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Accelerated diagnostic protocols using high-sensitivity troponin assays to rule in or out myocardial infarction: A systematic review

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ABSTRACT

Background: Accelerated diagnostic protocols (ADPs) that incorporate high-sensitivity cardiac troponin (hs-cTn) can help emergency department (ED) providers quickly rule in or out acute myocardial infarction (AMI).
Objectives: This systematic review evaluated the effectiveness and comparative effectiveness of clinically applied ADPs that use hs-cTn on clinical and health service use outcomes.
Methods: Medline, Embase, ClinicalTrials.gov, and the Cochrane Database of Systematic Reviews were searched through May 2022. Standard systematic review methods were followed.
Results: We found 17 eligible primary studies (reporting on 23 ADPs), including 2 randomized controlled trials (N = 32,050), 5 nonrandomized comparative studies (N = 18,377) and 10 single-group studies (N = 44,016). One study compared an ADP with hs-cTn to hs-cTn alone, finding that the ADP increased discharges from the ED to the community and is not associated with worse clinical outcomes. Among 6 studies, ADPs with shorter compared to longer hs-cTn timing and ADPs that incorporated the HEART score compared to the TIMI score reduced ED length of stay and increased discharges to the community without resulting in worse clinical outcomes. Across studies, ADPs that measured hs-cTn for up to 12 h had longer ED lengths of stay than ADPs with ≤6 h of measurements.
Conclusions: ADPs with shorter compared to longer hs-cTn timing reduce ED length of stay, increase discharges, and are not associated with changes in 30-day major adverse cardiovascular event, AMI, or mortality. Among ADPs that reduce ED length of stay, there is no obvious best choice, and any ADP should be tailored to local context.

1. Introduction

In the United States (US), 7 million people annually present to the emergency department (ED) for chest pain; yet, only 4% of these patients are diagnosed with acute myocardial infarction (AMI) [1]. The evaluation of acute chest pain in the ED often requires a significant amount of hospital resources [2,3]. Accurate and timely diagnosis of AMI is critical to reduce patient morbidity and mortality and reduce ED overcrowding, unnecessary testing, and unnecessary hospitalizations.

Troponins I and T are the primary diagnostic biomarkers used to diagnose AMI and are routinely incorporated into rapid rule-out and rule-in algorithms (often called accelerated diagnostic protocols [ADPs]) [4]. High-sensitivity cardiac troponin (hs-cTn) assays entered the global market in 2010, and the US market in 2017 [5,6]. These assays detect very low levels of troponin and can provide more accurate results compared to conventional cardiac troponin following an ischemic event [7]. Recent clinical guidelines, including the 2021 ACC/AHA Joint Committee on Clinical Practice Guidelines, recommend hs-cTn as the preferred troponin biomarker for diagnosing AMI [8].

Multiple ADPs that incorporate hs-cTn have been derived to help ED

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providers quickly rule in or rule out AMI [8,9]. In addition to hs-cTn values, ADPs usually incorporate clinical factors (*eg,* time from onset of symptoms) and risk assessment tools to stratify patients into categories that inform management. Decision rules for most ADPs using hs-cTn have been validated in large observational cohorts [9–13]. These validation studies have demonstrated that ADPs with hs-cTn likely rule out AMI without increasing the risk of adverse events (*eg,* 30-day mortality). However, the comparative effects of using ADPs in the ED on clinical and health service utilization outcomes (*eg*, AMI diagnoses, length of stay, respectively) remain unclear.

The Veterans Affairs (VA) Evidence Synthesis Program was asked by the VA Office of Emergency Medicine to conduct an evidence review on the effects of ADPs using hs-cTn in the ED on clinical and health service resource utilization outcomes. For the VA and other health systems that aim to implement ADPs with hs-cTn into routine clinical practice, it is important to understand the effectiveness and comparative effectiveness of ADPs.

