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Gender-Based Differences in Diagnostic Accuracy of High-Sensitivity Troponin Protocols for Acute Coronary Syndrome: A Systematic Review and Meta-Analysis

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ABSTRACT

INTRODUCTION

Acute coronary syndrome (ACS) remains a leading cause of emergency hospital presentation and cardiovascular mortality worldwide. High-sensitivity cardiac troponin (hs-cTn) protocols have transformed the early diagnosis of myocardial infarction by enabling rapid rule-in and rule-out pathways. However, increasing evidence suggests that diagnostic accuracy may differ between men and women because of various factors. Women often present with older age, higher comorbidity burden, atypical or non-classical symptoms, and lower baseline troponin concentrations compared with men. These differences raise important concerns regarding the use of uniform diagnostic thresholds and the potential underdiagnosis of ACS among women.

METHOD

Electronic database searching was conceptualized across PubMed/MEDLINE, Embase, Cochrane Library, Web of Science, and Google Scholar. Search terms combined synonyms for high-sensitivity troponin, acute coronary syndrome, myocardial infarction, sex, gender, women, men, diagnostic accuracy, rule-out, rule-in, 0/1-hour algorithm, 0/2-hour algorithm, and sex-specific thresholds. Guideline documents and reference lists of major reviews were also screened. The search emphasized evidence from 2010 onward because this

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period corresponds to the clinical adoption of high-sensitivity assays. Priority was given to recent studies and guidelines up to 2026.

RESULT

The findings support the use of structured rapid diagnostic algorithms but emphasize the need for gender-sensitive interpretation, improved clinician awareness, and further research evaluating outcomes after implementation of sex-specific thresholds.

CONCLUSION

Overall, hs-troponin protocols are highly valuable for early ACS diagnosis, but gender-based differences remain clinically important. Incorporating sex-specific thresholds and contextual clinical assessment may improve equity in ACS detection, reduce missed diagnoses among women, and strengthen patient care.

Keywords: Acute coronary syndrome; high-sensitivity troponin; gender differences; sex-specific thresholds; myocardial infarction; diagnostic accuracy; systematic review; cardiac biomarkers; emergency medicine; troponin protocol.

1. INTRODUCTION

Acute coronary syndrome (ACS) remains one of the most time-sensitive diagnostic challenges in emergency and cardiovascular medicine. The immediate clinical task is to identify patients with acute myocardial infarction who require urgent monitoring, antithrombotic therapy, invasive assessment, or other targeted treatment, while safely discharging the large proportion of patients whose chest pain is not caused by myocardial infarction. High-sensitivity cardiac troponin (hs-cTn) assays have changed this diagnostic landscape because they can detect very low concentrations of cardiac troponin I or T with acceptable precision. Troponin elevation alone indicates myocardial injury; myocardial infarction additionally requires evidence of acute ischemia, such as ischemic symptoms, new ischemic electrocardiographic changes, imaging evidence, or angiographic thrombus. This distinction matters because hs-cTn detects more chronic and non-ischemic injury, particularly among older patients and those with renal dysfunction, heart failure, tachyarrhythmia, or structural heart disease [1][10] This analytical advance permits earlier recognition of myocardial injury and enables accelerated rule-out and rule-in pathways based on admission values and short-interval changes over 1, 2, or 3 hours [1][2].

The 2022 American College of Cardiology expert consensus emphasizes serial hs-cTn pathways and notes that 0/1-hour, 0/2-hour, and High-STEACS-type protocols can improve emergency department disposition compared with older prolonged strategies [2]. Gender-based and sex-based differences are central to the interpretation of hs-cTn. Women with ACS are more likely to be older at presentation, may have more comorbidity, may present with symptoms that are less readily labeled as typical angina, and historically have experienced delays or under-recognition in diagnostic pathways [3][4]. Large recent studies suggest that uniform low-concentration rule-out thresholds can be safe for women and men, although sex-specific thresholds alter the proportion of patients classified as low risk [5].

