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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This report was prepared by the Evidence Synthesis Program Center located at the **VA Providence Health Care System,** directed by Eric Jutkowitz, PhD and James Rudolph, MD and funded by the Department of Veterans Affairs, Veterans Health Administration, Health Services Research and Development.

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.

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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

EXECUTIVE SUMMARY

Key Findings

- Accelerated diagnostic protocols (ADPs) with high-sensitivity cardiac troponins (hs-cTn) may increase discharges to the community but may not impact clinical outcomes.
- Shorter duration ADPs and an ADP that incorporates the History, Electrocardiogram, Age, Risk Factors, Troponin (HEART) score are associated with shorter emergency department (ED) stays and increased discharges to the community, but there is no evidence that clinical outcomes differ based on use of different ADPs.
- ADPs with hs-cTn compared to hs-cTn alone without an ADP:
    - ADP with hs-cTn compared to hs-cTn alone is associated with more discharges from the ED to the community and no difference in 30-day major adverse cardiovascular event (MACE), myocardial infarction (MI), death, and cardiac testing (low confidence for all findings).
    - It is unknown if an ADP with hs-cTn compared to hs-cTn alone is associated with revascularization (very low confidence).
    - No study reported on ED length of stay, 30-day return to the ED or hospital, cardiac testing, or hospital length of stay.
- ADPs with shorter compared to longer hs-cTn timing:
    - Shorter duration ADPs are probably associated with shorter ED length of stay and more discharges to the community (moderate confidence).
    - Duration of ADPs is probably not associated with the proportion of patients who experience 30-day MACE or MI (moderate confidence) and may not be associated with death rates (low confidence).
- ADPs with comparable hs-cTn timing but different risk scores:
    - ADPs with different risk scores probably have no difference in the proportion of patients who experience 30-day MACE (moderate confidence) and may have no difference in risk of return to the ED, MI, or death (low confidence).
    - A HEART-based ADP compared to a TIMI-based ADP may reduce ED length of stay and increase discharge to the community from the ED (low confidence).
- No study compared ADPs with 1-hour delta troponin to ADPs with 2-hour delta troponin.
- 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 (indirect comparison).

INTRODUCTION

In the United States (US), 7 million people annually visit the emergency department (ED) for chest pain, but only 4% of these patients are diagnosed with myocardial infarction (MI). Rapid rule-out and rule-in of MI should reduce time to correct patient diagnosis and 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 can be severe and may include mortality as well as medicolegal risk. In addition, incorrectly diagnosing an MI may put patients through unnecessary testing and treatment.

Newer high-sensitivity cardiac troponin (hs-cTn) assays entered the global market in 2010 and are now the preferred troponin biomarker for diagnosing MI, as per the 2021 ACC/AHA Joint Committee on Clinical Practice Guidelines. Multiple accelerated diagnostic protocols (ADPs) have been devised to help ED providers quickly rule out MI. ADPs can incorporate hs-cTn, risk scores, and other clinical criteria (*eg*, patient history or electrocardiogram findings) to stratify patients into categories that inform clinical management. Most ADPs that incorporate hs-cTn were initially evaluated in observational studies that computationally derived and validated the decision rules and concluded that they are likely safe and effective.

Health systems, including the VA, now aim to implement ADPs with hs-cTn into clinical practice. The VA Evidence Synthesis Program (ESP) was asked by the VA Office of Emergency Medicine for an evidence review on ADPs that use hs-cTn to rule in or rule out MI. In collaboration with VA stakeholders, we developed the following Key Questions (KQs):

KQ1: Among adults presenting to the ED with suspected acute coronary syndrome, what are the effectiveness and comparative effectiveness of ADPs that use hs-cTn on clinical and health service use outcomes?

KQ2: What are the clinical and health service use outcomes among adults presenting to the ED with suspected acute coronary syndrome who have indeterminant ("grey" or "observational" zone) results of ADPs that use hs-cTn?

METHODS

We conducted a systematic review using best contemporary standards. We searched for peer-reviewed articles in Medline (via PubMed), Embase, ClinicalTrials.gov, and the Cochrane Database of Systematic Reviews from January 2008 to May 2022. Eligible studies included adult participants presenting to the ED with suspected acute coronary syndrome (excluding studies of patients with ST-elevation MI or drug-related ED admissions). ADPs with hs-cTn were clinically applied in decision-making during the patients' ED visits. We excluded studies of ADPs with standard (non-hs) cTn or that evaluated ADPs or hs-cTn data that were not available to the ED staff. Eligible studies either compared ADPs with hs-cTn to hs-cTn alone, compared different ADPs (both with hs-cTn), or evaluated an ADP with hs-cTn (without a direct comparator). Studies could be randomized or observational (prospective or retrospective). Prioritized outcomes included 30-day MACE, ED length of stay, discharge from the ED, 30-day revisit to ED or rehospitalization, 30-day MI, 30-day mortality, follow-up cardiac testing, revascularization, and hospital length of stay. We extracted data into standardized forms and assessed risk of bias of each study. We planned to conduct meta-analyses, but studies were too heterogeneous to allow appropriate pooling. Using GRADE (Grading of Recommendations

Assessment, Development and Evaluation) methodology, we determined certainty of evidence for each major finding. The review protocol was registered in PROSPERO (CRD42022343247).

RESULTS

Evaluated ADPs

Seventeen studies reported on 23 ADPs with hs-cTn. ADPs included risk scores (*eg*, HEART) and/or patient features (*eg*, age and chest pain duration) and predefined hs-cTn timing. The ADPs allowed for variable earliest times that patients were eligible for discharge, and whether the final disposition included a “grey” or “observation” zone (in addition to rule in and rule out). However, analyses also included categorizations of low risk, high risk, and discharge. Six ADPs included HEART or a modification of HEART, 3 ADPs included EDACS, 2 ADPs included TIMI, 1 ADP included GRACE and TIMI, and 1 ADP included GRACE. Five ADPs included 0/1 hour serial hs-cTn, 6 ADPs included 0/3 hour serial hs-cTn, 2 ADPs included 0/1/3 hour serial hs-cTn, and the remaining ADPs used other combinations of serial hs-cTn up to 12 hours.

Effect of Using ADPs in the Emergency Department (ADP vs No ADP)

Only 1 eligible study addressed the effect of using ADPs in the ED by comparing an ADP with hs-cTn to hs-cTn without ADP. The pre-post study of 866 patients compared the ADP 0/3 HEART to a period during which the ED used only the hs-cTn value. Clinical outcomes were not independently adjudicated, so the study had moderate risk of bias for the effect on clinical measures. The study conducted multivariate regression to control for confounders for the effect on health service outcomes, and thus had low risk of bias for these outcomes.

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 (MACE: risk difference [RD] = -8%, 95% CI [-5.1, 1.5]; MI: RD = -0.1%, 95% CI [-2.9, 2.7]; death: RD = -0.8%, 95% CI [-1.8, 0.2]; revascularization: RD = -1.7%, 95% CI [-4.6, 1.1]). Discharges from the ED to the community versus hospital admission were higher for patients in the ADP group compared to the no ADP group (RD = 15.2%, 95% CI [8.7, 21.7]). We have low confidence in these findings primarily because they are based on evidence from a single observational study with some methodical concerns. The study did not provide evidence for ED length of stay, 30-day return to the hospital, cardiac testing, or hospital length of stay.

Comparisons of Different ADPs

Six comparative studies (2 randomized controlled trials [RCTs] and 4 nonrandomized comparative studies [NRCSs]) compared 12 unique ADPs in 49,561 patients. The 2 RCTs were low risk of bias for the clinical and health service use measures. Three of the 4 NRCSs were medium risk of bias for the clinical measures (due to lack of independent outcome adjudication) and low risk of bias for the health service measures. One NRCS that had incomplete reporting and reported only crude unadjusted analyses was at high risk of bias.

Comparisons of ADPs with Different Durations

Four studies compared ADPs with shorter versus longer times between first and last hs-cTn, which ranged from 1 to 12 hours. In most studies, the ADPs also varied by inclusion of risk score.

In summary, there is no evidence of differences in 30-day MACE (RD = -0.1%, 95% CI [-0.2, 0.03]) and 30-day MI (RD = -0.1%, 95% CI [-0.2, 0.01]) among patients administered shorter and longer ADPs. Shorter ADPs probably reduce ED length of stay (by about 2 to 4 hours in each study, mostly reported as statistically significant) and increase discharge to the community from the ED (by either 3% or 21% in 2 studies, both statistically significant). We have moderate confidence in these findings; studies were large and mostly did not have major methodological limitations, but most of these outcomes were reported by a single study each.

Rates of follow-up cardiac testing (RD = -3.2%, 95% CI [-6.7, 0.3]) and 30-day mortality (RD = 0.1%, 95% CI [-0.7, 0.9]) may not differ by ADP duration, but we have low confidence in these findings because they are based on a relatively small unadjusted NRCS (cardiac testing) or an NRCS that yielded an imprecise effect size (30-day mortality).

Evidence was insufficient to draw conclusions about differences in rates of coronary artery revascularization and studies did not report on return to ED or hospital length of stay.

Across 15 studies, including 10 noncomparative (single group) studies, ADPs with up to 12 hours of hs-cTn had considerably longer ED length of stay (range: 8.9–10 hours) than ADPs with 6 or less hours of hs-cTn timing (range: 2.5–6.5 hours).

Comparison of ADPs with Different Risk Scores

Two studies compared ADPs with similar hs-cTn timing but different risk scores. One RCT compared a novel 0/2 EDACS ADP to the ADAPT 0/2 TIMI ADP. One NRCS compared a novel STAT 0/2/6 HEART ADP to the ED’s standard 0/(2 or 3)/6 TIMI ADP.

In summary, there is no evidence of differences in 30-day MACE (RD = 0.3%, 95% CI [-0.9, 1.5]), 30-day MI (in 2 studies RD = 0% and 0.7%, both not statistically significant), and 30-day death (in 2 studies RD = 0% and -0.4%, both nonsignificant) among ADPs with similar hs-cTn timing and different risk scores. We have moderate confidence in these findings; the studies did not have major methodological limitations, but few ADPs were compared with each other.

One study reported that a HEART-based ADP, compared to a TIMI-based ADP with similar hs-cTn timing, may reduce ED length of stay (incident rate ratio = 0.71, 95% CI [0.65, 0.77]), may increase discharge to the community from the ED (RD = 25%, 95% CI [21.0, 29.0]), but 30-day return to the ED may be similar (RD = 1.1, 95% CI [-1.3, 3.4]). We have low confidence in these findings; only a single, relatively small NRCS reported these outcomes. Studies did not report on revascularization or hospital length of stay.

ADP Stratification of Patients into Risk Groups

Based on an indirect comparison of cohorts of patients in 17 studies, including 10 noncomparative (single group) studies, all ADPs appear to successfully stratify patients according to their risks of 30-day MACE, 30-day MI, and 30-day death. For example, 30-day MACE was between 0% and 0.5% for **ruled-out**/**low-risk** patients, 0.06% to 1.0% for **discharged** patients, and 2.3% to 5.3% for **grey zone**/**observe** patients. The risk of MACE varied widely across studies for patients categorized as **ruled in**/**high risk** (0.4% to 67%), but the median risk was 6.3%. Thirty-day return to the ED, cardiac testing, revascularization, and hospital length of stay also each increased according to risk categorization.

DISCUSSION

Rapid rule-in or rule-out of MI has the potential to reduce ED overcrowding and health care costs. To facilitate rapid triage, ED providers and administrators can choose from multiple described ADPs. Across 17 studies, we identified 23 ADPs that varied in complexity, hs-cTn timing, use of risk score, and other features. Heterogeneity across studies in ADPs, how patients were stratified and analyzed, and study design made comparisons challenging. No 2 studies compared the same ADPs and the studies stratified patients into multiple (often poorly defined) overlapping risk categories (*eg*, rule out, low risk, discharge).

Most comparative studies evaluated the effect of an ED’s implementation of a new ADP on clinical and health service use outcomes, compared with their prior ADP. However, findings from these studies may not generalize to an average ED due to differences in their ability to execute a specific hs-cTn timing (*eg*, 0/1), support across service lines from the ED, lab, and inpatient units, and capacity to implement different risk scores in real time, among others. The evaluated ADPs used multiple risk scores that may be more or less familiar to ED physicians, cardiologists, and ED staff in different settings. In addition, the ADPs differed on several other 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 made it challenging to know whether a specific risk score-based ADP would be effective in an average ED.

Overall, limited data from the included comparative studies did not find differential associations between ADPs and outcomes other than ED length of stay. Analyses of ADP disposition (*eg*, rule out or low risk vs rule in or high risk) demonstrated that the use of ADPs enabled appropriate patient triage. As expected, patients triaged to rule in or higher risk generally had more clinical events than patients triaged to low risk or rule out. 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. This finding was supported by both direct comparisons within studies and indirect comparisons across studies, including the single group studies.

Implications for VA Policy

No study was conducted in the VA. Furthermore, only 1 comparative study and 3 single group studies were conducted in the US. There are, therefore, some concerns in the generalizability of results from studies to the VA. 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. Only 1 eligible study reported outcomes within an ADP between males and females and it found no difference in 30-day MACE.

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 well 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 care. 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, there are opportunities for system-level implementation. The VA can use 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. A common ADP would allow infrastructure developments in the electronic medical record, automation of an ADP to generate a disposition suggestion, universal data collection, process measure construction, and outcome development necessary to create a high reliability system for chest pain management. Importantly, any VA Medical Center adopting an ADP should be aware of the natural variation between troponin I and T, which may pose challenges to standardizing an ADP across sites. 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.

Research Gaps/Future Research

Few studies have compared ADPs implemented in practice. There is a need to reduce the heterogeneity of study analyses to allow for better summarization, including possibly meta-analysis, across studies. Future studies should repeat comparisons of already-studied ADPs, with an eye toward clean comparisons of ADP duration and, separately, of ADP complexity. Given the complexity of ADPs, 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 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. There is an opportunity to conduct secondary database analyses to identify effects of ADPs in different subgroups (*eg*, sex and chest pain duration). Greater standardization of risk stratification would greatly improve interpretation and clarity of findings. Studies, and by extension ADPs, should categorize patients as rule in, rule out, grey zone rule out and grey zone rule in and clearly define the meaning of low or high risk.

Limitations

The focus of this 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. We also did not evaluate the factors that might make an ED, hospital, or health system a strong candidate to implement an hs-cTn ADP. Because of variable terminology that was commonly not well defined, we often had to infer items such as how ADPs were implemented, what factors were considered within ADPs, and the disposition (categorization) of patients.

Conclusions

Standardizing practice can help 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. An ADP with hs-cTn compared to hs-cTn alone may be associated with reduced admissions without compromising clinical outcomes. ADPs with comparable hs-cTn timing but that use HEART compared to TIMI may be associated with shorter ED length of stay.

Among ADPs that reduce ED length of stay, there is no obvious best choice. For an ED that seeks to implement an ADP, the best option is based on the available evidence (*eg*, validated risk tools and hs-cTn timing), but the specific structure likely needs 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 are required to determine the effects of a specific ADP on outcomes.

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.