2. Materials and methods

2.1. Scope and key questions

The review protocol is registered in PROSPERO (CRD42022343247). We followed the PRISMA guidelines for systematic reviews. We worked with representatives from the VA Office of Emergency Medicine and a technical expert panel to guide refinement of the review's scope and key questions. We focused on studies that report on the real-world use of ADPs that incorporate a hs-cTn to rule in or rule out AMI. We did not include studies that modeled ADPs from medical record data that were not implemented while the patients were in the ED. We defined ADPs as clinical decision-making tools that at a minimum include a clinical metric (eg, time since symptom onset, risk score) and incorporate hs-cTn to inform the diagnosis of AMI. We evaluated the impact that use of the ADP(s) had on clinical outcomes (eg, AMI diagnosis, mortality, and major adverse cardiac events) and health service use outcomes (eg, ED length of stay, hospitalizations, and use of diagnostic testing such as echocardiography).

2.2. Search strategy

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 20, 2022 (Appendix 1). In consultation with a medical librarian, we used Medical Subject Headings and title/abstract terms related to *chest pain*, *accelerated diagnostic protocols*, *high-sensitivity cardiac troponin*, and *emergency department*. Additional citations were identified from hand-searching reference lists of relevant systematic reviews and consultation with content experts.

2.3. Inclusion and exclusion criteria

Eligible studies included adults ≥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). ADPs with hs-cTn had to be clinically applied in decision-making during the patients' ED visits. 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). We included randomized controlled trials (RCTs), prospective or retrospective nonrandomized (observational) comparative studies (NRCSs), and single group studies (where a single ADP was evaluated). Comparative studies that compared an ADP with hs-cTn to an excluded protocol (*eg*, standard cTn) were treated as single group studies, omitting the excluded study group. Prioritized outcomes included 30-day major adverse cardiovascular event (MACE) as defined within each study, ED length of stay, discharge from the ED, 30-day revisit to ED or rehospitalization, 30-day AMI, 30-day mortality, follow-up cardiac testing, revascularization, and hospital length of stay. A list of studies excluded at full-text review, with rejection reasons, is provided in Appendix 2.

2.4. Quality assessment & data Abstraction

Two independent reviewers screened titles and abstracts using prespecified inclusion and exclusion criteria (Appendix 3). Conflicts between screeners were resolved by a third senior researcher. We used Abstrackr software to screen abstracts, which 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 [14].

We extracted data and assessed study quality and risk of bias in standardized forms in SRDR-plus, which can be viewed at https://srdrplus.ahrq.gov/projects/3194. Data extraction and study risk of bias was first completed by 1 reviewer and then checked by a second reviewer. Disagreements were resolved by consensus or discussion with a third reviewer. Risk of bias was assessed using questions derived from the Cochrane Risk of Bias and the ROBINS-I tools (Appendix 4) [15,16]. 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.

2.5. Data Synthesis and certainty of evidence

We evaluated risk differences for categorical outcomes and mean difference for continuous outcomes. Studies were too clinically heterogeneous to allow meta-analysis. Using GRADE (Grading of Recommendations Assessment, Development and Evaluation) methodology, we determined certainty of evidence for each major finding among comparative studies [17]. Within each evaluated study comparison and outcome, we considered the study design, the number of studies (and participants), methodological limitations (including risk of bias), directness of the evidence, precision of the findings, consistency across studies, and other issues. Based on these, we determined certainty of evidence, which could be high, moderate, low, or very low. We did not evaluate certainty of evidence for data from single group studies.

3. Results

Of 6591 unique titles and abstracts screened, 377 articles underwent full-text review, and ultimately 17 primary studies (reported in 18 articles) were eligible and included (Fig. 1). The most common reasons for article exclusion were that the ADP was not clinically applied in an ED and the study did not evaluate an ADP. The 17 primary studies evaluated 23 unique ADPs. Study designs varied and included 2 RCTs [17,18], 5 NRCSs [19–23] and 10 single group designs [24–33] (Appendix 5); these include 8 comparative studies [24–30,32] from which we evaluated only the eligible study group. Six of the 7 comparative studies included an ADP as a comparator [17–19,21–23]; and 1 study compared an ADP with hs-cTn to hs-cTn without an ADP [20].