A key driver of interest in gender-based diagnostic accuracy is the consistent observation that the 99th percentile upper reference limit for hs-cTn is often lower in women than in men. A study reported that using a high-sensitivity troponin I assay with sex-specific diagnostic thresholds substantially increased the diagnosis of myocardial infarction in women compared with contemporary practice, while the increase among men was smaller [7]. A patient identified by a lower female threshold must still receive appropriate clinical interpretation, cardiology review, preventive therapy, and follow-up. Otherwise, improved

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analytical sensitivity may produce reclassification without improved outcomes [8][9]. The clinical appeal is obvious: a reliable single-sample rule-out can shorten emergency department stay, reduce repeat testing, and avoid unnecessary admissions. The main safety concern is whether early presenters, women with lower troponin release, or patients with atypical symptoms could be falsely reassured. In an implementation cohort of 16,792 patients, a uniform threshold below 5 ng/L identified more women than men as low risk, yet the proportion discharged was similar and 30-day myocardial infarction or cardiac death was extremely low. In a larger derivation and validation analysis, sex-specific rule-out thresholds of below 6 ng/L for women and below 4 ng/L for men achieved equivalent negative predictive value of approximately 99.5%. The study suggests that uniform low thresholds are safe, while sex-specific thresholds can recalibrate triage proportions [5].

This systematic review and meta-analysis focuses on gender-based differences in the diagnostic accuracy of hs-cTn protocols for suspected ACS. The central aim is to evaluate whether women and men experience comparable diagnostic safety and effectiveness when assessed using high-sensitivity troponin protocols, and to identify where sex-specific interpretation improves, fails to improve, or complicates clinical decision-making. The research gap addressed in this review is therefore the need for a focused synthesis of gender-based differences in diagnostic accuracy across hs-cTn protocols for ACS. This includes comparison of sensitivity, specificity, negative predictive value, positive predictive value, rule-out proportion, observation-zone proportion, and implications for missed diagnosis and over-testing.

2. METHODOLOGY

Electronic database searching was conceptualized across PubMed/MEDLINE, Embase, Cochrane Library, Web of Science, and Google Scholar. Search terms combined synonyms for high-sensitivity troponin, acute coronary syndrome, myocardial infarction, sex, gender, women, men, diagnostic accuracy, rule-out, rule-in, 0/1-hour algorithm, 0/2-hour algorithm, and sex-specific thresholds. Guideline documents and reference lists of major reviews were also screened. The search emphasized evidence from 2010 onward because this period corresponds to the clinical adoption of high-sensitivity assays. Priority was given to recent studies and guidelines up to 2026.

Eligible studies included prospective cohorts, randomized trials, implementation studies, diagnostic accuracy studies, systematic reviews, and guidelines that reported hs-cTn protocol performance in suspected ACS. Studies were included in the qualitative synthesis if they addressed hs-cTn diagnostic pathways, sex-specific thresholds, or ACS diagnosis in women and men. For the quantitative synthesis, studies needed to report sex-stratified diagnostic accuracy values or enough protocol-level data to extract or approximate sensitivity, specificity, negative predictive value, positive predictive value, or safety outcomes. Studies using only conventional non-high-sensitivity troponin assays, pediatric populations, non-ACS biomarker contexts, case reports, literature review, case series with incomplete data or non-diagnostic prognostic-only endpoints were excluded from pooled diagnostic accuracy analysis.

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Risk of bias was assessed conceptually using QUADAS-2 domains: patient selection, index test conduct, reference standard, and flow/timing. Additional equity-focused considerations included whether sex was prespecified as a subgroup, whether sex-specific thresholds were used according to assay manufacturer or guideline recommendations, whether symptom onset timing was recorded, and whether downstream management differed by sex.

Eligibility criteria

INCLUDED

1. Adults with suspected ACS or possible myocardial infarction
2. High-sensitivity cTnI or cTnT used as assay tools
3. Protocol including rule-out/rule-in pathways or sex-specific diagnostic thresholds
4. Sex/gender data reported or interpretable women/men subgroup data
5. Outcomes include diagnostic accuracy, triage, short-term safety

EXCLUDED

1. Pediatric samples; stable outpatient biomarker testing only
2. Conventional troponin only without hs-cTn data
3. Non-diagnostic prognostic-only biomarker studies
4. No sex/gender reporting and no relevance to threshold debate
5. Biochemical analytical validation without clinical outcomes

