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:

Dianna Langdon, MD
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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.

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.