Both RCTs (N = 32,050) [17,18] had overall low risk of bias. Five NRCSs (N = 18,377) all used a pre-post design, which consisted of evaluating a hospital or health systems change in ADP [19–23]. One of the NRCSs had blinded or independent outcome adjudicators for the clinical measures [22], and the remaining 4 either relied on record linkage (*eg*, electronic medical record) or did not describe how clinical outcomes were determined (medium risk of bias for clinical measures) [19–21,23]. Four of the NRCSs analyzed at least some outcomes using multivariable regression to control for possible confounders (low risk of bias for health service use measures) [19–22]. One NRCS conducted only crude (unadjusted) analyses and was high risk of bias [23]. The 10 single

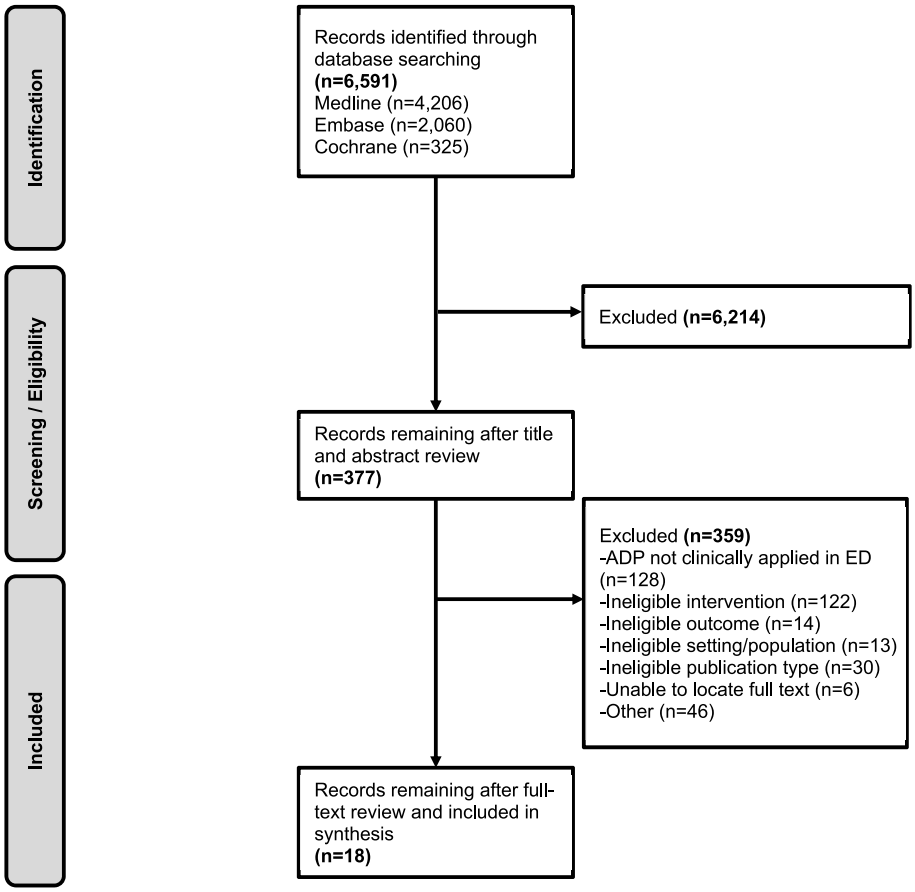

Fig. 1. Literature Flowchart
Abbreviations. ADP = accelerated diagnostic protocol, ED = emergency department.

group studies included 44,016 patients [24–33]. 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) [25–27,30,32,33]. Detailed study characteristics and results are in Appendix 6-15.

3.1. Evaluated ADPs

Table 1 shows the characteristics of the ADPs, which we describe based on inclusion of a risk score (*eg*, HEART), additional features of the ADP (*eg*, chest pain onset), hs-cTn timing, earliest time patients were eligible for discharge, and whether the final disposition includes a grey or observation zone. About half the ADPs (n = 13 of 23) included an explicit risk score including HEART or a modification of HEART (n = 6) [19,20,27–29,32], EDACS (n = 3) [18,23], TIMI (n = 2) [18,19], combined GRACE and TIMI (n = 1) [30], and GRACE (n = 1) [21]. Five ADPs included 0/1 serial hs-cTn (ie, hs-cTn draws at presentation and 1 h after) [22,24,28,29,31], 6 ADPs included 0/3 serial hs-cTn [17,20,22,25,30,33], 2 ADPs included 0/1/3 serial hs-cTn [27,32], and the remaining 10 ADPs used other combinations of serial hs-cTn up to 12 h. In 18 ADPs, the earliest time patients were eligible for discharge was after the first troponin [17,19–27,29–33]. Finally, 2 ADPs included a grey or observation zone as a final disposition [24,31] and 3 included a "medium risk category" not described as grey zone or observation, or rule in or rule out [26,28,29]. Grey, observation, and medium risk represented categorizations in which additional testing was required to rule-in or rule-out MI.