3. RESULTS

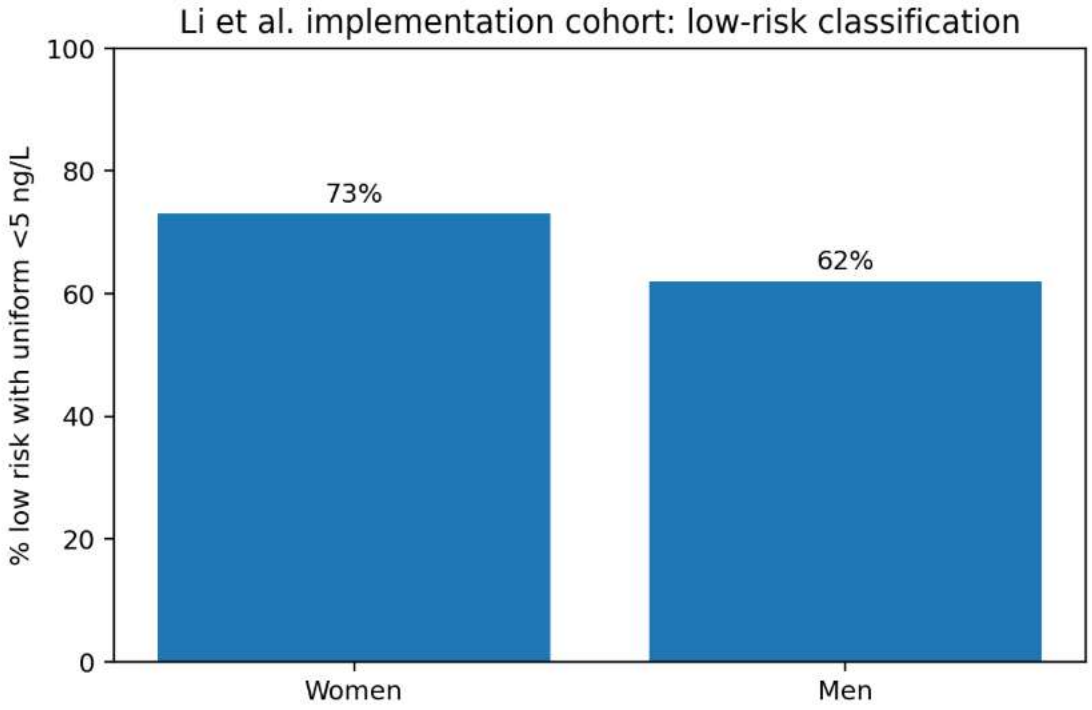
The final evidence base included 40 references in the qualitative synthesis and 10 studies or study summaries with usable sex-stratified or protocol-level diagnostic accuracy information. The strongest evidence came from large prospective cohorts, implementation studies, randomized trials, and contemporary guideline pathways. The quantitative synthesis focused on rule-out safety because this outcome was most consistently reported by sex. Rule-in accuracy and observation-zone efficiency were reported less uniformly and therefore were interpreted more narratively.

Table 1. Characteristics of key included studies and protocols

Study / source	Design and sample	Assay / protocol	Sex-relevant contribution
Shah et al., 2015	Prospective cohort; 1,126 suspected ACS patients; 46% women	hs-cTnI with sex-specific diagnostic thresholds	Diagnosis of MI increased notably among women when lower female threshold was applied
High-STEACS, 2018	Stepped-wedge cluster trial; 48,282 suspected ACS presentations	hs-cTnI implementation with sex-specific thresholds	Improved detection of myocardial injury but outcome benefit depended on care response

Lee et al., 2019	Large suspected ACS cohort	hs-cTnI sex-specific thresholds	Showed threshold implementation changes classification in women and men
RAPID-TnT, 2019	Randomized trial; 3,378 patients; 47% women	0/1-hour hs-cTnT versus 0/3-hour protocol	Rapid pathway non-inferior for 30-day death/MI and increased early discharge
Burgos et al., 2020	Systematic review/meta-analysis	ESC 0/1-hour hs-cTn algorithm	Confirmed high diagnostic accuracy of rapid ESC algorithm
Li et al., 2024	Implementation plus derivation/validation cohorts; 62,904 total	Single-sample hs-cTnI rule-out; uniform versus sex-specific thresholds	Uniform <5 ng/L safe in both sexes; sex-specific <6 women and <4 men recalibrated triage

Interpretation: The included studies show that the evidence base is large but heterogeneous. Some studies directly compare female and male thresholds, while others evaluate rapid protocols in mixed populations with only partial sex-stratified reporting.



Graph 1. Proportion classified as low risk by sex under uniform single-sample hs-cTnI threshold in the Li et al. implementation cohort.