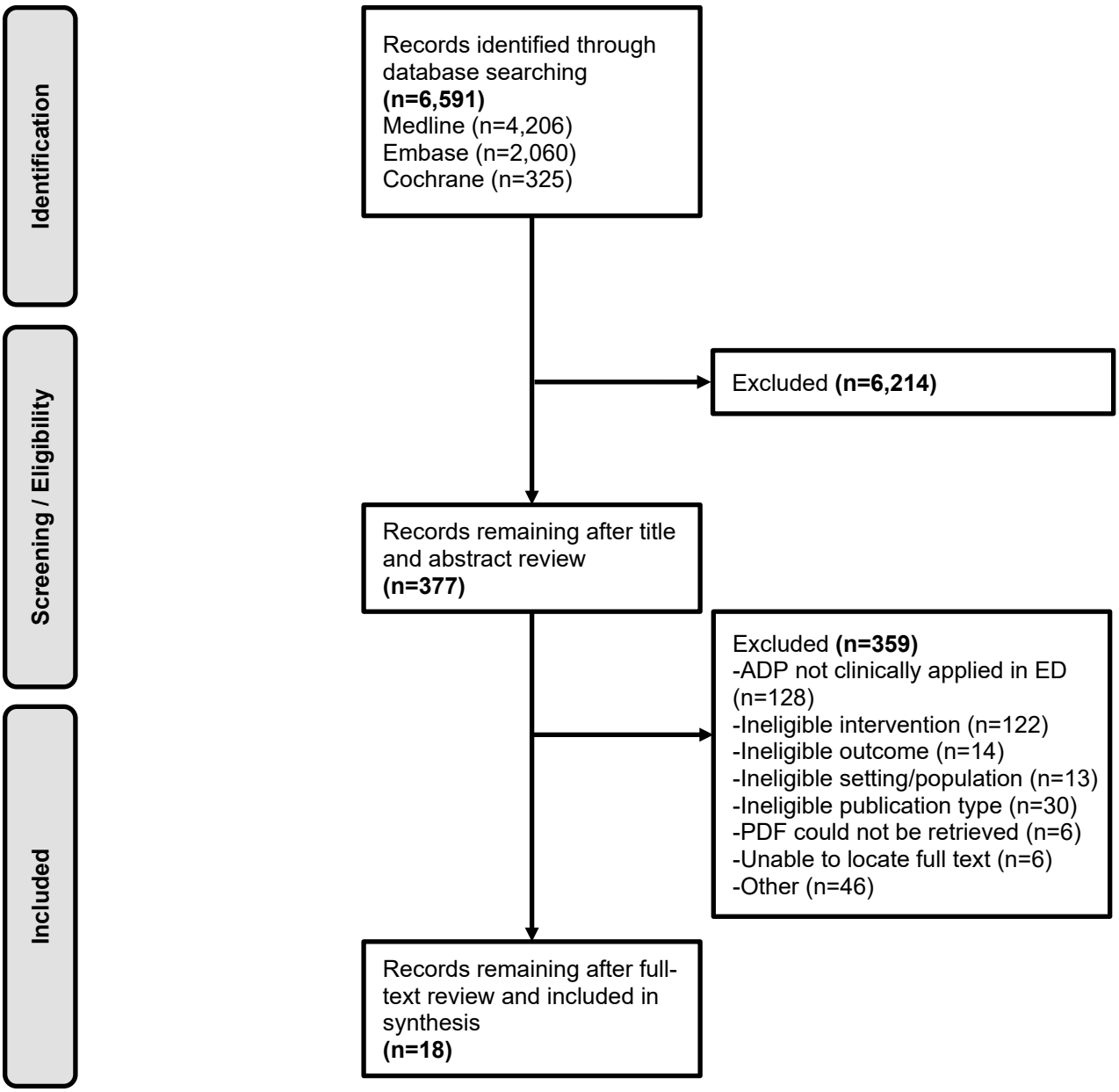
LITERATURE OVERVIEW

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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APPENDIX A. SEARCH STRATEGIES

MEDLINE

1	((((("Chest Pain"[Mesh] OR "Myocardial Ischemia"[Mesh] OR "Acute Coronary Syndrome"[Mesh] OR "Myocardial Infarction"[Mesh] OR (acute coronary syndrome*[tiab]) OR (preinfarc*[tiab] AND Angina*[tiab]) OR (pre-infarc*[tiab] AND Angina*[tiab]) OR "Unstable angina*"[tiab] OR ((heart*[tiab] OR myocardi*[tiab] OR cardiac[tiab] OR coronary[tiab]) AND (preinfarc*[tiab] OR infarc*[tiab] OR attack*[tiab] OR arrest*[tiab] OR occlusion*[tiab] OR ischemia*[tiab] OR ischaemia[tiab]) OR occlusi*[tiab]) OR MI[tiab] OR ACS[tiab] OR STEMI[tiab] OR NSTE-ACS[tiab] OR NSTEACS[tiab] OR nonSTEMI[tiab] OR NSTEMI[tiab] OR AMI[tiab] OR UAP[tiab] OR OMI[tiab] OR ((acute[tiab] OR ischem*[tiab] OR ischaem*[tiab]) AND (coronar*[tiab] OR cardiac*[tiab] OR heart[tiab])) OR ((heart[tiab] OR myocard*[tiab]) AND infarct*[tiab]))))
2	(("troponin T"[Mesh] OR "troponin I"[Mesh] OR troponin[Mesh] OR "trop I"[tiab] OR "trop t"[tiab] OR "troponin I"[tiab] OR "troponin T"[tiab] OR accu-tni[tiab] OR accutni[tiab] OR ctni-hs[tiab] OR ctni-ultra[tiab] OR ctni[tiab] OR ctnihs[tiab] OR ctnt-hs[tiab] OR ctnt[tiab] OR cTnT[tiab] OR ctnths[tiab] OR hs-ctni[tiab] OR hs-cTnT[tiab] OR hs-tni[tiab] OR hs-TnT[tiab] OR hsctni[tiab] OR hscTnT[tiab] OR Hstni[tiab] OR hsTnT[tiab] OR tni[tiab] OR tnt-hs[tiab] OR tnt[tiab] OR tnths[tiab] OR tropI[tiab] OR troponin*[tiab] OR tropT[tiab] OR "Accelerated diagnostic protocol*" OR "HEART Pathway" OR "EDACS-ADP" OR "EDACS" OR ADP)))
3	(("Emergency Service, Hospital"[Mesh] OR emergency room* OR emergency department* OR ED OR ER OR "Triage"[Mesh] OR "Emergencies"[Mesh] OR "Emergency Responders"[Mesh] OR "Emergency Treatment"[Mesh] OR "Emergency Medicine"[Mesh] OR "Emergency Medical Technicians"[Mesh] OR "Emergency Medical Services"[Mesh] OR "Ambulances"[Mesh] OR "Hospital Rapid Response Team"[Mesh] OR triage OR emergenc* OR ambulance* OR EMT OR EMS OR "Cardiology Service, Hospital"[Mesh]))))
5	#1 AND #2 AND #3
6	((((("2008/01/01"[Date - Entry] : "3000"[Date - Entry])) OR (("2008/01/01"[Date - Publication] : "3000"[Date - Publication]))) OR (("2008/01/01"[Date - Create] : "3000"[Date - Create]))))
7	AND/5-6

EMBASE

1	Heart muscle ischemia/exp OR heart muscle ischemia
2	Myocardial ischemia
3	Acute coronary syndrome
4	Heart infarction
5	Myocardial infarction
6	Unstable angina pectoris
7	Unstable angina
8	(heart* OR myocardi* OR cardiac OR coronary) AND ((preinfarc* OR infarc* OR attachk* OR arrest*or) AND occlusion* OR ischemia* OR ischaemia* OR occlusi*)
9	mi OR acs OR stemi OR ‘nste acs’ OR nsteacs. OR nonstemi OR nstemi OR ami OR uap OR omi
10	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9
11	troponin i
12	troponin t
13	trop i OR trop t OR troponin i OR troponin t OR accu tni OR accutni OR ctni hs OR ctni ultra OR ctni OR ctnihs OR ctnt hs OR ctnt OR ctnths OR hs ctni OR hs tni OR hs tnt OR hsctni OR hsctnt

	OR hstni OR hstnt OR tni OR tnt hs OR tnt OR tnths OR tropi OR troponin* OR tropt OR accelerated diagnostic protocol* OR heart pathway OR edacs-adp OR edacs OR adp
14	#11 OR #12 OR #13
15	emergency ward
16	(Emergency AND room* OR emergency) AND department* OR ed OR er OR triage OR emergenc* OR emt OR ems
17	#15 OR #16
18	#10 AND #14 AND #17
19	#10 AND #14 AND #17 AND ([article/lim OR [article in press]/lim) AND [humans]/lim AND [2008-2022-04-15]/py

COCHRANE

1	MeSh descriptor: [Chest Pain] explode all trees
2	MeSh descriptor: [Myocardial Ischemia] explode all trees
3	MeSh descriptor: [Acute Coronary Syndrome] explode all trees
4	MeSh descriptor: [Myocardial Infarction] explode all trees
5	((hear* OR myocardi* OR cardiac OR coronary) AND (preinfarc* OR infarc* OR attack* OR arrest* OR ischemia* OR ischaemia* OR occlusi*))
6	#1 OR #2 OR #3 OR #4 OR #5
7	MeSh descriptor: [Troponin I] explode all trees
8	MeSh descriptor: [Troponin T] explode all trees
9	*trop I OR trop T OR troponin I OR troponin T OR accu-tni OR accutni OR ctni-hs OR ctni-ultra OR ctnihs OR ctnt-hs OR ctnt OR cTnT OR ctnths OR hs-ctni OR hs-cTnT OR hs-tni OR hs-TnT OR hsctni OR hscTnT OR Hstni OR hsTnT OR tni OR tnt-hs OR tnt OR tnths OR tropl OR troponin* OR tropT OR Accelerated diagnostic protocol* OR HEART Pathway OR EDACS-ADP OR EDACS OR ADP
10	#7 OR #8 OR #9
11	MeSh descriptor: [Emergency Medicall Services] explode all trees
12	Triage OR emergenc* OR ambulance* OR EMT OR EMS
13	#11 OR #12
14	#6 AND #10 AND #13

APPENDIX B. EXCLUDED STUDIES

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for myocardial infarction using high-sensitivity troponin-T. *Cjem*. Sep 2020;22(5):712-720. doi:10.1017/cem.2020.349. *Not prospective.*

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score. *Am J Emerg Med*. Apr 2014;32(4):293-6. doi:10.1016/j.ajem.2013.11.043. *Not prospective.*

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APPENDIX C. CRITERIA USED IN QUALITY ASSESSMENT

Question	Yes	No	Unclear
1. Design a. Randomized control trial b. Nonrandomized comparison of interventions c. Single group			
2. Was the article free of discrepancies (eg, between text and tables)? Add note if No (High concern)?			
3. Were patient eligibility criteria sufficiently clear? Add note if No (High concern).			
4. Were the ADP (and comparator) sufficiently clear? Add note if No (High concern)			
5. Were outcomes adequately defined without problem? Add note if No (High concern). Not every outcome requires an explicit definition (*eg*, duration of ED stay).			
6. Was the setting sufficiently clearly defined? (*eg,,* do we know the hospital (and ED) type?) Add note if No (High concern).			
7. Were there missing results data for ANY patients for outcomes that occurred in ED or hospital? Were there missing results data for >20% of patients (or imbalance between study groups) for outcomes that occurred after ED/hospital discharge? Add Note if Yes			
8. Outcome assessment a. No (or inadequate) description of how final determination of MI was diagnosed [Unclear RoB] b. Independent or blind adjudication of MI for each patient by reference to secure medical records [Low RoB] c. Record linkage (eg identified through ICD codes on database records) [Moderate RoB] d. Self report (by patient or family) with no reference to original structured injury data or imaging [High RoB]			
9. If RCT, was there inadequate randomization method or allocation concealment? Whether randomization was done at the level of the ED or the patient, answer No (low RoB), unless there’s an obvious flaw.			
10. If observational study, eligible patients having ADP were all selected or a random selection was selected. No concerns about biased selection of ADP patients. Add note if No (high RoB)			
11. If observational study, comparator group (or ED) was sufficiently similar (and selected patients were all included or a random sample were included). Add note if No (high RoB)			
12. If observational study, Adjustment for confounders. a. Crude analysis (unadjusted comparison between ADP and no ADP) [High RoB] b. Regression adjustment or patient-matching (accounting for at least age, sex, and symptom duration OR a risk score) [Low RoB] c. Regression adjustment or patient-matching (not accounting at least one of for age, sex, symptom duration, or risk score) [Moderate RoB] d. Propensity score analysis (or equivalent) [Low RoB]			

APPENDIX D. QUALITY RATINGS FOR ALL ELIGIBLE STUDIES

Appendix Table D-1. Quality Rating for Comparative Studies

Author, Year, PMID	Free of Discrepancies	Eligibility Clear	ADP Clear	Outcomes Adequately Defined	Setting Clearly Defined	Missing Results	Outcome Assessment Blind / Independent	RCT	Observational study			Effect on Clinical Measures Overall	Effect on Health Service Use Measures Overall
								Adequate Randomization and Allocation Concealment	Patients Selected at Random	Comparator Group Similar	Adjustment for Confounders		
RCT													
Anand 2021 33752439 RCT	Yes (low concern)	Yes (low concern)	Yes (low concern)	Yes (low concern)	Yes (low concern)	No (low RoB)	Yes (low RoB)	Yes (low RoB)				Low RoB (RCT)	Low RoB (RCT)
Than 2016 26947800 RCT	Yes (low concern)	Yes (low concern)	Yes (low concern)	Yes (low concern)	Yes (low concern)	Yes (high RoB)	Yes (low RoB)	Yes (low RoB)				Low RoB (RCT)	Low RoB (RCT)
NRCS													
Barnes 2021 33436490 NRCS	Yes (low concern)	Yes (low concern)	Yes (low concern)	Yes (low concern)	Yes (low concern)	No (low RoB)	No or inadequate description (unclear RoB)		Yes (low RoB)	Yes (low RoB)	Yes regression adjustment (low RoB)	Medium RoB (NRCS)	Low RoB (NRCS)
Hyams 2018 29478861 NRCS	Yes (low concern)	Yes (low concern)	Yes (low concern)	Yes (low concern)	Yes (low concern)	No (low RoB)	No (moderate RoB)		Yes (low RoB)	Yes (low RoB)	Yes regression adjustment (low RoB)	Medium RoB (NRCS)	Low RoB (NRCS)
Sandeman 2021 34824100 NRCS	Yes (low concern)	Yes (low concern)	Yes (low concern)	Yes (low concern)	Yes (low concern)	No (low RoB)	Record linkage (moderate RoB)		Yes (low RoB)	Yes (low RoB)	Yes regression adjustment (low RoB)	Medium RoB (NRCS)	Low RoB (NRCS)
Stoyanov 2020 31298551 NRCS	Yes (low concern)	Yes (low concern)	Yes (low concern)	Yes (low concern)	Yes (low concern)	No (low RoB)	Yes (low RoB)		Yes (low RoB)	No (high RoB)	Yes regression adjustment (low RoB)	Medium RoB (NRCS)	Low RoB (NRCS)
Than 2021 33753972 NRCS	Yes (low concern)	Yes (low concern)	Yes (low concern)	Yes (low concern)	Yes (low concern)	No (low RoB)	No or inadequate description (unclear RoB)		Yes (low RoB)	No or inadequate description (unclear RoB)	Crude analysis (high RoB)	High RoB (NRCS)	High RoB (NRCS)