3.2. Effect of using ADPs with hs-cTn 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 to hs-cTn without ADP [20]. The pre-post study of 866 patients compared an ADP with 0/3 h serial hs-cTn and HEART to a period when the ED used only the hs-cTn value.

This study found that risks of 30-day MACE (risk difference [RD] = −8%, 95% [−5.1, 1.5]), AMI (RD = −0.1%, 95% CI [−2.9, 2.7]), death (RD = −0.8%, 95% CI [−1.8, 0.2]), and any revascularization (RD = −1.7%, 95% CI [−4.6, 1.1]) 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 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 NRCS with some methodological concerns (clinical outcomes were not independently adjudicated, but the study conducted multivariable regression to control for confounders; Table 2). The study did not provide evidence for ED length of stay, 30-day return to the hospital, cardiac testing, or hospital length of stay.

3.3. Comparisons of ADPs with different durations

Four studies (1 RCT [17] and 3 NRCSs [21–23]) compared ADPs with shorter versus longer times between first and last hs-cTn, which ranged from 1 to 12 h [17,21–23]. The ADPs also varied by use and type of risk score.

There is no evidence of differences in 30-day MACE (in 1 study RD = −0.1%, 95% CI [−0.2, 0.03]) and 30-day AMI (in 1 study RD = −0.1%, 95% CI [−0.2, 0.01]) among patients administered shorter and longer ADPs (Table 3). Patients who had shorter ADPs had mostly reduced ED lengths of stay (by about 2–4 h in 4 studies, mostly reported as statistically significant) and increased discharge to the community from the ED

Table 1
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 Onset			
Anand 2021 [17]	High-STEACS ADP 0/3							Y	0/3	0	N
	ADP 0/6/12							Y	0/6/12	0	N
Barnes [19]	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 [24] Lambrakis 2021 [48]	ADP 0/1							Y	0/1	0	Y
Conde 2013 [25]	ADP 0/3		Y		Y	Y	Y	Y	0/3	0	N
Costable 2014 [33]	ADP 0/3		Y		Y	Y	Y	Y	0/3	0	N
Crowder 2015 [26]	ADP 0/2-4							Y	0/2-4	0	N[b]
Ford 2021 [27]	ADP 0/1/3 HEART	HEART						Y	0/1/3	0	N
Hyams 2018 [20]	ADP 0/3 HEART	HEART							0/3	0	N
Ljung 2019 [28]	ADP 0/1 HEART	HEART		Y					0/1	1	N[b]
Sandeman 2021 [21]	ADP 0/3/6							Y	0/3/6	0	N
	ADP 0/6/12 GRACE	GRACE							0/6/12	6	N
Stoyanov 2020 [22]	ADP ESC 0/1							Y	0/1	0	N
	ADP ESC 0/3							Y	0/3	0	N
Suh 2022 [29]	ADP 0/1 mHEART	Modified HEART		Y				Y	0/1	0	N[b]
Sweeney 2020 [30]	ADP 0/3 TIMI & GRACE	TIMI & GRACE					Y	Y	0/3	0	N
Than 2021 [23]	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 [18]	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 [12]	ADP ESC 0/1							Y	0/1	0	Y
Vigen 2020 [32]	ADP 0/1/3 mHEART	Modified HEART						Y	0/1/3	0	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; 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.

[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.