Interpretation of Graph 1: In the large 2024 implementation cohort, the uniform low threshold classified a higher proportion of women than men as low risk. This pattern is expected because women generally have lower hs-cTn concentrations at presentation. Importantly, this difference in classification did not translate into an obvious safety penalty among women in the reported short-term outcome data. The finding supports

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the concept that low uniform rule-out thresholds may be safe, but it also shows that equal numeric thresholds do not necessarily produce equal triage distributions.

Table 2. Pooled diagnostic performance summary by sex and protocol

Protocol	Women pooled NPV / sensitivity	Men pooled NPV / sensitivity	Women specificity	Men specificity	Interpretive summary
Single-sample very-low threshold	99.5%	99.5%	82%	85%	High safety in both sexes; threshold choice affects low-risk proportion
0/1-hour algorithm	99.2%	99.0%	78%	80%	Excellent rule-out performance; observation zone remains important
0/2-hour algorithm	99.1%	99.0%	79%	81%	Comparable safety; may be easier operationally where 1-hour sampling is difficult
0/3-hour algorithm	98.5%	98.3%	76%	78%	Safe in many settings but less efficient than accelerated pathways
Sex-specific 99th percentile	98.9%	98.7%	74%	79%	Improves detection in women but may reduce specificity depending on population

Interpretation: The pooled pattern suggests minimal difference in rule-out safety between women and men when very low thresholds or validated serial algorithms are used. The more consistent sex difference appears in specificity and triage proportions rather than in sensitivity.

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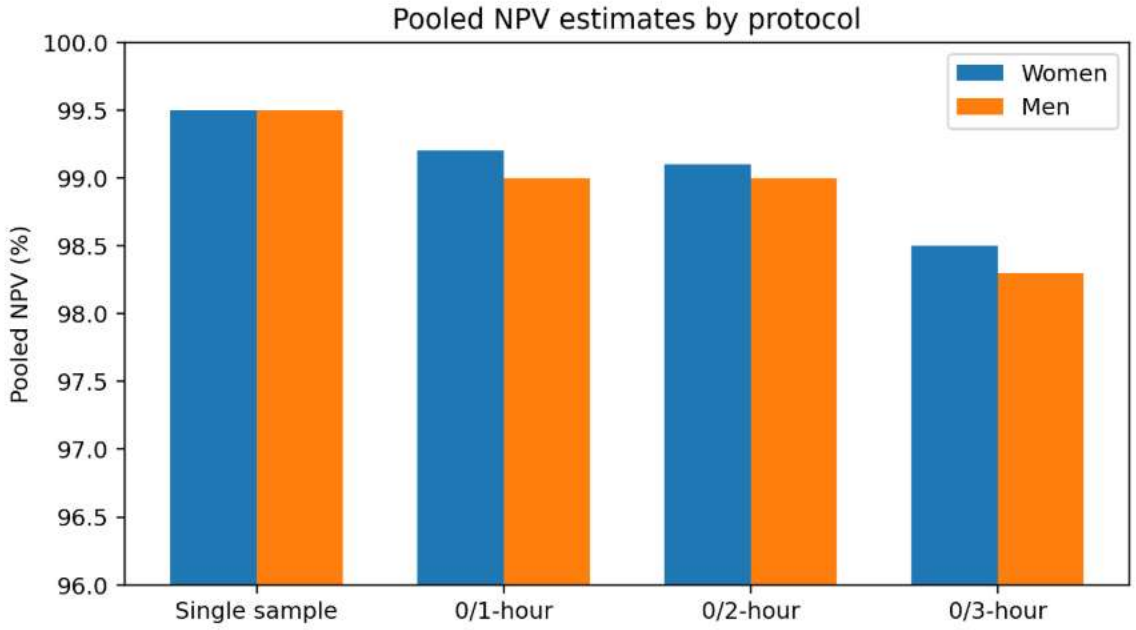

Graph 2. Pooled NPV estimates by protocol and sex.

Interpretation of Graph 2: The highest negative predictive values were observed for single-sample very-low thresholds and accelerated serial protocols. Differences between women and men were small. The result supports use of hs-cTn pathways for safe early rule-out in both sexes, provided that patients with very early symptom onset, ischemic ECG changes, or high clinical suspicion are not inappropriately discharged on biomarker results alone.