Appendix Table D-2. Quality Rating for Single Group Studies

Author, Year, PMID	Free of Discrepancies	Eligibility Clear	ADP Clear	Outcomes Adequately Defined	Setting Clearly Defined	Missing Results	Outcome Assessment Blind / Independent	RCT	Observational study			Measurement of Clinical Measures Overall	Measurement of Health Service Use Measures Overall
								Adequate Randomization and Allocation Concealment	Patients Selected at Random	Comparator Group Similar	Adjustment for Confounders		
Single Group													
Chew 2019 31478763 Lambrakis 2021 33998255 RCT (analyzed as single group)	Yes (low concern)	Yes (low concern)	Yes (low concern)	Yes (low concern)	Yes (low concern)	No (low RoB)	Yes (low RoB)		Yes (low RoB)			Low RoB (single)	Low RoB (single)
Conde 2013 23810070 NRCS (analyzed as single group)	Yes (low concern)	Yes (low concern)	Yes (low concern)	Yes (low concern)	Yes (low concern)	No (low RoB)	No or inadequate description (unclear RoB)		Yes (low RoB)			Medium RoB (single)	Low RoB (single)
Costable 2014 NA Single group	Yes (low concern)	Yes (low concern)	Yes (low concern)	Yes (low concern)	Yes (low concern	No (low RoB)	No or inadequate description (unclear RoB)		Yes (low RoB)			Medium RoB (single)	Low RoB (single)
Crowder 2015 26387473 NRCS (analyzed as single group)	Yes (low concern)	Yes (low concern)	Yes (low concern)	Yes (low concern)	Yes (low concern)	No (low RoB)	No or inadequate description (unclear RoB)		Yes (low RoB)			Low RoB (single)	Low RoB (single)
Ford 2021 33662739 NRCS (analyzed as single group)	Yes (low concern)	Yes (low concern)	Yes (low concern)	Yes (low concern)	Yes (low concern)	No (low RoB)	Record linkage (moderate RoB)		Yes (low RoB)			Medium RoB (single)	Low RoB (single)
Ljung 2019 30661856 NRCS (analyzed as single group)	Yes (low concern)	Yes (low concern)	Yes (low concern)	Yes (low concern)	Yes (low concern)	No (low RoB)	Yes (low RoB)		Yes (low RoB)			Low RoB (single)	Low RoB (single)

Author, Year, PMID	Free of Discrepancies	Eligibility Clear	ADP Clear	Outcomes Adequately Defined	Setting Clearly Defined	Missing Results	Outcome Assessment Blind / Independent	RCT	Observational study			Measurement of Clinical Measures Overall	Measurement of Health Service Use Measures Overall
								Adequate Randomization and Allocation Concealment	Patients Selected at Random	Comparator Group Similar	Adjustment for Confounders		
Suh 2022 35571147 NRCS (analyzed as single group)	Yes (low concern)	Yes (low concern)	Yes (low concern)	Yes (low concern)	Yes (Low concern)	No (low RoB)	Yes (low RoB)		Yes (low RoB)			Low RoB (single)	Low RoB (single)
Sweeney 2020 32104767 NRCS (analyzed as single group)	Yes (low concern)	Yes (low concern)	Yes (low concern)	Yes (low concern)	Yes (low concern)	No (low RoB)	No or inadequate description (unclear RoB)		Yes (low RoB)			n/a	Low RoB (single)
Twerenbold 2019 31345421 Single group	Yes (low concern)	Yes (low concern)	Yes (low concern)	Yes (low concern)	Yes (l ow concern)	No (low RoB)	Yes (low RoB)		Yes (low RoB)			Low RoB (single)	Low RoB (single)
Vigen 2020 32320036 NRCS (analyzed as single group)	Yes (low concern)	Yes (low concern)	Yes (low concern)	Yes (low concern)	Yes (low concern)	No (low RoB)	Record linkage (Moderate RoB)		Yes (low RoB)			Medium RoB (single)	Medium RoB (single)

APPENDIX E. PEER REVIEW DISPOSITION

Comment #	Reviewer #	Comment	Author Response
Are the objectives, scope, and methods for this review clearly described?			
1	1	Yes	Thank you.
2	2	Yes	Thank you.
3	3	Yes	Thank you.
4	5	Yes	Thank you.
5	6	Yes	Thank you.
6	11	Yes	Thank you.
Is there any indication of bias in our synthesis of the evidence?			
7	1	No	Thank you.
8	2	No	Thank you.
9	3	No	Thank you.
10	5	No	Thank you.
11	6	No	Thank you.
12	11	No	Thank you.
Are there any published or unpublished studies that we may have overlooked?			
13	1	Yes - references to consider are included in comments	Thank you. Please see our response to Comment #19.
14	2	No	Thank you.
15	3	No	Thank you.
16	5	No	Thank you.
17	6	No	Thank you.
18	11	No	Thank you.
Additional suggestions or comments can be provided below.			
19	1	This report from the ESP seeks to summarize current available knowledge on the topic of using high-sensitivity troponin (HSTN) assays in combination with accelerated diagnostic protocols. A variety of important clinical	Thank you.

Comment #	Reviewer #	Comment	Author Response
		comparisons are made with appropriate notation on the confidence of each comparison. The implications of adopting the findings to clinical practices could result in fewer hospital admissions without any appreciable increase in adverse cardiovascular events. The executive summary provides concise, understandable statements of key findings that should be easy for clinicians in the field to understand and adopt. The Key Questions are well reasoned and applicable to clinical care in the ED. The methods are thoroughly described and readily reproducible. Inclusion/exclusion criteria are appropriate for the intended analysis. ROBINS-I, PROSPERO, and appropriate online software options were applied. Studies are organized in a thoughtful manner based on the clinical importance of the reported outcomes. The tables supplement the text by providing greater detail in a format that is digestible to the reader, the tables also help demonstrate the heterogeneity of the literature. The limitations section adequately reflects the fact that most of the work on hstn, ADPs, and implementation has been done internationally and very little in the VA. As noted, the international work, often done in countries with integrated health care systems, may actually have good overlap with the VA due to similar infrastructures. The authors identify one of the more important gaps in the literature as being the documentation of best practices for implementation. The authors express optimism in what the widespread adoption of HSTN/ADP could mean for the VA, but acknowledge that local practices groups are often difficult to convince into a change in practice.	

Comment #	Reviewer #	Comment	Author Response
		If the authors wish to expand on the discussion about implementation, some references to consider are (PMIDs): 36328155, 35604774, 34224384 And the following description of implementation in a VAMC: https://vpjournal.net/article/view/3867	Thank you. The Discussion now comments on the potential implementation challenges associated with hs-cTn in the US and VA. Per the suggested references, we highlight the experience of one large VA’s transition to hs-cTn.
20	2	Thorough	Thank you.
21	3	I appreciate the authors’ thoroughness and skill in navigating a challenging set of evidence on an important topic that is highly relevant to an emergency department clinical scenario that is common, costly, and will benefit from this synthesis. I think the manuscript could be improved in a few areas, primarily around the framing of some of the discussion points.	Thank you.
		Major - Title: Need to include some reference to “emergency department” in the title given the focus of the literature review was restricted to that care setting.	We revised the title to reference the Emergency Department.
		- Discussion: Generally agree with statement that given the state of available evidence regarding ADPs that individual EDs should have freedom to create their own approach (page 5, line 8; page 38, line 9). However, I think it is important to caveat that this should still be based on the available evidence. The way this is currently worded, it implies that there are no limits, when, in fact, it should be about adopting and adapting what is supported by the evidence (risk tools, troponin timing, etc) to their local requirements. I think this should be the overall message and main take-home points from the evidence review: (1) importance of standardizing practice to avoid overuse of health services and testing; but, (2) no clear and obvious best in choice from the evidence; with (3) support for a variety of approaches; therefore, (4) importance of factoring in local structural needs and preferences in adopting a tailored but still standardized approach.	We agree that EDs should implement evidence-based ADPs, and we do not want to give the impression that there are no limits. We revised the Discussion and Conclusion to note the importance of adopting evidence-based interventions and EDs may need to tailor an evidence-based ADP to fit within their local context. We also revised the Discussion and Conclusions to highlight the helpful key messages proposed by the reviewer.

Comment #	Reviewer #	Comment	Author Response
		- Discussion: Really liked the last paragraph under “Implications for VA Policy” (page 6, lines 6-16). These are excellent points and describes many of the features of an integrated health system that could be leveraged and are ripe for adopting and standardizing into routine practice. This approach seems like a natural and obvious next step in implementing this evidence synthesis. Recognize the focus of this review was not on implementation, but still wondering if there is a way to elevate this point within the manuscript?—could it even go in the Executive Summary?	We revised the Discussion to provide additional context on potential implementation challenges (see response to Comment 19, Reviewer 1). The Discussion now highlights the experience of one large VA during their transition to hs-cTn. We also revised the Executive Summary to elevate the importance of implementation.
		Minor - Introduction: In general, probably better to use a more general term than “ED physicians” when referencing providers who may be drawing on this evidence for incorporation in ED care (page 2, line 18). For example, there are increasingly advance practice providers (PAs, NPs) being used in this role. Options could include “ED provider” or “ED clinicians”—I tend to lean toward the latter in my work.	Thank you. We revised the text to be more inclusive in our definition of individuals who provide care in an ED setting.
		- Results: When introducing ADPs, I think worth referencing the table on clinical risk tools (Appendix C, page 93) that summarizes those evaluated in this evidence review (page 3, lines 12). Given ADPs are the major focus of this review, readers will quickly want to understand which chest pain risk scores (beyond just the abbreviations) were being evaluated and the references for these.	The text referenced by the reviewer is in the Executive Summary. Per ESP style, we do reference appendices in the Executive Summary.
		- Discussion: “administers” should be “administrators” (page 5, line 6)	Thank you.
		- Discussion: Definitely a minor point, but I don’t agree with this statement: “Studies, and by extension ADPs,	The intent of our comment was for the need for standardized language in the literature. We clarified the

Comment #	Reviewer #	Comment	Author Response
		should categorize patients as rule-in, rule-out, grey zone rule-out and grey zone rule-in and avoid terms that do not correspond to clinical diagnosis (e.g., low risk, discharge) which only muddy interpretation of results” (page 6, lines 33-36). Agree with need to approach with a standard language, but disagree with need to correspond these to categories of clinical diagnoses. That later approach is not consistent with how emergency providers approach these clinical scenario—their heuristic is more consistent with the process of stratifying patients into categories of risk rather than arriving at definitive diagnoses. Even if a patient is “ruled-out” for acute MI in that moment, most emergency providers would still consider that patient to be in a low risk category because their heuristic is simultaneously both excluding MI and also assessing the patient’s risk for having MACE within the short term (studies usually assess this to be a 4-6 week horizon).	text to note terms like low or high risk should be clearly defined.
		- Limitations: Agree with the point regarding effect rather than implementation. Also seems this section should reinforce some of the limitations noted throughout the rest of the manuscript: heterogeneity of studies with respect to populations, locations, methods, outcomes, etc.	The objective of the Limitations section is to describe the limitations of the review (e.g., methods or focus) and not the limitations identified literature. As noted, we describe in other sections the limitations of the scientific literature.
22	5	Congratulations on an amazing job of organizing this complicated report in a clinically meaningful way. Despite the lack of clarity within the literature on defining ADP’s the criteria used in the quality assessment distilled the studies to a more manageable number for the readers to digest. There is enough confidence in the ADPs to answer meaningful questions as well as highlight area where further studies are needed. Although no “best protocol” for ADP plus hs-TN with low MACE risk stood out, this report provides a foundation which will help subsequent pilots and research to narrow the scope of questions that will provide meaningful clinical answers for the VA. This work will save a lot of time for groups that wish to use this report for future meta-analysis	Thank you.

Comment #	Reviewer #	Comment	Author Response
		when more studies are completed. I appreciate the complexity and the challenge that it took to create, distill, and synthesize this data. The information is descriptive which adds to its length which appears to be necessary to provide adequate understanding of the protocols as medical definitions and terminology variability was notable. The inconsistent descriptions proved to be difficult to combine studies in a typical meta-analytic approach. It provides information on which source trials are most informative. A reader can find relevant information pertinent to their interest in the tables (Table 3. Description of Accelerated Diagnostic Protocol on pg 22) that categorize the accelerated diagnostic protocol with the more descriptive information in the body of the report. The prioritization presents the more important data of MACE, LOS, admit status and ED revisits as well as cardiac testing and revascularization. Overall, the report does not have enough comparable data to support new VA protocols and highlights the need for further investigation to attempt to single out an ADP + hs TN with low risk for the VA emergency Departments. As there are not uniformity in terms and uniformity in ADPs to supply comparable data, the report supplies the data needed for the additional work required. If future studies present similar metrics and comparable ADPs, even underpowered studies could be combined though the cumulative reporting to gain power across studies. As noted in the Research Gaps/Future Research on page 6, it will continue to be 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. On page 3, last paragraph is meaningful as direct comparisons of shorter vs longer duration ADPS as noted with a moderate confidence, the studies reported “no	

Comment #	Reviewer #	Comment	Author Response
		evidence of difference between shorter and longer duration ADPs in 30 day MACE (RD – 0.1%, 95% CI – 0.2 – 0.03) or 30 day MI (RD – 0.1%, 95% CI – 0.2 to 0.01), but shorter ADPs probably reduce ED length of stay (by 2 to 4 hours in each study, mostly reporting as statistically significant and probably increase discharge to the community from the ED (in two studies, by either 3% or 21% both statistically significant)”. Summarizing across different ADPs studies using common risk scores adds meaningful information that the 01 vs 03 vs 06 appears not to make a difference in outcomes. This supports the metric concerns of ED LOS does not impact negatively on quality of care and may actually improve quality by reducing crowding and provides supports to narrow future studies to use ADPs with 02 or possibly 01 analysis.	
		Page 15 Synthesis and Certainty of evidence fourth paragraph, it would be important to comment that CIs can be used in place of P values to test hypotheses, so studies using CIs in place of p values is using statistics correctly. In Appendix Table J-5 in Appendix F, if a confidence interval (CI) is reported statistical significance can be inferred.	Thank you. We edited for clarity and revised the text that describes the method for conducting synthesis & certainty of evidence. Edits also included removing language around the specific GRADE domains (e.g., precision and the role of p-values / 95% CI) and instead we reference the interested reader to the relevant GRADE publication (ref 22).
		This sentence it the last paragraph is unclear: “In both studies, the novel ADP was associated with a significantly shorter length of stay (mean [SD] High-STEACS 0/3 ADP 6.8 [4.1] vs. 0/6/12 ADP 10 [4.1]; p<0.001;21 and median [inter quartile range] 0/3/6 ADP 6.5 [6.3 to 19.8] vs. 0/6/12 GRACE ADP 8.9 [3.7 to 38]; p<0.001); Appendix Table K-1).” The p values suggest the medians are different in the two groups, but when you look at the IQR they do not seem that different. So maybe the p values are testing each median? Perhaps comment on the lack of clarity? How were these p values interpreted?	We revised the sentence to clarify the findings.
		In Appendix Table K-6 pg 102, I’m not sure what the p values are testing. What is the “Beta” parameter in the MD	We revised the Appendix table to clarify the interpretation of the beta coefficient. Specifically, the coefficient is the

Comment #	Reviewer #	Comment	Author Response
		(95% CI) column. In appendix table K-6 should it note what the parameters are for column MD (95% CI) and what is the P value testing in the column Reported P value?	association of the novel ADP compared to standard ADP and the outcome is log-transformed duration of stay. The coefficient is adjusted by age, sex, diabetes, creatinine, and history of MI, heart failure or cerebrovascular disease. For example, the coefficient -0.0135 is interpreted as the novel ADP results in a -1.34% reduction in ED length of stay.
		Page 36 minor spelling error on mortality as “morality” in paragraph three and disposition as “disposotion” in paragraph four.	Thank you.
23	6	This was a very much needed report, at the least to describe the current state of literature and evidence for clinical use of hs-cTn in risk-stratifying chest pain.	Thank you.
24	11	This is an excellent synthesis of review on the topic of use of HsTn in the clinical evaluation of patients. It fairly summarizes the literature on this topic, which is indeed a bit over-interpreted by the field. The suggestions for further study and for VA implications are fair and in line with what is actually published on the subject.	Thank you.
		My only suggestion is to add one element in the Discussion sections. There is little to no discussion in the review on the natural variation between hsTroponin I and hsTroponin T. TnT is only marketed by Roche, but we have a lot of Roche labs in the VA system (and thus will have both markers in use in VA longitudinally). The two troponin markers are not exactly the same and cannot necessarily be protocolized interchangeably. A note to this effect in the discussion is likely sufficient at this juncture, as I'm not aware of any literature that addresses the impact of marker variation on the specifics of protocol synthesis and validation. Bottom-line: Any VA-wide protocols or studies will need to account for the inherent differences between these two markers.	Thank you. We revised the Discussion to comment that troponin I and T are not interchangeable. Any ED that aims to implement a protocol will need to account for these inherit differences.