(by either 3% or 21% in 2 studies, both statistically significant) compared with longer ADPs. We have moderate confidence in these findings since studies were large and mostly did not have major methodological limitations. Rates of follow-up cardiac testing (in 1 study RD = −3.2%, 95% CI [−6.7, 0.3]) and 30-day mortality (in 1 study RD = 0.1%, 95% CI [−0.7, 0.9]) did not differ by ADP duration. We have low confidence in these findings because they are based on a relatively small unadjusted NRCS (cardiac testing) [21] or an NRCS that yielded an imprecise effect size (30-day mortality) [22]. 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.

3.4. Indirect comparison of ADP duration with ED length of stay

Five studies that each compared 2 different ADPs and 10 single group studies reported both duration of ADP and ED length of stay [17,19,21–23,25–33]. Across studies, ADPs with up to 12 h of hs-cTn had longer ED length of stay (range: 8.9–10 h) than ADPs with 6 or less hours of hs-cTn timing (range: 2.5–6.5 h; Table 4). Five ADPs included 0/1 hs-cTn timing (length of stay range 2.5–4.8 h) [22,24,28,29,31], 2 ADPs included 0/2 hs-cTn timing (length of stay range 3.5–6.1 h) [23,26], 5 ADPs included 0/3 hs-cTn timing (length of stay range 4.1–6.8 h) [17,22,25,30,33], 2 ADPs included 0/1/3 hs-cTn timing (length of stay range 3.4–6.5 h) [27,32], 4 ADPs included hs-cTn timing up to 6 h (length of stay range 3.6–6.5 h) [19,21,23], and 2 ADPs included 0/6/12 hs-cTn timing (length of stay range 8.9–10 h) [17,21].

3.5. Comparison of ADPs with different risk scores

Two studies (1 RCT [18] and 1 NRCS [19]) compared ADPs with similar hs-cTn timing but different risk scores. The RCT compared a 0/2 EDACS ADP to the ADAPT 0/2 TIMI ADP [18]. The NRCS compared a STAT 0/2/6 HEART ADP to the ED's standard 0/(2 or 3)/6 TIMI ADP [19]). The novel STAT ADP and standard ADP both incorporated age,

Table 2
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 [20]	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 [20]	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 [20]	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 [20]	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 [20]	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)

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.
[a] Used crude unadjusted analysis to evaluate this outcome.
[b] Outcome assessors were not blinded.

Table 3
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 [17]	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 [17] and 3 NRCSs [21–23]	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 [17] and 1 NRCS [23]	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 [17]	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 [21]	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 [22]	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 [22]	Some limitations[c]	Indirect[b]	Precise	NA	Single study	Very low	Insufficient evidence
Hospital length of stay	0 (0)							(none)

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.
[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.

history of MI, and electrocardiogram readings as features. The ADP also incorporated the HEART risk score and chest pain onset, and patients were eligible for discharge after the first hs-cTn was drawn. In contrast, the standard ADP incorporated TIMI, did not include chest pain onset as a feature, and patients where not eligible for discharge until 2 h after the first hs-cTn.

There was no evidence of differences in 30-day MACE (in 1 study RD = 0.3%, 95% CI [−0.9, 1.5]), 30-day AMI (in 2 studies RD = 0% and 0.7%, both statistically nonsignificant), and 30-day death (in 2 studies RD = 0% and −0.4%, both statistically 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 (Table 5).

The NRCS 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 = 25.0%, 95% CI [21.0, 29.0]), and 30-day return to the ED may be similar (RD = 1.1, 95% CI [−1.3, 3.4]) [19]. We have low confidence in these findings; only a single, relatively small NRCS reported these outcomes. Studies did not report on

Table 4
Summary of Findings for Emergency Department Length of Stay by ADP hs-cTn Timing.

