups (*eg*, sex and chest pain duration).

ADPs stratified patients into different risk groups, but studies used inconsistent and poorly defined terminology to describe such groups. Use of standardized, clinically meaningful, and interpretable risk categorizations is needed. ADPs should categorize patients as rule in, rule out, grey zone rule out and grey zone rule in and clearly define terms that do not correspond to clinical disposition (*eg*, low risk that is not equivalent to rule out). In addition, all studies, whether comparative or single group, should report important clinical and resource outcomes by risk categories. Related to terminology, each study uniquely defined MACE. This challenge is not unique to the ADP literature and there are competing consensus statements on definitions of MACE.[52,53,54]

LIMITATIONS

This evidence review has several limitations. The focus of the review was on the effect and not the implementation of hs-cTn ADPs. The organizational factors that affect implementation may be important for clinical and health service use outcomes. Relatedly, we did not evaluate the factors that make an ED, hospital, or health system a strong candidate to implement an hs-cTn ADP. We excluded studies or data from studies that implemented a conventional troponin. We did this because evidence is consistent that the performance of hs-cTn is superior to conventional troponin. However, hs-cTn is relatively new in the US and many EDs, including those in the VA, may still be using conventional troponin. Outpatient care and ED structure may also be different between VA EDs and the mostly international EDs that implemented ADPs in the eligible studies. We categorized some outcomes for high-risk patients if an ADP implied this categorization even if the term was not explicitly used. Finally, depending on one’s perspective, an additional limitation is that we included only studies evaluating real-world implementation of ADPs and we excluded numerous studies of theoretical ADPs, which may have provided some further insights.

CONCLUSIONS

ADPs can help standardize practice, which may avoid overuse of health services and reduce ED congestion. ADPs with shorter compared to longer hs-cTn timing may reduce ED length of stay, increase discharges to the community, and probably are not associated with changes in 30-day MACE, MI, or mortality. Use of an ADP (with hs-cTn), compared to no ADP, may be associated with reduced admissions, but without worsening clinical outcomes. An ADP that used HEART may be associated with shorter ED length of stay than a TIMI-based ADP, but with no difference in clinical outcomes. Among ADPs that reduce ED length of stay, there is no clear or obvious best choice. For an ED that seeks to implement an ADP, the best option will be based on the available evidence (*eg*, validated risk tools and hs-cTn timing), but the specific structure likely will need to be tailored to local context and preferences. Findings were limited due to great variability across studies in evaluated ADPs and inconsistent reporting and analyses. These findings may generalize to the VA, which is a large integrated care system capable of providing follow-up outpatient care. More comparative studies evaluating a homogenous set of ADPs with rigorous analysis of a range of clinical and resource-related outcomes are required to determine the effects of ADPs and comparisons between ADPs.

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