APPENDIX F. DESIGN DETAILS

Author, Year, PMID, Cohort Name, Protocol Number, Country, Funder	Study Design	Study Dates	Study Location Details	Inclusion Criteria	Exclusion Criteria
Anand 2021 33752439 *HiSTORIC* NCT03005158 Scotland Non-industry	RCT	2014-16	Multiple EDs	Sites able to implement rule-out pathway and submitted data to national registry. ED or acute medical patients with suspected ACS and a hs-cTnI < sex-specific 99th percentile url	STEMI, out-of-hospital cardiac arrest, admitted previously during the trial
Barnes 2021 33436490 *STAT-Chest Pain* ACTRN12618000797279 Australia Non-industry	Pre-Post comparison	2018-19	Single ED	ED patients with potential ACS, ≥18 yo	STEMI, myocardial revascularization within the preceding 6 mo, admission to hospital for other reasons, a clear non-cardiac cause of the symptoms, or prior enrolment in the study
Chew 2019 31478763 **Lambrakis 2021** 33998255 *RAPID-TnT* ACTRN12615001379505 Australia Industry and non-industry	RCT [analyzed as single group]	2015-2019	Multiple EDs	Chest pain or suspected ACS as the principal cause for investigation and a baseline ECG interpreted as not definitive for coronary ischemia, ≥18 yo, intention to undertake troponin testing, willing to give written consent	STEMI, comorbidity that precludes completing the clinical history questionnaire, non-cardiac chest pain, transfer from another hospital, presented for suspected ACS within 30 days of last presentation, required permanent dialysis
Conde 2013 23810070 NA Argentina NR	Pre-post comparison [analyzed as single group]	2011-2012	Single ED	ED patients with probable ACS, >18 yo	Unstable angina or MI without STEMI, angina equivalent.

Author, Year, PMID, Cohort Name, Protocol Number, Country, Funder	Study Design	Study Dates	Study Location Details	Inclusion Criteria	Exclusion Criteria
Costable 2014 NA Argentina NR	Single group	2013	Single ED	ED patients with suspected ACS and who were evaluated according to the chest pain unit protocol, > 18 yo.	STEMI, non-cardiac chest pain, admission indicated by another physician, transfer of patient due to lack of beds, patient refusal to stay for observation, impossibility of follow-up
Crowder 2015 26387473 NR NR Canada NR	Pre-post comparison [analyzed as single group]	2011-2012	Multiple EDs	Patients with chest pain or potential ACS and who had a troponin assay performed during the study periods.	STEMI
Ford 2021 33662739 NR NR US None	Pre-post comparison [analyzed as single group]	2017-2018	Single ED	ED patients with a chief complaint of chest pain, ≥ 18 yo.	NR
Hyams 2018 29478861 NR NR US NR	Pre-post comparison	2014-2016	Single ED	ED patients with a chief complaint of ‘‘chest pain,’’ ‘‘chest tightness,’’ or ‘‘chest pressure, >18 yo	STEMI, patients with nonpainful ACS presentations such as shortness of breath unless accompanied by symptoms related to chest discomfort. Patients without a documented follow-up at least 6 wks after the ED visit, without adequate information (such as ECG or troponin) documented in their electronic medical record to calculate a HEART score

Author, Year, PMID, Cohort Name, Protocol Number, Country, Funder	Study Design	Study Dates	Study Location Details	Inclusion Criteria	Exclusion Criteria
Ljung 2019 30661856 *FASTEST* NR Sweden Industry and non-industry	Pre-post comparison [analyzed as single group]	2013-2016	Multiple EDs	Chest pain suggestive of ACS with a duration ≥10 minutes and an onset of last episode ≤12 hours. ≥18 yo, willing to have blood samples taken according to the study protocol, a signed written informed consent in Swedish	STEMI, new left bundle branch block on ECG at presentation or previous participation in the study
Sandeman 2021 34824100 NR NR Scotland Industry and non-industry	Pre-post comparison	2014-2017	Single ED	Patients with suspected ACS presenting to a secondary care hospital, all patients who had an hs-cTnT measurement on presentation to hospital since the introduction of the assay	STEMI, patient were not residents in Scotland, had a previous presentation during the study period
Stoyanov 2020 31298551 *RAPID-CPU* NCT03111862 Germany Industry	Pre-post comparison	2016-2017	Single ED	Initial presentation of clinically suspected ACS (based on a broad spectrum of symptoms including atypical symptoms and dyspnea)	STEMI, patients on chronic haemodialysis, repeated presentations beyond the index admission ('frequent flyer'); patients referred from other hospitals for early or primary PCI without receiving a standard diagnostic work-up; diagnostic set of hsTnT samples not available (*eg*, missing initial or consecutive blood sample). Patients with atrioventricular nodal re-entrant tachycardia. Inappropriate command of the English/German language or permanent residence in a foreign country.
Suh 2022 35571147 NR NCT03590535 US Industry	Pre-post comparison [analyzed as single group]	2018-2020	Single ED	Patients with ACS and received troponin testing as part of their evaluation, ≥19 yo	STEMI, pre-heart transplant, without capacity to consent, left ventricular assist device, who were presenting after a cardiac arrest, lacked fluency in either English or Spanish, or were

Author, Year, PMID, Cohort Name, Protocol Number, Country, Funder	Study Design	Study Dates	Study Location Details	Inclusion Criteria	Exclusion Criteria
					otherwise unable to participate in telephone follow-up
Sweeney 2020 32104767 NR NR UK NR	Pre-post comparison [analyzed as single group]	2015-2018	Multiple EDs	ED patients with a triage diagnosis of chest pain	NR
Than 2021 33753972 NR NR New Zealand NR	QIP and Pre-post comparison	2020-2020	Single ED	Patients presenting with symptoms of chest pain and symptoms of MI, ≥18 yo	STEMI, <18 yo, a clear cause of symptoms other than MI; transfer from another hospital; pregnancy; unable to be followed-up; or staff considered recruitment inappropriate (*eg,* receiving palliative care), unable or unwilling to consent
Than 2016 26947800 NR ACTRN126130007457 41 New Zealand Non-industry	RCT	2013-2014	Single ED	Possible cardiac symptoms suggestive of MI and for which serial cTn analysis were performed, ≥18 yo	STEMI, noncoronary pathology of symptoms; transfer from another hospital; pregnancy; unable to be followed-up; or staff considered recruitment inappropriate (*eg,* receiving palliative care); need for admission because of other medical conditions regardless of a negative cTn result; previously enrolled in this study; unable to consent.
Twerenbold 2019 31345421 NR NR Switzerland, Argentina Industry and non-industry	Single group	2015-2017	Multiple EDs	Adult ED patients with symptoms suggestive of MI	STEMI

Author, Year, PMID, Cohort Name, Protocol Number, Country, Funder	Study Design	Study Dates	Study Location Details	Inclusion Criteria	Exclusion Criteria
Vigen 2020 32320036 NR NR US Non-industry	Pre-post comparison, [analyzed as single group]	2017-2018	Single ED	Patients had both ECG and troponin testing obtained within 3 hr of arrival and prior to the disposition decision, did not undergo hemodialysis in the ED.	Patients undergoing emergent hemodialysis, testing was done on an outpatient basis or in day surgery, missing values for time from cTn draw to disposition time, disposition decision time was recorded prior to a cTn draw time, redundant encounters.

APPENDIX G. SUMMARY OF RISK SCORES

Risk Score [Key Reference]	Items
HEART (History, Electrocardiogram, Age, Risk factors, Troponin), [Hyams 2018 29478861]	• History • Electrocardiogram • Age • Risk factors • Troponin Each item is scored 0, 1, or 2. High risk = 7-10; Medium risk = 4-6; Low risk = 0-3
TIMI (Thrombolysis in Myocardial Infarction), [Than 2016 26947800]	• Age ≥65 y • Coronary artery disease (CAD) risk factor ≥3 (family history of premature coronary artery disease (CAD), dyslipidemia, diabetes, hypertension, current smoker) • Known coronary artery disease (CAD) (stenosis ≥50%) • Acetylsalicylic acid/aspirin use in the last 7 days • Recent severe angina (*eg*, ≥2 events in last 24 h) Each item is score 0 or 1. Not low risk ≥1; Low risk = 0
EDACS (the Emergency Department Assessment of Chest Pain Score), [Than 2016 26947800]	• Age (classified by predefined age ranges: ≤30, 30-39, 40-49, 50-59, 60-69, 70-79, 80-89, ≥90); scored 2-20 [even numbers only]; • If age 18-50 ys then coronary artery disease event (CAD) or coronary artery disease risk factors; scored 3, 4 or 5 • Symptoms (diaphoresis, pain radiates to arm or shoulder, pain occurs or worsened with inspiration, pain reproduced by palpation); scored 3, 5, -4, or -6. • Male; scored 6 Not low risk ≥16; Low risk <16
GRACE (Global Registry of Acute Coronary Events), [Fox 2006 17032691]	• Killip class (4 classes: I, II, III, IV); scored 0, 20, 39, or 59 • SBP mm Hg; scored 58, 53, 43, 34, 24, 10, 0 • Heart rate beats/min; scored 0, 3, 9, 15, 24, 38, or 46 • Age; scored 0, 8, 25, 41, 58, 75, 91, or 100 • Creatinine level mg/dL; scored 1, 4, 7, 10, 13, 21, or 28 • Cardiac arrest at admission; scored 39 • ST-segment deviation; scored 28

	• Elevated cardiac enzyme levels; scored 14 High risk >140; intermediate risk 109-140; low risk <109.

APPENDIX H. SUMMARY OF HS-CTN

Author, Year, PMID	Arm	Test Manufacturer & Name	Troponin Var (I or T)	Limit of Detection	99th Percentile
Anand 2021 33752439	Early rule-out pathway (High-STEACS): High-STEACS ADP 0/3	Abbott Architect STAT	hs-cTnI	NR	Women; 16 ng/L; Men; 34 ng/L
	Standard rule-out pathway: ADP 0/6/12			Same	
Barnes 2021 33436490	Single Troponin Accelerated Triage (STAT)-Chest Pain: STAT ADP 0/2/6 HEART	Abbott Architect	hs-cTnI	1.2 ng/L (reported as <2 ng/L)	Women upper limit of normal; <16 ng/L; Men upper limit of normal; <26 ng/L
	Standard pathway: ADP 0/(2 or 3)/6 TIMI			Same	
Chew 2019 31478763 Lambrakis 2021 33998255	ADP 0/1	5th generation Roche Elecys	hs-cTnT	5 ng/L	14 ng/L
	ADP 0/3 [arm excluded from analysis due to hs-cTnT being blinded]			Same	
Conde 2013 23810070	Post-implementation: ADP 0/3	NR	hs-cTnT	NR	NR
	Pre-implementation [arm excluded from analysis due to standard troponin]	4th generation troponin	cTnT	NR	NR
Costable 2014	hs-cTn Chest Pain Protocol: ADP 0/3	NR	hs-cTnT	NR	NR
Crowder 2015 26387473	Post-implementation: ADP 0/2-4	Roche	hs-cTnT	NR	14 ng/L
	Pre-implementation [arm excluded from analysis due to standard troponin]	4th generation Roche	cTnT	NR	NR
	Historical control [arm excluded from analysis due to standard troponin]	NA	NA	NA	NA
Ford 2021 33662739	Post-implementation: ADP 0/1/3 HEART	5th generation Roche	hs-cTnT	NR	19 ng/L
	Pre-implementation [arm excluded from analysis due to standard troponin]	TnI-Ultra Siemens	cTnI	NR	40 ng/L

Author, Year, PMID	Arm	Test Manufacturer & Name	Troponin Var (I or T)	Limit of Detection	99th Percentile
Hyams 2018 29478861	HEART Pathway Post-implementation: ADP 0/3 HEART	Roche	hs-TnT	NR	NR
	Pre-implementation hs-cTn alone			Same	
Ljung 2019 30661856	Post-implementation: ADP 0/1 HEART	Roche and Abbott	hs-cTnT, hs-cTnI	Roche; 5 ng/L; Abbott; 1.2-1.9 ng/L	Roche; 14 ng/L; Abbott; Women; 15.6 ng/L; Abbott; Men; 34.2 ng/L
	Pre-implementation [arm excluded from analysis due to standard troponin]	Roche, Abbott, Siemens-Stratus	hs-cTnT, hs-cTnI, cTn	Roche; 5 ng/L; Abbott; 1.2-1.9 ng/L; Siemens-Stratus; 30 ng/L	Roche; 14 ng/L; Abbott; Women; 15.6 ng/L; Abbott; Men; 34.2 ng/L; Stratus; 70 ng/L
Sandeman 2021 34824100	Post-implementation: ADP 0/3/6	Roche Cobas e602 platform	hs-TnT	3 ng/L	14 ng/L
	Pre-implementation: ADP 0/6/12 GRACE			Same	
Stoyanov 2020 31298551	ESC 0/1 Post-implementation: ADP ESC 0/1	Roche Cobas e411	hs-TnT	5 ng/L	NR
	ESC 0/3 Pre-implementation: ADP ESC 0//3			Same	
Suh 2022 35571147	Post-implementation: ADP 0/1 mHEART	5th generation Roche Elecsys	hs-TnT	6 ng/L	Women; 14 ng/L; Men; 22 ng/L (the US (FDA)-approved sex-specific 99th percentile values)
	Pre-implementation [arm excluded from analysis due to standard troponin]	Abbott i-STAT and 4th generation Roche	POC cTnI or cTnT	NR	NR
Sweeney 2020 32104767	Post-implementation chest pain algorithm: ADP 0/3 TIMI & GRACE	Abbott Architect STAT cTnI	hs-cTnI	NR	NR
	Pre-implementation [arm excluded from analysis due to standard troponin]	NR	cTn	NR	NR
Than 2021 33753972	COVID-ADP: COVID-ADP 0/2 EDACS	Abbott Architect i2000	hs-TnI	1.9 ng/L	Women; 16 ng/L; Men; 34 ng/L; Overall; 26 ng/L
	EDACS: ADP 0/2/6 EDACS			Same	
	EDACS-ADP: ADP 0/2 EDACS	Abbot Architect	hs-cTnI	NR	Women; 16 ng/L; Men; 34 ng/L

Author, Year, PMID	Arm	Test Manufacturer & Name	Troponin Var (I or T)	Limit of Detection	99th Percentile
Than 2016 26947800	ADAPT-ADP: ADP 0/2 TIMI			Same	
Twerenbold 2019 31345421	ADP ESC 0/1	Roche Elecsys 2010	hs-cTnT	5 ng/L	14 ng/L
Vigen 2020 32320036	Post-implementation: ADP 0/1/3 mHEART	NR	hs-cTnT	NR	NR
	Pre-implementation [arm excluded from analysis due to standard troponin]	4th generation Roche	cTnT	0.01 ng/L	NR