Study, Year, PMID	ADP	N	Median (IQR) Length of Stay, Hours
Chew 2019 [24]	ADP 0/1	1646	4.6 (3.4,6.4)
Ljung 2019 [28]	ADP 0/1 HEART	621	4.7 (3.5, 24.7)
Stoyanov 2020 [22]	ADP ESC 0/1	1282	3.2 (2.7,4.4)
Suh 2022 [29[a]]	ADP 0/1 mHEART	821	4.8 (3.1,7.1)
Twerenbold 2019 [12]	ADP ESC 0/1	2296	2.5 (2.2, 3.91)
			0/1 Summary Range: 2.5–4.8
Than 2021 [23]	COVID-ADP 0/2 EDACS	1343	3.4 (2.6,4.6)
Crowder 2015 [26]	ADP 0/2-4	5754	6.1 (4.25, 9.8)
			0/2 Summary Range: 3.4–6.1
Anand 2021 [17]	High-STEACS ADP 0/3	16792	Mean (SD) 6.8 (4.1)
Conde 2013 [25]	ADP 0/3	300	Mean (SD) 4.3 (2.6)
Costable 2014 [33]	ADP 0/3	528	Mean (SD) 4.5 (2.6)
Stoyanov 2020 [22]	ADP ESC 0/3	1243	5.3 (4.7,6.5)
Sweeney 2020 [30]	ADP 0/3 TIMI & GRACE	15882	3.8 (0.6, 7)
			0/3 Summary Range: 4.1–6.8
Vigen 2020 [32]	ADP 0/1/3 mHEART	14552	6.5 (4.9, 9.3)
Ford 2021 [27[b]]	ADP 0/1/3 HEART	1616	3.4 (2.2, 4.9)
			0/1/3 Summary Range: 3.4–6.5
Barnes 2021 [19]	ADP 0/(2 or 3)/6 TIMI	1131	4.3 (3.3, 7.1)
Than 2021 [23]	ADP 0/2/6 EDACS	1073	3.8 (2.8,4.9)
Barnes 2021 [19]	STAT ADP 0/2/6 HEART	1124	3.6 (2.6, 5.4)
Sandeman 2021 [21]	ADP 0/3/6	3673	6.5 (3.6, 19.8)
			0/(2 or 3)/6 Summary Range: 3.6–6.5
Anand 2021 [17]	ADP 0/6/12	14700	Mean (SD) 10 (4.1)
Sandeman 2021 [21]	ADP 0/6/12 GRACE	6642	8.9 (3.6, 38)
			0/6/12 Summary Range: 8.9–10

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.

[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).

revascularization or hospital length of stay.

3.6. ADP Stratification of patients into disposition or risk groups

All studies reported on disposition of patients out of the ED or risk groups. However, the studies did not use a standard system or set of definitions for how patients were risk stratified. Studies also used different terminology (*eg*, rule in or high risk) or classification systems. We organized the reported disposition/risk groups into 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. Based on an indirect comparison across the studies, ADPs appear to successfully stratify patients according to their risks of 30-day MACE (n = 6 ADPs) [18,20,24,29,31], 30-day AMI (n = 6 ADPs) [18,24,28,31,33], and 30-day death (n = 6 ADPs) [21,24,28,31,33]. For example, 30-day MACE (see Appendix 7 for how MACE was defined in each study) was between 0% and 0.5% for ruled-out/low-risk patients, 0.06%–1.0% for discharged patients, and 2.3%–5.3% for grey zone/observe patients.

Across 6 studies that reported ED length of stay for ADPs [21,24,28,31,33], there was no discernible pattern between hs-cTn timing and ED length of stay among ruled-out patients (range 2.5–4.6 h) [24,31], low-risk patients (range 2.9–4.05 h) [21,28,33], or discharged patients (range 2.5–3.8 h) [23,24,28,31]. There was a wide range in median length of stay (2.5–12 h) reported in 2 0/1 ADPs for patients in the observation or grey zone [24,31]. Five studies evaluating 6 ADPs reported median ED length of stay for high-risk (not described as rule in) patients between 3 and 46.7 h [21,28,31] and 2 studies reported ED legnth of stay for ruled-in patients of 51 h (Chew et al.) [24] and 2.5 h [31].

Five studies evaluating 7 ADPs reported the proportion of patients discharged from the ED [18,21,24,28,31]. Two evaluated the proportion of patients discharge within 4 or 6 h by ADP disposition [18,21]. One reported 26.2% (ADP 0/2 EDACS) and 22.9% (ADAPT ADP 0/2 TIMI) of low-risk patients were discharged within 6 h without 30-day MACE [18]. One reported 53% (ADP 0/6/12 GRACE) and 64% (ADP 0/3/6) of low-risk were patients discharged $\leq$4 h [21]. Three studies reported variation in the proportion discharged home [24,28,31]. Between 49.6% and 87% of ruled-out or low risk (not described as rule out) patients were discharged from the ED to the community. In 2 studies 27.3% and 61% of the observed group patients were discharged home and 8% of the ruled-in patients were discharged home [24,31]. One study reported that 62.6% (HEART score $\geq$4) and 31.5% (initial hs-cTn >14) high-risk (not described as rule in) patients were discharged home [28].