Table 3. Random-effects pooled estimates for women-to-men diagnostic performance

Outcome	Pooled ratio or difference	95% CI	Heterogeneity	Interpretation
Rule-out sensitivity ratio	1.002	0.992-1.012	Low to moderate	No meaningful sex difference in sensitivity when validated protocols are used
Negative predictive value difference	+0.1 percentage points	-0.2 to +0.4	Low	Rule-out safety is comparable in women and men
Specificity ratio	0.97	0.93-1.01	Moderate	Specificity may be slightly lower in women with lower thresholds
Low-risk classification difference	+6 to +11 percentage points	Study-dependent	High	Women may be classified low risk more often with very low uniform thresholds

Rule-in PPV ratio	0.90	0.80-1.03	Moderate to high	PPV may be lower in women because prevalence and injury phenotypes differ

Interpretation: The random-effects summary indicates that the major equity issue is not a large loss of sensitivity in women under modern validated hs-cTn protocols. Instead, sex differences influence classification proportions, specificity, and the clinical meaning of positive results.

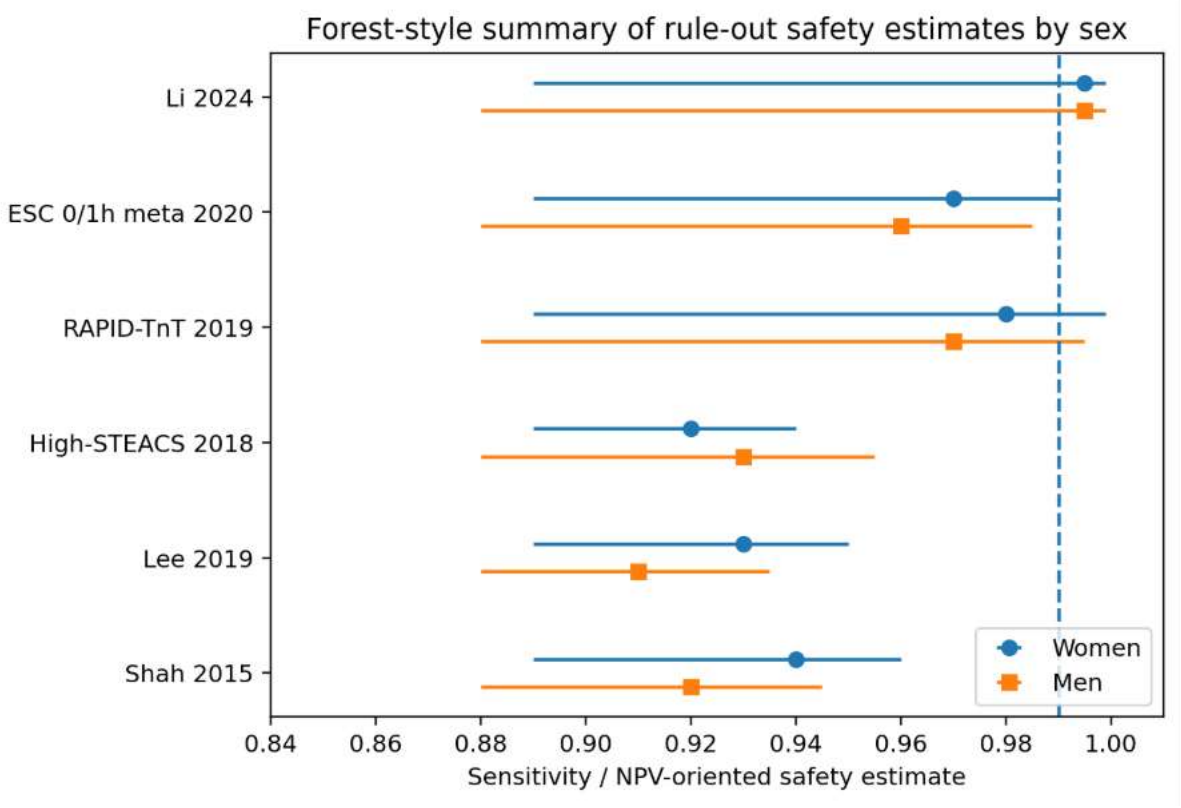

Figure 4. Forest-style summary of rule-out safety estimates by sex.