APPENDIX I. BASELINES

Author, Year, PMID	N Enrolled	Race/Ethnicity, %	Age, Mean (SD) or %	Male, %	History of CVD, %	CVD Risk Factors, %
Anand 2021 33752439	31492	NR	59 (17)	55%	Prior MI; 8% Prior revascularization; 10.4% History CVD; NR Stroke/TIA; NR PAD; NR MI 30 days: 0.3%	Hypertension; NR Diabetes; 6% Smoking; NR BMI; NR FHx; NR Hyperlipidemia; NR
Barnes 2021 33436490	2255	NR	54 (17)	53%	Prior MI; 10% Prior revascularization; 10% History CVD; NR Stroke/TIA; 4% PAD; 2% MI 30 days: 0.0%	Hypertension; 35% Diabetes; 14% Smoker, current; 19% BMI; 13% FHx CAD; 9% Hyperlipidemia; 29%
Chew 2019 31478763 Lambrakis 2021 33998255	1646	NR	Median (IQR) 58.7 (48.6,69.4)	53.2%	Prior MI; 10.3% Prior revascularization; 10.4% Stroke/TIA; 3.2% History CVD; 27.8% PAD; NR MI 30 days: 1%	Hypertension; 19.7% Diabetes; 15.8% Smoking; 34.6% BMI; NR FHx; 61.2% Hyperlipidemia; 43.3%
Conde 2013 23810070	300	NR	65	51%	Prior MI; 1% Prior revascularization; 23% History CVD; 3% Stroke/TIA; NR PAD; NR MI 30 days: NR	Hypertension; 58% Diabetes; 15% Smoking; 50% BMI; NR FHx; NR Hyperlipidemia; 64%
Costable 2014	528	NR	58 (13)	58%	Prior MI; 8% Prior revascularization; 16.8% History CVD; 3.6% Stroke/TIA; NR PAD; NR MI 30 days: 6.3%	Hypertension; 38% Diabetes; 12% Smoking; 39% BMI; NR FHx; NR Hyperlipidemia; 45%

Author, Year, PMID	N Enrolled	Race/Ethnicity, %	Age, Mean (SD) or %	Male, %	History of CVD, %	CVD Risk Factors, %
Crowder 2015 26387473	5754	NR	61.4	49.9%	Prior MI; NR Prior revascularization; NR History CVD; NR Stroke/TIA; NR PAD; NR MI 30 days: NR	Hypertension; NR Diabetes; NR Smoking; NR BMI; NR FHx; NR Hyperlipidemia; NR
Ford 2021 33662739	1616	NR	Median (IQR) 55 (41, 66)	51%	Prior MI; NR Prior revascularization; NR History CVD; NR Stroke/TIA; NR PAD; NR MI 30 days: NR	Hypertension; NR Diabetes; NR Smoking; NR BMI; NR FHx; NR Hyperlipidemia; NR
Hyams 2018 29478861	866	NR	54.7	50.1%	Prior MI; 11.8% Prior revascularization; 15.4% History CVD; NR Stroke/TIA; 2.2% PAD; NR MI 6 weeks: 4.8%	Hypertension; 50.5% Diabetes;22.5% Smoking; 22.6% BMI; 46.4% FHx; 31.3% Hyperlipidemia; 32%
Ljung 2019 30661856	621	NR	63 (53, 71)	54%	Prior MI; 19% Prior revascularization; 19% History CVD; 21% Stroke/TIA; 8% PAD; 2% MI 30 days: 0.5%	Hypertension; 43% Diabetes; 12% Smoking; 52% BMI (≥ 30 kg/m2); 19% FHx; 29% Hyperlipidemia; NR
Sandeman 2021 34824100	10315	NR	63.6 (16.4)	54%	Prior MI; 6.4% Prior revascularization; NR History CVD; 4.2% Stroke/TIA; NR PAD; NR MI 30 days: NR	Hypertension; NR Diabetes; 17.7% Smoking; NR BMI; NR FHx; NR Hyperlipidemia; NR
Stoyanov 2020 31298551	2525	NR	62 (18)	58%	Prior MI; 17% Prior revascularization; 6.6% History CVD; NR	Hypertension; 65.4% Diabetes; 21.2% Smoking; 21.8%

Author, Year, PMID	N Enrolled	Race/Ethnicity, %	Age, Mean (SD) or %	Male, %	History of CVD, %	CVD Risk Factors, %
					Stroke/TIA; NR PAD; NR MI 30 days: NR	BMI; NR FHx; 26.3% Hyperlipidemia; 44.9%
Suh 2022 35571147	821	White (Non-Hispanic) 13.4% Black 25.5% Hispanic/Latino 60.4% Asian (Any) 2.6% Other1 53.7% Other2 1.1%	60.4 (15.9)	45.6%	Prior MI; NR Prior revascularization; NR History CVD; 25.9% Stroke/TIA; NR PAD; 32.9% MI 30 days: 2.6%	Hypertension; 68.6% Diabetes; 36.2% Smoking; 11.2% BMI; 41.2% FHx; 15.4% Hyperlipidemia; 44.7%
Sweeney 2020 32104767	15882	NR	49.9 (14.2)	NR	Prior MI; NR Prior revascularization; NR History CVD; NR Stroke/TIA; NR PAD; NR MI 30 days: NR	Hypertension; NR Diabetes; NR Smoking; NR BMI; NR FHx; NR Hyperlipidemia; NR
Than 2021 33753972	2416	White 72.2% Other1 Pacific 0.9% Other2 New Zealand Maori 3.5% Other3 11.1%	63 (13)	61.8%	Prior MI; NR Prior revascularization; NR History CVD; 35.3% Stroke/TIA; NR PAD; NR MI 30 days: NR	Hypertension; 55% Diabetes; 15% Smoking; 15.2% BMI; NR FHx; 54.3% Hyperlipidemia; 55.6%
Than 2016 26947800	558	Asian (Any) 2.5% Other1 Maori; 3.8% Other2 Pacific Islander; 1.6% Other3 (New Zealand European +	58.7 (11.9)	60.9%	Prior MI; 23.3% Prior revascularization; 27.4% History CVD; NR Stroke/TIA; 5.9% PAD; 5.7% MI 30 days: NR	Hypertension; 52% Diabetes; 14% Smoking; 15.1% BMI; NR FHx; 35.7% Hyperlipidemia; 50.9%

Author, Year, PMID	N Enrolled	Race/Ethnicity, %	Age, Mean (SD) or %	Male, %	History of CVD, %	CVD Risk Factors, %
		Other European); 84.0%				
Twerenbold 2019 31345421	2296	NR	Median 60	64%	Prior MI; 17% Prior revascularization; 30% History CVD; 29% Stroke/TIA; 2% PAD; 3% MI 30 days: 9.9%	Hypertension; 51% Diabetes; 13% Smoking; 19% BMI; NR FHx; 16% Hyperlipidemia; 41%
Vigen 2020 32320036	14552	White 55% Black 41.9% Hispanic/Latino 38.2% Non-Hispanic 61.8% Other1 3%	54.2 (14.6)	53%	Prior MI; NR Prior revascularization; NR History CVD; NR Stroke/TIA; NR PAD; NR MI 30 days: NR	Hypertension; NR Diabetes; NR Smoking; NR BMI; NR FHx; NR Hyperlipidemia; NR

Abbreviations. BMI=body mass index; CVD=cardiovascular disease; FHx=family history; IQR=interquartile range; MI=myocadiac infarction; N=sample size; NR=not reported; PAD=peripheral arterial disease; PMID=PubMed identifier; SD=standard deviation; TIA=transient ischemic attack.

APPENDIX J. MACE OUTCOMES

Appendix Table J-1. MACE Comparative Studies

Study PMID, Study	Follow-up Time (days)	Outcome Definition	Subgroup	Arm	n/N (%)	OR (95% CI)*	Reported P value
Overall Comparison: ADP vs hs-cTn without ADP							
Hyams 2018 29478861	6 wk	Mortality, nonfatal MI, revascularization		ADP 0/3 HEART	25/449 (5.6)	0.73 (0.42,1.24) RD -1.8 (-5.1, 1.5)*	NR
				Hs-cTn	31/417 (7.4)		
Overall Comparison: ADP vs ADP							
Anand 2021 33752439	30	MI (type 1/4b/4c) or cardiac death		High-STEACS ADP 0/3	56/16792 (0.3)	0.86 (0.59, 1.24) RD -0.1 (-0.2, 0.03)*	0.068
				ADP 0/6/12	57/14700 (0.4)		
Anand 2021 33752439	30	MI (type 1/2/4b/4c) or cardiac death		High-STEACS ADP 0/3	68/16792 (0.4)	0.84 (0.60, 1.17)* RD -0.1 (-0.2, 0.05)*	NR
				ADP 0/6/12	71/14700 (0.5)		
Than 2016 26947800	30	Death, cardiac arrest, emergency revascularization, cardiogenic shock, ventricular arrhythmia needing intervention, high-degree atrioventricular block needing intervention, and MI		ADP 0/2 EDACS	2/279 (0.7) (all events occurred in non-low risk patients)	RD 0.3 (-0.9, 1.5)*	NR
				ADPAT ADP 0/2 TIMI	1/279 (0.4) (all events occurred in non-low risk patients)		
Subgroup Comparison							
Hyams 2018 29478861	6 wk	Mortality, nonfatal MI, revascularization	HEART score ≤3	ADP 0/3 HEART	0/denominator NR (0)		NR
				Hs-cTn	0/denominator NR (0)		

Study PMID, Study	Follow-up Time (days)	Outcome Definition	Subgroup	Arm	n/N (%)	OR (95% CI)*	Reported P value
Than 2016 26947800	30	Death, cardiac arrest, emergency revascularization, cardiogenic shock, ventricular arrhythmia needing intervention, high-degree atrioventricular block needing intervention, and MI	Low risk patients	ADP 0/2 EDACS	0/116 (0)		NR
				ADAPT ADP 0/2 TIMI	0/85 (0)		
Twerenbold 2019 31345421	30	Cardiovascular death and MI	CP ≤3h and rule-out group	ADP ESC 0/1	0/655 (0.0)	RD -0.3 (-0.6, 0.04)*	0.171
			CP >3h and rule-out group	ADP ESC 0/1	3/1063 (0.3)		
Twerenbold 2019 31345421	30	Cardiovascular death and MI	Female and rule-out group	ADP ESC 0/1	2/663 (0.3)	RD 0.2 (-0.3, 0.7)*	0.372
Twerenbold 2019 31345421	30	Cardiovascular death and MI	Male and rule-out group	ADP ESC 0/1	1/1049 (0.1)		
Twerenbold 2019 31345421	30	Cardiovascular death and MI	Age >65 years and rule-out group	ADP ESC 0/1	2/500 (0.3)	RD 0.1 (-0.4, 0.6)*	0.688
Twerenbold 2019 31345421	30	Cardiovascular death and MI	Age ≤65 years and rule-out group	ADP ESC 0/1	3/1219 (0.2)		
Twerenbold 2019 31345421	30	Cardiovascular death and MI	CP ≤3h and discharge	ADP ESC 0/1	0/614 (0)	RD -0.1 (-0.3, 0.1)*	0.435
Twerenbold 2019 31345421	30	Cardiovascular death and MI	CP >3h and discharge	ADP ESC 0/1	1/1004 (0.1)		
Twerenbold 2019	30	Cardiovascular death and MI	Female and discharge	ADP ESC 0/1	1/614 (0.2)	RD 0.2 (- 0.2, 0.5)*	0.202

Study PMID, Study	Follow-up Time (days)	Outcome Definition	Subgroup	Arm	n/N (%)	OR (95% CI)*	Reported P value
31345421							
Twerenbold 2019 31345421	30	Cardiovascular death and MI	Male and discharge	ADP ESC 0/1	0/1004 (0)		
Twerenbold 2019 31345421	30	Cardiovascular death and MI	Age >65 years and discharge	ADP ESC 0/1	0/509 (0)	RD -0.1 (- 0.3, 0.1)*	0.501
Twerenbold 2019 31345421	30	Cardiovascular death and MI	Age ≤65 years and discharge	ADP ESC 0/1	1/1120 (0.1)		

Notes. * Calculated by research team.
*Abbreviation*s. ADP=accelerated diagnostic protocol; CI=confidence interval; CP=chest pain; EDACS=Emergency Department Assessment of Chest Pain Score; ESC=European Society of Cardiology; 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; MACE=major adverse cardiac events; MI= myocardial infarction, n/N%=(number of events/sample size)%; NR=not reported; OR=odds ratio; PMID=PubMed identifier; RD=risk difference; TIMI=Thrombolysis in Myocardial Infarction; wk=week.

Appendix Table J-2. MACE: Rule Out, Low Risk Not Described as Rule Out, Discharge or Grey Zone, and Rule In or High Risk

Study, Year, PMID	ADP	Follow-up Time (days)	Outcome Definition	n/N (%)
Rule Out				
Chew 2019 31478763	ADP 0/1	30	Death and MI	6/1187 (0.5)
			Death, MI, and unstable angina	10/1187 (0.8)
Twerenbold 2019 31345421	ADP ESC 0/1	30	Cardiovascular death and MI	3/1420 (0.2)
Low Risk Not Described as Rule Out				
Than 2016 26947800	ADP 0/2 EDACS	30	Death, cardiac arrest, emergency revascularization, cardiogenic shock, ventricular arrhythmia needing intervention, high-degree atrioventricular block needing intervention, and MI	0/116 (0)
	ADAPT ADP 0/2 TIMI	30	Death, cardiac arrest, emergency revascularization, cardiogenic shock, ventricular arrhythmia needing intervention, high-degree atrioventricular block needing intervention, and MI	0/85 (0)
Hyams 2018 29478861	ADP 0/3 HEART	6 wk	Death, nonfatal MI, revascularization (based on HEART score ≤3)	0/denominator NR (0)
Discharge				
Suh 2022 35571147	ADP 0/1 mHEART	30	MI, revascularization, ventricular arrhythmia, high degree atrioventricular block requiring intervention, cardiogenic shock requiring mechanical support, cardiac arrest with return of spontaneous circulation, and death	4/381 (1)
Twerenbold 2019 31345421	ADP ESC 0/1	30	Cardiovascular death and MI	1/1619 (0.06)
Observe / Grey Zone				
Chew 2019 31478763	ADP 0/1	30	Death and MI	7/308 (2.3)
			Death, MI, and unstable angina	9 /308 (2.9)
			MI with or without revascularization	3/308 (1)
Twerenbold 2019 31345421	ADP ESC 0/1	30	Cardiovascular death and MI	31/581 (5.3)
Rule In				
Chew 2019 31478763	ADP 0/1	30	Death and MI	5/136 (3.7)

Study, Year, PMID	ADP	Follow-up Time (days)	Outcome Definition	n/N (%)
Twerenbold 2019 1345421	ADP ESC 0/1	30	Cardiovascular death and MI	197/295 (66.8)
High Risk Not Described as Rule In				
Suh 2022 35571147	ADP 0/1 mHEART	30	MI, revascularization, ventricular arrhythmia, high degree atrioventricular block requiring intervention, cardiogenic shock requiring mechanical support, cardiac arrest with return of spontaneous circulation, and death	35/395 (8.9)
Twerenbold 2019 1345421	ADP ESC 0/1	30	Cardiovascular death and MI (Based on admitted)	230/677 (34)
Than 2016 26947800	ADP 0/2 EDACS	30	Death, cardiac arrest, emergency revascularization, cardiogenic shock, ventricular arrhythmia needing intervention, high-degree atrioventricular block needing intervention, and MI	2/279 (0.7)
	ADAPT ADP 0/2 TIMI	30	Death, cardiac arrest, emergency revascularization, cardiogenic shock, ventricular arrhythmia needing intervention, high-degree atrioventricular block needing intervention, and MI	1 /279 (0.4)

*Abbreviation*s. ADP=accelerated diagnostic protocol; EDACS=Emergency Department Assessment of Chest Pain Score; ESC=European Society of Cardiology; HEART=History, Electrocardiogram, Age, Risk factors, Troponin; MACE=major adverse cardiac events; mHEART=modified HEART; MI=myocardial infarction; n/N%=(number of events/sample size)%; NR=not reported; PMID=PubMed identifier; TIMI=Thrombolysis in Myocardial Infarction; wk=week.