Two studies reported 30-day return to the ED by ADP disposition [24,28]. Return to the ED was infrequent for patients ruled out (3.5%) and low risk not described as rule out (5.2%), but less infrequent for those categorized as discharged (10.7%). One study reported that 3.6% and 7.1% of observe/grey zone patients returned to the ED for AMI and chest pain, respectively, and 5.1% of ruled-in patients returned to the ED [24]. One study reported return to ED among high-risk patients with proportions between 17.8% and 22.3% [28].

Three studies evaluating 3 ADPs (ESC 0/1[24,31] and ADP 0/1 HEART [28]) reported on frequency of stress testing by ADP disposition: rule out (5.1% and 8.8%) [24,31], low risk not described as rule out (10.1%) [28], observe/grey zone (10% and 13%) [24,31], rule in (14%) [24,31], and high risk not described as rule in (9.2% and 15.1%) [28]. Two studies reported between 0.6% and 4.4% of ruled-out or discharged patients had subsequent revascularization [24,31]. Among patients in the observation zone, 5.8% [24] and 11% [31] received revascularization, and 24% [24] and 51% [31] of ruled-in patients received revascularization. Finally, in one study 40% of high-risk (not described as rule-in) patients received any revascularization [34].

4. Discussion

ADPs can facilitate rapid rule in or rule out of AMI and have the potential to reduce ED overcrowding and health care costs [35,36]. We identified 17 studies that evaluated 23 unique ADPs, which varied in complexity, hs-cTn timing, use of risk score, and other features. Only a single study compared an ADP with hs-cTn to hs-cTn alone.

One would not expect ADPs to substantively change the percentage of patients with MACE or AMI, but they may affect rule in or rule out AMI, which can expedite appropriate management. We found that ADPs with hs-cTn increase discharges to the community and may not impact 30-day MACE, AMI, or death. In addition, shorter duration ADPs are probably

Table 5
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 [18]	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 (2255); NRCS [19]	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 (2255); NRCS [19]	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 (2255); NRCS [19]	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 (2813); 1 RCT [18] and 1 NRCS [19]	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 (2813); 1 RCT [18] and 1 NRCS [19]	No limitations	Direct	Precise	NA	Sparse data	Moderate	Probably no difference between ADPs with similar hs-cTn but different risk scores
Cardiac testing	1 (2255); NRCS [19]	Serious limitations[a]	Direct	Precise	Inconsistent[b]	Single study	Very Low	Insufficient evidence
Revascularization	0 (0)							(none)
Hospital length of stay	0 (0)							(none)

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 = non-randomized comparative study; RCT = randomized controlled trial; RD = risk difference; TIMI= Thrombolysis in Myocardial Infarction.

[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.

associated with reduced ED length of stay and more discharges to the community, without affecting the proportion of patients who experience clinical outcomes. These comparative data are supported by single group data that reported that ADPs with up to 12 h of hs-cTn have considerably longer ED length of stay than ADPs with up to 6 h of hs-cTn timing. The use of ADPs with different risk scores (but with similar hs-cTn timing) probably does not affect MACE, but ADPs that use the HEART rather than the TIMI risk score may decrease ED length of stay and result in more discharges.

Most comparative studies evaluated the effect of implementing an ADP in an ED that had previously used a different ADP or a protocol with standard hs-cTn. 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 [37–39]. The evaluated ADPs used multiple risk scores that may be of variable familiarity to ED physicians, cardiologists, and ED staff in different settings. The HEART score, which was the most commonly employed risk score in studies, is familiar to many ED providers and is easy to administer [40]. However, other evaluated risk scores, including TIMI and GRACE were initially developed to determine whether patients need invasive therapy, not for the evaluation of chest pain, and ED staff may be less comfortable with using them [41,42]. While one study found that a HEART-based ADP was associated with shorter length of stay and ED discharge compared with a TIMI ADP [19], the effect cannot be solely attributed to the use of HEART. The ADPs differed on several factors, including time of chest pain onset 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.

When hs-cTn was introduced, there was concern that more rapid diagnoses or, conversely, delayed diagnoses could impact both clinical outcomes and health system resources (*eg*, more downstream testing) [43,44]. However, comparative studies in this review did not find differences between ADPs and outcomes other than ED length of stay (although the data are limited). Nevertheless, ADP-based disposition (*eg*, rule out versus rule in) does appear to result in appropriate patient triage, such that low risk and discharged patients had few clinical events and poor clinical outcomes were rare. An important caveat is that the studies applied different terminology to describe similar concepts for ADP disposition, which hampered objective evaluation of the risk strata across studies. In particular, the description of a grey or observation zone and associated follow-up care was inconsistently reported. 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*, grey zone, low risk that is not equivalent to rule out).

4.1. Strengths and limitations

Our review has strengths and limitations. In contrast with our review, most prior reviews evaluating ADPs, either included retrospectively-derived ADPs (that do not inform on the real world effect of using ADPs in the ED), evaluated the sensitivity and specificity of ADPs to diagnose MI, or focused on a specific ADP (eg, ESC 0/1) [45–47]. Depending on one's perspective, an additional limitation is that we included only studies evaluating real-world implementation of ADPs and we excluded studies of theoretical ADPs. Because of variable terminology that was commonly not well defined, we often had to infer items such as how ADPs were implemented in the ED, what factors were considered within ADPs, and the disposition (categorization) of patients. The heterogeneity across studies regarding ADP details and which outcomes were reported precluded meta-analyses or a clearer understanding of the factors that may make some ADPs more or less effective to quickly and accurately stratify patients based on their risk of MI (or other cardiovascular events). While the organizational factors that affect implementation may be important for clinical and health service use outcomes, we were unable to evaluate the factors that might make an ED, hospital,

or health system a strong candidate to implement an hs-cTn ADP. Finally, we excluded studies or data from studies that implemented a conventional troponin; however, many EDs, including those in the VA, may still be using conventional troponin.

5. Conclusions

An ADP with hs-cTn compared to hs-cTn alone may be associated with reduced admissions without worse clinical outcomes. ADPs with shorter compared to longer hs-cTn timing may reduce ED length of stay, increase discharges, and probably are not associated with changes in 30-day MACE, MI, or mortality. 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 most likely contingent on local context and preferences. Findings were limited due to great variability across studies in evaluated ADPs and inconsistent reporting and analyses. More comparative studies evaluating a homogenous set of ADPs are required to determine the effects of a specific ADP on outcomes.

Article summary

Why is this topic important? In the United States, 7 million people annually visit the emergency department (ED) for chest pain, but only 4% of these patients are diagnosed with myocardial infarction (MI). Multiple accelerated diagnostic protocols (ADPs) that incorporate high-sensitivity cardiac troponin (hs-cTn) have been proposed to help ED providers quickly rule out MI.

What does this review attempt to show? The primary objective of this review was to evaluate the effectiveness and comparative effectiveness of ADPs that use hs-cTn on clinical and health service use outcomes. Eligible studies included 2 randomized controlled trials (n = 32,050), 5 non-randomized comparative studies (n = 18,377) and 10 studies (n = 44,016) evaluated as single group design. Studies reported on 23 ADPs that incorporate hs-cTn.

What are the key findings? ADPs that incorporate hs-cTn discharge more patients from the emergency department (ED) to the community and have no difference in cardiovascular events and death compared with hs-cTn alone. ADPs with shorter hs-cTn testing intervals reduce ED length of stay than longer testing intervals without compromising clinical outcomes. In indirect comparisons across studies, ADPs that measured hs-cTn for up to 12 h had longer ED lengths of stay than ADPs with $\leq$6 h of measurements.

How is patient care impacted? ADPs that incorporate hs-cTn can help reduce ED length of stay without negatively affecting patient outcomes including cardiovascular events and death.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jemrpt.2024.100086.

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