APPENDIX K. ED LENGTH OF STAY OUTCOMES

Appendix Table K-1. ED Length of Stay (Continuous) Comparative Studies

Study, Year, PMID	Outcome Definition	Subgroup	Arm*	N	Mean (SD)	MD (95% CI)	Reported P Value
Overall Comparison: ADP vs ADP							
Anand 2021 33752439	LOS		High-STEACS ADP 0/3	16792	6.8 (4.1)	Geometric Mean 0.78 (0.73, 0.83)	<0.001
			ADP 0/6/12	14700	10 (4.1)		
Barnes 2021 33436490	LOS		STAT ADP 0/2/6 HEART	1124	Median (IQR) 3.6 (2.6, 5.4)	IRR 0.71 (0.65, 0.77)	<0.001
			ADP 0/(2 or 3)/6 TIMI	1131	Median (IQR) 4.3 (3.3, 7.1)		
Sandeman 2021 34824100	LOS		ADP 0/3/6	3673	Median (IQR) 6.5 (6.3,19.8)	1.34% (-2.21%, -0.26%) reduction in LOS associated with early rule-out	<0.001
			ADP 0/6/12 GRACE	6642	Median (IQR) 8.9 (3.7,38.0)		
Stoyanov 2020 31298551	LOS		ADP ESC 0/1	1282	Median (IQR) 3.2 (2.7,4.4)	Difference in median hours: -2.1*	<0.001
			ADP ESC 0/3	1243	Median (IQR) 5.3 (4.7,6.5)		
Than 2021 33753972	LOS		COVID-ADP 0/2 EDACS	1343	Median (IQR) 3.4 (2.6,4.6)	Difference in median hours: -0.4*	<0.001
			ADP 0/2/6 EDACS	1073	Median (IQR) 3.8 (2.8,4.9)		
Subgroup Comparisons							
Costable 2014	LOS	CP >6h	ADP 0/3	264	2.9 (2)		0.352
		CP ≤6h	ADP 0/3	264	5.1 (2.8)		
Sandeman 2021 34824100	LOS	Patients with troponin <5 ng/L	ADP 0/3/6	945	Median (IQR) 3.7 (170,329)	2.99% (-4.32, -1.64) reduction in LOS associated with early rule-out pathway	NR
			ADP 0/6/12 GRACE	2188	Median (IQR) 3.9 (3,8.1)		

Study, Year, PMID	Outcome Definition	Subgroup	Arm*	N	Mean (SD)	MD (95% CI)	Reported P Value
Sandeman 2021 34824100	LOS	Patients with troponin 5–14 ng/L	ADP 0/3/6	1380	Median (IQR) 5.2 (3.6,14.0)	3.61% (-5.30%, -1.90%) reduction in LOS associated with early rule-out pathway with	NR
			ADP 0/6/12 GRACE	1885	Median (IQR) 7 (3.6,20.2)		
Sandeman 2021 34824100	LOS	Patients with troponin >14 ng/L	ADP 0/3/6	1348	Median (IQR) 42.8 (11.3,103.1)	0.99% (-0.95%, 2.98%) reduction in LOS associated with early rule-out pathway with duration of stay	NR
			ADP 0/6/12 GRACE	2569	Median (IQR) 37.7 (11.1,100.1)		
Than 2021 33753972	LOS	Discharged from ED	COVID-ADP 0/2 EDACS	NR	Mean 3.4 Median (IQR) 3.1 (2.4,4.1)	Difference in median hours: -0.5 hours*	NR
			ADP 0/2/6 EDACS	NR	Mean 3.9 Median (IQR) 3.7 (2.7,4.6)		

Notes. * Calculated by research team.

*Abbreviation*s. ADP=accelerated diagnostic protocol; CI=confidence interval; CP=chest pain; ED=emergency department; EDACS=Emergency Department Assessment of Chest Pain Score; ESC=European Society of Cardiology; GRACE=Global Registry of Acute Coronary Events; h=hour; HEART=History, Electrocardiogram, Age, Risk factors, Troponin; High-STEACS=High-Sensitivity Troponin in the Evaluation of Patients With Suspected Acute Coronary Syndrome; IQR=interquartile range; IRR=incidence rate ratio; LOS=length of stay; MD=mean difference; N=sample size; NR=not reported; PMID=PubMed identifier; SD=standard deviation; STAT=single troponin accelerated triage; TIMI=Thrombolysis in Myocardial Infarction.

Appendix Table K-2. ED Length of Stay (Categorical) Comparative Studies

Study PMID, Study Design	Follow-up Time (days)	Outcome Definition	Subgroup	Arm	n/N (%)	OR (95% CI)	Reported P value
Overall Comparison: ADP vs. ADP							
Barnes 2021 33436490	ED visit	Discharge <3h		STAT ADP 0/2/6 HEART	425/1124 (37.8)	aOR 2.1 (1.73,2.55) RD 16.5 (12.8, 20.2)*	<0.001
				ADP 0/(2 or 3)/6 TIMI	241/1131 (21.3)		
Sandeman 2021 34824100	ED visit	Discharge ≤4h		ADP 0/3/6	1281/3650 (34.9)	RD 2.3 (0.4, 4.2)*	NR
				ADP 0/6/12 GRACE	2150/6597 (32.6)		
Than 2016 26947800	ED visit	Discharge <6h[a]		ADP 0/2 EDACS	90 /279 (32.3)	RD -2.1 (-10.3, 6)	0.65
				ADAPT ADP 0/2 TIMI	96/279 (34.4)		
Than 2021 33753972	ED visit	Discharge <2h		COVID-ADP 0/2 EDACS	109/1343 (8.1)	44.6% increase	NR
				ADP 0/2/6 EDACS	60/1073 (5.6)		
Than 2021 33753972	ED Visit	Discharge <3h		COVID-ADP 0/2 EDACS	594/1343 (44.2)	35.2% increase	NR
				ADP 0/2/6 EDACS	351/1073 (32.7)		
Subgroup Comparison							
Sandeman 2021 34824100	30	Discharge ≤4h	Patients with troponin <5 ng/L	ADP 0/3/6	604/945 (63.9)	RD 11.4 (7.7, 15.1)*	NR
				ADP 0/6/12 GRACE	1149/2188 (52.5)		
Sandeman 2021 34824100	30	Discharge ≤4h	Patients with troponin 5–14 ng/L	ADP 0/3/6	512/1380 (37.1)	RD 2 (-1.3, 5.3)*	NR
				ADP 0/6/12 GRACE	661/1885 (35.1)		

Study PMID, Study Design	Follow-up Time (days)	Outcome Definition	Subgroup	Arm	n/N (%)	OR (95% CI)	Reported P value
Sandeman 2021 34824100	30	Discharge ≤4h	Patients with troponin >14 ng/L	ADP 0/3/6	165/1348 (12.2)	RD* -1 (-3.2, 1.2)	NR
				ADP 0/6/12 GRACE	340/2569 (13.2)		
Than 2016 26947800	ED visit	Discharge <6h[a]	Low-risk patients	ADP 0/2 EDACS	73/279 (26.2)	RD 3.2 (-4.3,10.7)	NR
				ADAPT ADP 0/2 TIMI	64/279 (22.9)		

Notes. [a] Discharge <6h and no MACE defined as death, cardiac arrest, emergency revascularization, cardiogenic shock, ventricular arrhythmia needing intervention, high-degree atrioventricular block needing intervention, and MI.

Abbreviations. ADP=accelerated diagnostic protocol; aOR=adjusted odds ratio; CI=confidence interval; 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); n/N%=(number of events/sample size)%; NR=not reported; OR=odds ratio; PMID=PubMed identifier; RD=risk difference; STAT=single troponin accelerated triage; TIMI=Thrombolysis in Myocardial Infarction.

Appendix Table K-3. ED Length of Stay (Continuous): Rule Out, Low Risk Not Described as Rule Out, Discharge or Grey Zone, and Rule In or High-Risk

Study, Year, PMID	ADP	N	Median (IQR) Length of Stay
Rule Out			
Chew 2019 31478763	ADP 0/1	1187	4.6 (3.5, 7.5)
Twerenbold 2019 31345421	ADP ESC 0/1	1420	2.5 (2.2, 3.6)
Low Risk Not Described as Rule Out			
Ljung 2019 30661856	ADP 0/1 HEART	308	4.05 (3.3,5.4)
Costable 2014	ADP 0/3	264	Mean (SD) 2.9 (2)
Sandeman 2021 34824100	ADP 0/3/6	945	3.65 (2.8, 5.5)
	ADP 0/6/12 GRACE	2188	3.9 (3, 8.1)
Discharge			
Lambrakis 2021 33998255 Chew 2019 31478763	ADP 0/1	737	3.8 (3.1,4.7)
Ljung 2019 30661856	ADP 0/1 HEART	419	3.8 (3.1,4.9)
Twerenbold 2019 31345421	ADP ESC 0/1	1619	2.5 (2.2,3.4)
Than 2021 33753972	COVID-ADP 0/2 EDACS	NR	3.1 (2.4, 4.1)
	ADP 0/2/6 EDACS	NR	3.7 (2.7, 4.6)
Observe / Grey Zone			
Chew 2019 31478763	ADP 0/1	308	12.0 (5.1,34.4)
Twerenbold 2019 31345421	ADP ESC 0/1	581	2.6 (2.4, 4.6)
Rule In			
Chew 2019 31478763	ADP 0/1	270	51 (27.6, 77.6)
Twerenbold 2019 31345421	ADP ESC 0/1	295	2.5 (2.3, 4.4)
High Risk Not Described as Rule In			
Ljung 2019 30661856	ADP 0/1 HEART (based on admitted)	202	46.7 (24.4,73.6)
	ADP 0/1 HEART (based on HEART score ≥4)	139	4.53 (3.4,24.7)
	ADP 0/1 HEART (based on hs-TnT>14 ng/L hs-cTnI ≥35 ng/L (♂) hs-cTnI ≥16 ng/L (♀))	130	45.2 (5.1,74.1)

Study, Year, PMID	ADP	N	Median (IQR) Length of Stay
Twerenbold 2019 31345421	ADP ESC 0/1 (based on admitted)	677	3 (2.3,5.3)
Sandeman 2021 34824100	ADP 0/3/6 (based on hs-TnT >14 ng/L)	1384	42.8 (11.3,103.1)
	ADP 0/6/12 GRACE (based on hs-TnT >14 ng/L)	2569	37.6 (11.2,100.9)

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; hs-cTnI/T=highly-sensitive cardiac troponin I/T; IQR=interquartile range; N=sample size; NR=not reported; PMID=PubMed identifier; SD=standard deviation.

Appendix Table K-4. ED Length of Stay (Categorical): Rule Out, Low Risk Not Described as Rule Out, Discharge or Grey Zone, and Rule In or High Risk

Study, Year, PMID	ADP	Outcome Definition	n/N (%)
Low Risk Not Described as Rule Out			
Than 2016 26947800	ADP 0/2 EDACS	Discharge <6h and no MACE within 30 days[a]	73/279 (26.2)
	ADAPT ADP 0/2 TIMI	Discharge <6h and no MACE within 30 days[a]	64/279 (22.9)
Sandeman 202134824100	ADP 0/3/6	Discharge ≤4h (based on hs-TnT <5 ng/L)	604/945 (63.9)
	ADP 0/6/12 GRACE	Discharge ≤4h (based on hs-TnT <5 ng/L)	1149/2188 (52.5)
High Risk Not Described as Rule In			
Sandeman 2021 34824100	ADP 0/3/6	Discharge ≤4h (based on hs-TnT >14 ng/L)	165/1348 (12.2)
	ADP 0/6/12 GRACE	Discharge ≤4h (based on hs-TnT >14 ng/L)	340/2569 (13.2)

Notes. [a] Discharge <6h and no MACE defined as death, cardiac arrest, emergency revascularization, cardiogenic shock, ventricular arrhythmia needing intervention, high-degree atrioventricular block needing intervention, and MI.
Abbreviations. ADP=accelerated diagnostic protocol; ED=emergency department; EDACS=Emergency Department Assessment of Chest Pain Score; GRACE=Global Registry of Acute Coronary Events; h=hour; hs-cTnT=high-sensitivity cardiac troponin T; MACE=major adverse cardiac events; n/N %=(number of events/sample size) %; PMID=PubMed identifier; TIMI=Thrombolysis in Myocardial Infarction.

APPENDIX L. DISCHARGE OUTCOMES

Appendix Table L-1. ED Discharge to Community versus Hospital Admission Comparative Studies

Study PMID, Study Design	Follow-up Time (days)	Outcome Definition	Subgroup	Arm	n/N (%)	OR (95% CI)*	Reported P Value
Overall Comparison: ADP vs hs-cTn without ADP							
Hyams 2018 29478861	ED Visit	ED discharge*		ADP 0/3 HEART	232/449 (51.7)*	RD 15.2 (8.7, 21.7)*	<0.001
				Hs-cTn	152/417 (36.5)*		
Overall Comparison: ADP vs ADP							
Anand 2021 33752439	ED Visit	ED discharge		High-STEACS ADP 0/3	11842/16792 (71)	aOR 1.59 (1.45, 1.75) RD 21 (20.0, 22.0)*	<0.001
				ADP 0/6/12	7407/14700 (50)		
Barnes 2021 33436490	ED Visit	ED discharge		STAT ADP 0/2/6 HEART	709/1124 (63)	aOR 2.75 (2.29, 3.29) RD 25 (21.0, 29.0)*	<0.001
				ADP 0/2 or 3/6 TIMI	430/1131 (38)		
Than 2021 33753972	ED visit	ED discharge for patients with chest pain presentation*		COVID-ADP 0/2 EDACS	90.7%*	RD 3 (0.5, 5.5)*	NR
				ADP 0/2/6 EDACS	87.7%*		

Notes. * Calculated by research team.
Abbreviations. ADP=accelerated diagnostic protocol; aOR=adjusted odds ratio; CI=confidence interval; ED=emergency department; EDACS=Emergency Department Assessment of Chest Pain Score; High-STEACS=High-sensitivity Troponin in the Evaluation of Patients With Suspected Acute Coronary Syndrome; HEART=History, Electrocardiogram, Age, Risk factors, Troponin; hs-cTn=high-sensitivity cardiac troponin; n/N %=(number of events/sample size) %; NR=not reported; OR=odds ratio; PMID=PubMed identifier; RD=risk difference; STAT=single troponin accelerated triage; TIMI=Thrombolysis in Myocardial Infarction.

Appendix Table L-2. ED Discharge to Community versus Hospital Admission: Rule Out, Low Risk Not Described as Rule Out, Discharge or Grey Zone, and Rule In or High Risk

Study, Year, PMID	ADP	Outcome Definition	n/N (%)
Rule Out			
Chew 2019 31478763	ADP 0/1	ED discharge to home	589/1187 (49.6)
Twerenbold 2019 31345421	ADP ESC 0/1	ED discharge to home	1243/1420 (88)
Low Risk Not Described as Rule Out			
Ljung 2019 30661856	ADP 0/1 HEART	ED discharge to home (based on HEART score ≤3)	269/308 (87.3)
Observe / Grey Zone			
Chew 2019 31478763	ADP 0/1	ED discharge to home	84/308 (27.3)
Twerenbold 2019 31345421	ADP ESC 0/1	ED discharge to home	352/581 (61)
Rule In			
Chew 2019 31478763	ADP 0/1	ED discharge to home	12/136 (8.8)
Twerenbold 2019 31345421	ADP ESC 0/1	ED discharge to home	2/295 (8)
High Risk Not Described as Rule In			
Ljung 2019 30661856	ADP 0/1 HEART	ED discharge (based on HEART score ≥4)	87/139 (62.6)
		ED discharge (based on hs-cTnT >14 ng/L hs-cTnI ≥35 ng/L (♂) hs-cTnI ≥16 ng/L (♀))	41/130 (31.5)

Abbreviations. ADP=accelerated diagnostic protocol; ED=emergency department; ESC=European Society of Cardiology; HEART=History, Electrocardiogram, Age, Risk factors, Troponin; hs-cTnI/T=high-sensitivity cardiac troponin I/T; n/N %=(number of events/sample size) %; PMID=PubMed identifier.

APPENDIX M. RETURN TO ED OR HOSPITAL OUTCOMES

Appendix Table M-1. Return to ED or Hospital Comparisons

Study PMID, Study	Follow-up Time (days)	Outcome Definition	Subgroup	Arm	n/N (%)	RD (95% CI)*	Reported P Value
ADP Comparison							
Barnes 2021 33436490	30	All cause		STAT ADP 0/2/6 HEART	107/1124 (9.5)	RD 1.1 (-1.3, 3.4)*	NR
				ADP 0/(2 or 3)/6 TIMI	95/1131 (8.4)		
Subgroup Comparison							
Barnes 2021 33436490	30	Chest pain	Patients who returned to ED	STAT ADP 0/2/6 HEART	33/107 (31.0)	RD -2 (-14.9, 10.9)*	NR
				ADP 0/2 or 3/6 TIMI	31/95 (33.0)		

Notes. * Calculated by research team.
Abbreviations. ADP=accelerated diagnostic protocol; CI=confidence interval; ED=emergency department; HEART=History, Electrocardiogram, Age, Risk factors, Troponin; n/N %=(number of events/sample size) %; OR=odds ratio; PMID=PubMed identifier; RD=risk difference; STAT=single troponin accelerated triage; TIMI=Thrombolysis in Myocardial Infarction.

Appendix Table M-2. Return to ED or Hospital Comparisons: Rule Out, Low Risk Not Described as Rule Out, Discharge or Grey Zone, and Rule In or High Risk

Study, Year, PMID	ADP	Follow-up Time (Days)	Outcome Definition	n/N (%)
Rule Out				
Chew 2019 31478763	ADP 0/1	30	Chest pain related	41/1187 (3.5)
Low Risk Not Described as Rule Out				
Ljung 2019 30661856	ADP 0/1 HEART	30	All-cause (Based on HEART score ≤3)	16/308 (5.2)
Discharge				
Ljung 2019 30661856	ADP 0/1 HEART	30	All-cause	45/419 (10.7)
Observe / Grey Zone				
Chew 2019 31478763	ADP 0/1	30	Myocardial injury related	11/308 (3.6)
			Chest pain related	22/308 (7.1)
Rule In				
Chew 2019 31478763	ADP 0/1	30	Chest pain related	7/136 (5.1)
High Risk Not Described as Rule In				
Ljung 2019 30661856	ADP 0/1 HEART	30	All-cause (Based on admitted)	36/202 (17.8)
			All-cause (Based on HEART score ≥4)	27 /139 (19.4)
			All-cause (Based on hs-TnT >14 ng/L hs-cTnI ≥35 ng/L (♂) hs-cTnI ≥16 ng/L (♀)	29/130 (22.3)

Abbreviations. ADP=accelerated diagnostic protocol; ED=emergency department; HEART=History, Electrocardiogram, Age, Risk factors, Troponin; hs-cTnI/T=high-sensitivity cardiac troponin I/T; n/N %=(number of events/sample size) %; PMID = PubMed identifier.

APPENDIX N. MI OUTCOMES

Appendix Table N-1. MI Comparative Studies

Study PMID, Study Design	Follow-up Time (days)	Outcome Definition	Subgroup	Arm	n/N (%)	OR (95% CI)	Reported P Value
Overall Comparison: ADP vs hs-cTn without ADP							
Hyams 2018 29478861	6 wk	MI		ADP 0/3 HEART	21/449 (4.7)	0.96 (0.52,1.81) RD -0.1 (-2.9, 2.7)*	NR
				hs-cTn	20/417 (4.8)		
Overall Comparison: ADP vs ADP							
Anand 2021 33752439	30	Type 1/4b/4c		High-STEACS ADP 0/3	38/16792 (0.2)	0.76 (0.49, 1.17)* RD -0.1 (-0.2, 0.01)*	NR
				ADP 0/6/12	44/14700 (0.3)		
Anand 2021 33752439	30	Type 1/2/4b/4c		High-STEACS ADP 0/3	50/16792 (0.3)	0.75 (0.52, 1.10)* RD -0.1 (-0.2,0.03)*	NR
				ADP 0/6/12	58/14700 (0.4)		
Barnes 2021 33436490	30	MI		STAT ADP 0/2/6 HEART	0/1124 (0)		NR
				ADP 0/(2 or 3)NR/6 TIMI	0/1131 (0.0)		
Than 2016 26947800	30	NSTEMI		ADP 0/2 EDACS	2/279 (0.7)	RD 0.7 (-2.1,0.6)	NR
				ADAPT ADP 0/2 TIMI	0/279 (0)		
Than 2016 26947800	30	STEMI		ADP 0/2 EDACS	0/279 (0)	RD -0.4 (-0.7,1.4)	NR
				ADAPT ADP 0/2 TIMI	1/279 (0.4) all in non–low-risk patients		

Study PMID, Study Design	Follow-up Time (days)	Outcome Definition	Subgroup	Arm	n/N (%)	OR (95% CI)	Reported P Value
Than 2016 26947800	ED visit	STEMI		ADP 0/2 EDACS	2/279 (0.7)	RD -0.4 (-1.6,2.3)	NR
				ADAPT ADP 0/2 TIMI	3 /279 (1.1)		
Than 2016 26947800	ED visit	NSTEMI		ADP 0/2 EDACS	34/279 (12.2) all in non-low-risk patients	RD 2.9 (-8.4,2.6)	NR
				ADAPT ADP 0/2 TIMI	26 /279 (9.3) all in non-low-risk patients		
Subgroup Comparison							
Than 2016 26947800	30	NSTEMI	Low-risk patients	ADP 0/2 EDACS	0/116 (0)		NR
				ADAPT ADP 0/2 TIMI	0/85 (0)		
Than 2016 26947800	30	STEMI	Low-risk patients	ADP 0/2 EDACS	0/116 (0)		NR
				ADAPT ADP 0/2 TIMI	0/85 (0)		

Notes. * Calculated by research team.
Abbreviations. ADP=accelerated diagnostic protocol; CI=confidence interval; ED=emergency department; EDACS=Emergency Department Assessment of Chest Pain Score; 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; MI=myocardial infarction; n/N %=(number of events/sample size) %; NR=not reported; NSTEMI=non ST-elevation myocardial infarction; OR=odds ratio; PMID=PubMed identifier; RD=risk difference; STAT=single troponin accelerated triage; STEMI=ST-elevation myocardial infarction; TIMI=Thrombolysis in Myocardial Infarction; wk=week.

Appendix Table N-2. MI: Rule Out, Low Risk Not Described as Rule Out, Discharge or Grey Zone, and Rule In or High Risk

Study, Year, PMID	ADP	Follow-up Time (days)	Outcome Definition	n/N (%)
Rule Out				
Chew 2019 31478763	ADP 0/1	30	Type 1/2/4a/5	5/1187 (0.4)
			MI or myocardial injury	9/1187 (0.8)
Twerenbold 2019 31345421	ADP ESC 0/1	30	MI	2/1420 (0.1)
Low Risk Not Described as Rule Out				
Ljung 2019 30661856	ADP 0/1 HEART	30	MI (Based on HEART score ≤3)	0/308 (0)
Than 2016 26947800	ADP 0/2 EDACS	30	NSTEMI	0/116 (0)
			STEMI	0/116 (0)
	ADAPT ADP 0/2 TIMI	30	NSTEMI	0/85 (0)
			STEMI	0/85 (0)
Discharge				
Ljung 2019 30661856	ADP 0/1 HEART	30	MI	2/419 (0.5)
Twerenbold 2019 31345421	ADP ESC 0/1	30	MI	0 /1619 (0)
Costable 2014	ADP 0/3	30	MI	0/479 (0)
Observe / Grey Zone				
Chew 2019 31478763	ADP 0/1	30	Type 1/2/4a/5	6/308 (1.9)
			MI or myocardial injury	9/308 (2.9)
Twerenbold 2019 31345421	ADP ESC 0/1	30	MI	30/581 (5.2)
Rule In				
Chew 2019 31478763	ADP 0/1	30	Type 1/2/4a/5	5/136 (3.7)
			MI or myocardial injury	8/136 (5.9)
Twerenbold 2019 31345421	ADP ESC 0/1	30	MI	195/295 (66.1)

Study, Year, PMID	ADP	Follow-up Time (days)	Outcome Definition	n/N (%)
High Risk Not Described as Rule In				
Ljung 2019 30661856	ADP 0/1 HEART	30	MI after discharge (among those who admitted)	1/202 (0.5)
			MI (patients with HEART ≥4)	0/139 (0)
			MI (patients with hs-cTnT >14 ng/L hs-cTnI ≥35 ng/L (♂) hs-cTnI ≥16 ng/L (♀))	1/130 (0.8)
	ADP 0/1 HEART	In-hospital stay	MI (among those who admitted)	44/202 (21.8)
Twerenbold 2019 31345421	ADP ESC 0/1	30	MI (based on admitted)	227/677 (33.5)
Than 2016 26947800	ADP 0/2 EDACS	30	NSTEMI	2/279 (0.7)
			STEMI	0/279 (0)
Than 2016 26947800	ADAPT ADP 0/2 TIMI	30	NSTEMI	0/279 (0)
			STEMI	1/279 (0.4)
Costable 2014	ADP 0/3	30	MI (based on admitted)	33/49 (67.3)

Abbreviations. ADP=accelerated diagnostic protocol; EDACS=Emergency Department Assessment of Chest Pain Score; ESC=European Society of Cardiology; HEART=History, Electrocardiogram, Age, Risk factors, Troponin; hs-cTnI/T=high-sensitivity cardiac troponin I/T; MI=myocardial infarction; n/N %=(number of events/sample size) %; NSTEMI=non ST-elevation myocardial infarction; PMID=PubMed identifier; STEMI=ST-elevation myocardial infarction; TIMI=Thrombolysis in Myocardial Infarction.

APPENDIX O. DEATH OUTCOMES

Appendix Table O-1. Death Comparative Studies

Study PMID, Study Design	Follow-up Time (Days)	Outcome Definition	Subgroup	Arm	n/N (%)	OR (95% CI)*	Reported P Value
Overall Comparison: ADP vs hs-cTn without ADP							
Hyams 2018 29478861	6 wk	All-cause		ADP 0/3 HEART	1/449 (0.2)	0.23 (0.03,2.08) RD -0.8 (-1.8, 0.2)*	NR
				hs-cTn	4/417 (1.0)		
Overall Comparison: ADP vs ADP							
Barnes 2021 33436490	30	All-cause		STAT ADP 0/2/6 HEART	0/1124 (0)		NR
				ADP 0/(2 or 3)/6 TIMI	0/1131 (0)		
Sandeman 2021 34824100	30	All-cause		ADP 0/3/6	141/3673 (3.8)	RD 0.1 (-0.7, 0.9)*	NR
				ADP 0/6/12 GRACE	245/6642 (3.7)		
Sandeman 2021 34824100	30	Cardiovascular		ADP 0/3/6	82/3673 (2.2)	RD 0.1 (-0.5, 0.7)*	NR
				ADP 0/6/12 GRACE	139/6642 (2.1)		
Than 2016 26947800	ED Visit	All-cause		ADP 0/2 EDACS	0/279 (0)	RD -0.4 (-0.7, 1.4)*	NR
				ADAPT ADP 0/2 TIMI	1/279 (0.4) occurred in non-low risk patients		
Subgroup Comparison							
Sandeman 2021 34824100	30	All-cause	Patients with troponin <5 ng/L	ADP 0/3/6	1/945 (0.1)	RD 0 (- 0.2, 0.2)*	NR
				ADP 0/6/12 GRACE	1/2188 (0.1)		
Sandeman 2021 34824100	30	All-cause	Patients with troponin 5–14 ng/L	ADP 0/3/6	12/1380 (0.9)	RD 0.2 (- 0.4, 0.8)*	NR
				ADP 0/6/12 GRACE	14/1885 (0.7)		
Sandeman 2021	30	All-cause		ADP 0/3/6	128/1348 (9.5)		NR

Study PMID, Study Design	Follow-up Time (Days)	Outcome Definition	Subgroup	Arm	n/N (%)	OR (95% CI)*	Reported P Value
34824100			Patients with troponin >14 ng/L	ADP 0/6/12 GRACE	230/2569 (9)	RD 0.5 (- 1.4, 2.4)*	
Sandeman 2021 34824100	30	Cardiovascular	Patients with troponin <5 ng/L	ADP 0/3/6	1/945 (0.1)	RD 0 (- 0.2, 0.2)*	NR
				ADP 0/6/12 GRACE	1/2188 (0.1)		
Sandeman 2021 34824100	30	Cardiovascular	Patients with troponin 5–14 ng/L	ADP 0/3/6	8/1380 (0.6)	RD 0.4 (-0.1, 0.9)*	NR
				ADP 0/6/12 GRACE	4/1885 (0.2)		
Sandeman 2021 34824100	30	Cardiovascular	Patients with troponin >14 ng/L	ADP 0/3/6	73/1348 (5.4)	RD 0.2 (-1.3, 1.7)*	NR
				ADP 0/6/12 GRACE	134/2569 (5.2)		

Notes. * Calculated by research team.
Abbreviations. ADP=accelerated diagnostic protocol; CI=confidence interval; ED=emergency department; EDACS=Emergency Department Assessment of Chest Pain Score; GRACE=Global Registry of Acute Coronary Events; HEART=History, Electrocardiogram, Age, Risk factors, Troponin; hs-cTn=high-sensitivity cardiac troponin; n/N %=(number of events/sample size) %; NR=not reported; OR=odds ratio; PMID=PubMed identifier; RD=risk difference; STAT=single troponin accelerated triage; TIMI=Thrombolysis in Myocardial Infarction; wk=week.

Appendix Table O-2. Death: Rule Out, Low Risk Not Described as Rule-Out, Discharge or Grey Zone, and Rule In or High Risk

Study, Year, PMID	ADP	Follow-up Time (Days)	Outcome Definition	n/N (%)
Rule Out				
Chew 2019 31478763	ADP 0/1	30	All-cause	1/1187 (0.1)
			Cardiovascular	1/1187 (0.1)
Twerenbold 2019 31345421	ADP ESC 0/1	30	All-cause	2/1420 (0.1)
			Cardiovascular	1/1420 (0.1)
Low-Risk Not Described as Rule Out				
Ljung 2019 30661856	ADP 0/1 HEART	30	All-cause after discharge (based on HEART score ≤3)	0/308 (0)
Sandeman 202134824100	ADP 0/3/6	30	All-cause (based on hs-TnT < 5 ng/L)	1/945 (0.1)
			Cardiovascular (based on hs-TnT < 5 ng/L)	1/945 (0.1)
Sandeman 2021 34824100	ADP 0/6/12 GRACE	30	All-cause (based on hs-TnT < 5 ng/L)	1/2188 (0.1)
			Cardiovascular (based on hs-TnT < 5 ng/L)	1/2188 (0.1)
Discharge				
Ljung 2019 30661856	ADP 0/1 HEART	30	All-cause	0/419 (0)
Twerenbold 2019 31345421	ADP ESC 0/1	30	All-cause	1/1619 (0.1)
			Cardiovascular	1/1619 (0.1)
Costable 2014	ADP 0/3	30	All-cause	0/479 (0)
Observe / Grey Zone				
Chew 2019 31478763	ADP 0/1	30	All-cause	1/308 (0.3)
			Cardiovascular	1/308 (0.3)
Twerenbold 2019 31345421	ADP ESC 0/1	30	All-cause	1/581 (0.2)
			Cardiovascular	1/581 (0.2)

Study, Year, PMID	ADP	Follow-up Time (Days)	Outcome Definition	n/N (%)
Rule In				
Chew 2019 31478763	ADP 0/1	30	All-cause	0/136 (0.0)
			Cardiovascular	0/136 (0.0)
Twerenbold 2019 31345421	ADP ESC 0/1	30	All-cause	5/295 (1.7)
			Cardiovascular	3/295 (1)
High Risk Not Described as Rule In				
Ljung 2019 30661856	ADP 0/1 HEART	30	All-cause after discharge (based on admitted)	0/202 (0)
Ljung 2019 30661856	ADP 0/1 HEART	30	All-cause after discharge (based on HEART score ≥4)	0/139 (0)
Ljung 2019 30661856	ADP 0/1 HEART	30	All-cause after discharge (based on hs-TnT >14 ng/L hs-cTnI ≥35 ng/L (♂) hs-cTnI ≥16 ng/L (♀))	0/130 (0)
Twerenbold 2019 31345421	ADP ESC 0/1	30	All-cause (based on admitted)	7/677 (1)
			Cardiovascular (based on admitted)	4/677 (0.6)
Costable 2014	ADP 0/3	30	All-cause (based on admitted)	0/49 (0)
Sandeman 2021 34824100	ADP 0/3/6	30	All-cause (based on hs-TnT >14 ng/L)	128/1348 (9.5)
			Cardiovascular (based on hs-TnT >14 ng/L)	73/1348 (5.4)
Sandeman 2021 34824100	ADP 0/6/12 GRACE	30	All-cause (based on hs-TnT >14 ng/L)	230/2569 (9)
			Cardiovascular (based on hs-TnT >14 ng/L)	134/2569 (5.2)

Abbreviations. ADP=accelerated diagnostic protocol; ESC=European Society of Cardiology; GRACE=Global Registry of Acute Coronary Events; HEART=History, Electrocardiogram, Age, Risk factors, Troponin); hs-TnI/T=high-sensitivity cardiac troponin I/T; n/N %=(number of events/sample size) %; PMID=PubMed identifier.

APPENDIX P. CARDIAC TESTING OUTCOMES

Appendix Table P-1. Cardiac Testing Comparative Studies

Study, Year, PMID	Test Category	Test	Subgroup	ADP	n/N (%)	OR (95% CI)*
Overall Comparison: ADP vs ADP						
Barnes 2021 33436490	Stress test, ECG	Stress ECG	-	STAT ADP 0/2/6 HEART	90/1124 (8.0)	1.2 (0.85, 1.57)* RD 1 (-1.2, 3.2)*
				ADP 0/(2 or 3)/6 TIMI	79 /1131 (7.0)	
	Stress test, imaging	Myocardial perfusion scan	-	STAT ADP 0/2/6 HEART	23/1124 (2.0)	0.50 (0.30, 0.83)* RD -2 (-3.4, -0.6)*
				ADP 0/(2 or 3)/6 TIMI	45/1131 (4.0)	
	Angiogram, standard	Angiogram	-	STAT ADP 0/2/6 HEART	10/1124 (0.9)	0.77 (0.34, 1.77)* RD -0.2 (-1.0, 0.6)*
				ADP 0/(2 or 3)/6 TIMI	13/1131 (1.1)	
	Angiogram, imaging	CT angiogram	-	STAT ADP 0/2/6 HEART	52/1124 (4.6)	1.6 (1.04, 2.5)* RD 1.7 (0.1, 3.3)*
				ADP 0/(2 or 3)/6 TIMI	33/1131 (2.9)	
Stoyanov 2020 31298551	Stress test, ECG	Stress ECG	Rule out and direct discharge	ADP ESC 0/1	89/806 (11)	1.1 (0.77,1.49)* RD 0.6 (-2.6, 3.8)*
				ADP ESC 0/3	70/672 (10.4)	
	Stress test, imaging	Myocardial perfusion scan	-	-	-	
		Stress echocardiogram	Rule out and direct discharge	ADP ESC 0/1	5/806 (0.6)	0.69 (0.21, 2.28)* RD -0.3 (-1.2, 0.6)*
				ADP ESC 0/3	6/672 (0.9)	
		Cardiac MRI stress test	Rule out and direct discharge	ADP ESC 0/1	7/806 (0.9)	1.9 (0.50, 7.6)* RD 0.5 (-0.3, 1.3)*
				ADP ESC 0/3	3/672 (0.4)	
	Angiogram, standard	Angiogram	-	ADP ESC 0/1	328/1282 (25.6)	0.85 (0.73, 0.99)* RD -3.2 (-6.7, 0.3)*
				ADP ESC 0/3	358/1243 (28.8)	
	Angiogram, imaging	CT angiogram	Rule out and direct discharge	ADP ESC 0/1	9/806 (1.1)	1.5 (0.50, 4.5)* RD 0.4 (-0.6, 1.4)*
				ADP ESC 0/3	5/672 (0.7)	

Notes. * Calculated by research team.
Abbreviations. ADP=accelerated diagnostic protocol; CI=confidence interval; CT=computerized tomography scan; ECG=electrocardiogram; ESC=European Society of Cardiology; HEART=History, Electrocardiogram, Age, Risk factors, Troponin; MRI=magnetic resonance imaging; n/N %=(number of events/sample size) %; OR=odds ratio; PMID=PubMed identifier; RD=risk difference; STAT=single troponin accelerated triage; TIMI=Thrombolysis in Myocardial Infarction.

Appendix Table P-2. Cardiac Testing: Rule Out, Low Risk Not Described as Rule Out, Discharge or Grey Zone, and Rule In or High Risk

Outcome (Test)	Diagnosis Category	Study, Year, PMID	ADP	n/N	%
Stress test, any	Rule out	Chew 2019 31478763	ADP 0/1	61/1187	5.1
		Twerenbold 2019 31345421	ADP ESC 0/1	125/1420	8.8
	Low risk	Ljung 2019 30661856	ADP 0/1 HEART	31/308	10.1
	Discharge	Twerenbold 2019 31345421	ADP ESC 0/1	104/1619	6.4
	Observe/grey zone	Chew 2019 31478763	ADP 0/1	41/308	13.2
		Twerenbold 2019 31345421	ADP ESC 0/1	58/581	10.0
	Rule in	Chew 2019 31478763	ADP 0/1	19/136	14.0
		Twerenbold 2019 31345421	ADP ESC 0/1	92/677	13.6
	High risk	Ljung 2019 30661856[a]	ADP 0/1 HEART	21/139	15.1
		Ljung 2019 30661856[b]	ADP 0/1 HEART	12/130	9.2
Stress test, ECG	Rule out	Chew 2019 31478763	ADP 0/1	17/1187	1.4
		Twerenbold 2019 31345421	ADP ESC 0/1	81/1420	5.7
		Stoyanov 2020 31298551[c]	ADP ESC 0/1	89/806	11
		Stoyanov 2020 31298551[c]	ADP ESC 0/3	70/672	10.4
	Discharge	Twerenbold 2019 31345421	ADP ESC 0/1	61/1619	3.8
	Observe/grey zone	Chew 2019 31478763	ADP 0/1	15/308	4.9
		Twerenbold 2019 31345421	ADP ESC 0/1	39/581	6.7
	Rule in	Chew 2019 31478763	ADP 0/1	3/136	2.2
		Twerenbold 2019 31345421[d]	ADP ESC 0/1	11/295	3.7
		Twerenbold 2019 31345421[e]	ADP ESC 0/1	70/677	10.3
	High risk	-	-	-	-
Stress test, imaging	Rule out	Chew 2019 31478763[f]	ADP 0/1	40/1187	3.4
		Chew 2019 31478763[g]	ADP 0/1	4/1187	0.3
		Stoyanov 2020 31298551[h]	ADP ESC 0/1	5/806	0.6
		Stoyanov 2020 31298551[h]	ADP ESC 0/3	6/672	0.9

Outcome (Test)	Diagnosis Category	Study, Year, PMID	ADP	n/N	%
		Stoyanov 2020 31298551[i]	ADP ESC 0/1	7/806	0.9
		Stoyanov 2020 31298551[i]	ADP ESC 0/3	3/672	0.4
	Discharge	-	-	-	-
	Observe/grey zone	Chew 2019 31478763[f]	ADP 0/1	25/308	8.1
		Chew 2019 31478763[g]	ADP 0/1	3/308	1.0
	Rule in	Chew 2019 31478763	ADP 0/1	7/136	5.1
	High risk	-	-	-	-
Angiogram, Standard	Rule out	Chew 2019 31478763	ADP 0/1	59/1187	5.0
		Twerenbold 2019 31345421	ADP ESC 0/1	82/1420	5.8
		Stoyanov 2020 31298551	ADP ESC 0/1	328/1282	25.6
		Stoyanov 2020 31298551	ADP ESC 0/3	358/1243	28.8
	Discharge	Twerenbold 2019 31345421	ADP ESC 0/1	14/1619	0.9
	Observe/grey zone	Chew 2019 31478763	ADP 0/1	43/308	14.0
		Twerenbold 2019 31345421	ADP ESC 0/1	109/581	18.8
	Rule in	Chew 2019 31478763	ADP 0/1	69/136	50.7
		Twerenbold 2019 31345421[d]	ADP ESC 0/1	211/295	71.5
		Twerenbold 2019 31345421[e]	ADP ESC 0/1	388/677	57.3
	High risk	-	-	-	-
Angiogram, imaging	Rule out	Stoyanov 2020 31298551[c]	ADP ESC 0/1	9/806	1.1
		Stoyanov 2020 31298551[c]	ADP ESC 0/3	5/672	0.7
	Discharge	-	-	-	-
	Observe/grey zone	-	-	-	-
	Rule in	Chew 2019 31478763	ADP 0/1	0/136	0.0
	High risk	-	-	-	-

Notes. [a] High risk based on HEART score ≥4; [b] High risk based on hs-TnT > 14 ng/L hs-cTnI ≥ 35 ng/L (♂) hs-cTnI ≥16 ng/L (♀); [c] Rule out and discharge subgroup; [d] Rule in subgroup; [e] Admitted subgroup; [f] Stress echocardiogram; [g] Cardiac MRI stress test; [h] Stress echocardiogram in rule out and direct discharge group; [i] Stress MRI in rule out and direct discharge group.

Abbreviations. ADP=accelerated diagnostic protocol; ECG=electrocardiograph; ESC=European Society of Cardiology; HEART=History, Electrocardiogram, Age, Risk factors, Troponin; n/N=number of events/sample size; PMID=PubMed identifier.

APPENDIX Q. REVASCULARIZATION OUTCOMES

Appendix Table Q-1. Revascularization Comparative Studies

Study PMID, Study Design	Follow-up Time (days)	Outcome Definition	Subgroup	Arm	n/N (%)	OR (95% CI)*	Reported P Value
Overall Comparison: ADP vs hs-cTn without ADP							
Hyams 2018 29478861	6 wk	CABG		ADP 0/3 HEART	5/449 (1.1)	0.3 (0.11,0.84) RD -2.5 (-4.5, -0.5)*	NR
				hs-cTn	15/417 (3.6)		
Hyams 2018 29478861	6 wk	PCI		ADP 0/3 HEART	13/449 (2.9)	1.33 (0.53,3.84) RD 0.7 (-1.4, 2.8)*	NR
				hs-cTn	9/417 (2.2)		
Hyams 2018 29478861	6 wk	Any revascularization		ADP 0/3 HEART	18/449 (4.0)	RD -1.7 (-4.6, 1.1)*	NR
				hs-cTn	24/417 (5.8)		
Subgroup Comparison							
Stoyanov 2020 31298551	30	PCI	Patients who received coronary angiography	ADP ESC 0/1	140/328 (42.7)	RD 0.2 (-7.2, 7.6)*	NR
				ADP ESC 0/3	152/358 (42.5)		

Notes. * Calculated by research team.
Abbreviations. ADP=accelerated diagnostic protocol; CABG=coronary artery bypass graft; CI=confidence interval; ESC=European Society of Cardiology; HEART=History, Electrocardiogram, Age, Risk factors, Troponin; hs-cTn=high-sensitivity cardiac troponin; n/N %=(number of events/sample size) %; NR=not reported; OR=odds ratio; PCI=percutaneous coronary intervention; PMID=PubMed identifier; RD=risk difference; wk=week.

Appendix Table Q-2. Revascularization: Rule Out, Low Risk Not Described as Rule Out, Discharge or Grey Zone, and Rule In or High Risk

Study, Year, PMID	ADP	Follow-up Time (Days)	Outcome Definition	n/N (%)
Rule Out				
Chew 2019 31478763	ADP 0/1	30	PCI	11/1187 (0.9)
			CABG	4/1187 (0.3)
			Any revascularization	15/1187 (1.3)
Twerenbold 2019 31345421	ADP ESC 0/1	30	PCI	49/1420 (3.5)
			CABG	1/1420 (0.1)
			Any revascularization	62/1420 (4.4)
Discharge				
Twerenbold 2019 31345421	ADP ESC 0/1	30	PCI	1/1619 (0.1)
			CABG	0/1619 (0)
			Any revascularization	10/1619 (0.6)
Observe / Grey Zone				
Chew 2019 31478763	ADP 0/1	30	PCI	15/308 (4.9)
			CABG	3/308 (1.0)
			Any revascularization	18/308 (5.8)
Twerenbold 2019 31345421	ADP ESC 0/1	30	PCI	53/581 (9.1)
			CABG	17/581 (2.9)
			Any Revascularization	69/581 (11.9)
Rule In				
Chew 2019 31478763	ADP 0/1	30	PCI	27/136 (19.9)
			CABG	6/136 (4.4)
			Any revascularization	33/136 (24.3)

Study, Year, PMID	ADP	Follow-up Time (Days)	Outcome Definition	n/N (%)
Twerenbold 2019 31345421	ADP ESC 0/1	30	PCI	116/295 (39.3)
			CABG	36/295 (12.2)
			Any revascularization	151/295 (51.2)
High Risk Not Described as Rule In				
Twerenbold 2019 31345421	ADP ESC 0/1	30	CABG (based on admitted)	54/677 (8)
			PCI (based on admitted)	217/677 (32.1)
			Any revascularization (based on admitted)	272/677 (40.2)

Abbreviations. ADP=accelerated diagnostic protocol; CABG=coronary artery bypass graft; ESC=European Society of Cardiology; n/N %=(number of events/sample size) %; PCI=percutaneous coronary intervention; PMID=PubMed identifier.Appendix R. Hospital length of Stay outcomes

APPENDIX R. HOSPITAL LENGTH OF STAY OUTCOMES

Appendix Table R-1. Hospital Length of Stay: Rule Out, Low Risk Not Described as Rule Out, Discharge or Grey Zone, and Rule In or High Risk

Study, Year, PMID	ADP	Follow-up Time (Days)	Outcome Definition	N	Median (IQR)
Rule Out					
Twerenbold 2019 1345421	ADP 0/1	30	Nights	1420	0 (0,0)
Discharge					
Twerenbold 2019 1345421	ADP 0/1	30	Nights	1619	0 (0,0)
Observe / Grey Zone					
Twerenbold 2019 31345421	ADP 0/1	30	Nights	581	1 (0,5)
Rule In					
Twerenbold 2019 31345421	ADP 0/1	30	Nights	295	5 (3,9)
High Risk Not Described as Rule In					
Twerenbold 2019 31345421	ADP 0/1	30	Nights	677	5 (2,8)

Abbreviations. ADP=accelerated diagnostic protocol; ESC=European Society of Cardiology; IQR=interquartile range; N=sample size; PMID=PubMed identifier.