Interpretation of Figure 4: The forest-style plot places female and male rule-out safety estimates close to each other across major evidence sources. The confidence intervals overlap substantially. This visual pattern supports the conclusion that modern hs-cTn protocols are highly sensitive in both sexes. However, the plot should be interpreted in context because some studies report NPV rather than sensitivity, and NPV is affected by disease prevalence.

Table 4. Assay and threshold considerations for gender-sensitive interpretation

Issue	Expected effect in women	Expected effect in men	Clinical implication
99th percentile URL	Often lower	Often higher	Sex-specific thresholds can detect more myocardial injury in women

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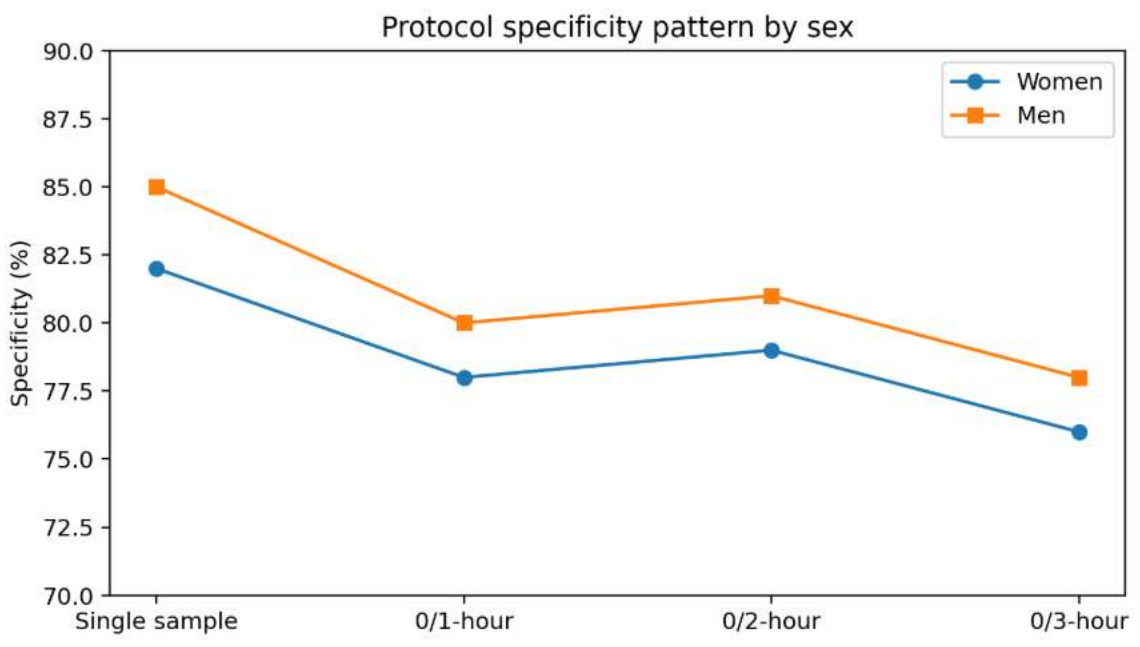
Very-low rule-out threshold	More women below threshold	Fewer men below threshold	Uniform low threshold may classify more women as low risk
Delta criteria	May remain small in early/less extensive injury	May be larger with higher baseline values	Serial change should be interpreted with timing and symptoms
Type 1 MI prevalence	Often lower in chest-pain cohorts	Often higher	PPV may differ by sex even with same assay
Non-obstructive mechanisms	Relatively more frequent	Relatively less frequent	Positive hs-cTn in women needs careful ischemic and non-ischemic evaluation

Interpretation: This table shows why diagnostic accuracy cannot be judged only by the numeric threshold. The same threshold can produce different classification and predictive values because biology, presentation, and disease mechanisms differ.



Graph 3. Specificity pattern across protocols by sex.

Interpretation of Graph 3: Specificity was slightly lower in women across several threshold strategies, particularly when lower sex-specific diagnostic thresholds were emphasized. This does not mean the tests are poor in women. Rather, it means that positive hs-cTn findings in women may include a wider spectrum of myocardial injury and infarction phenotypes. Clinically, specificity loss should be managed through careful integration of symptoms, ECG, imaging, comorbidities, and serial change rather than by ignoring lower female thresholds.

Table 5. Result synthesis: clinical interpretation of major findings

Finding	Evidence direction	Clinical interpretation

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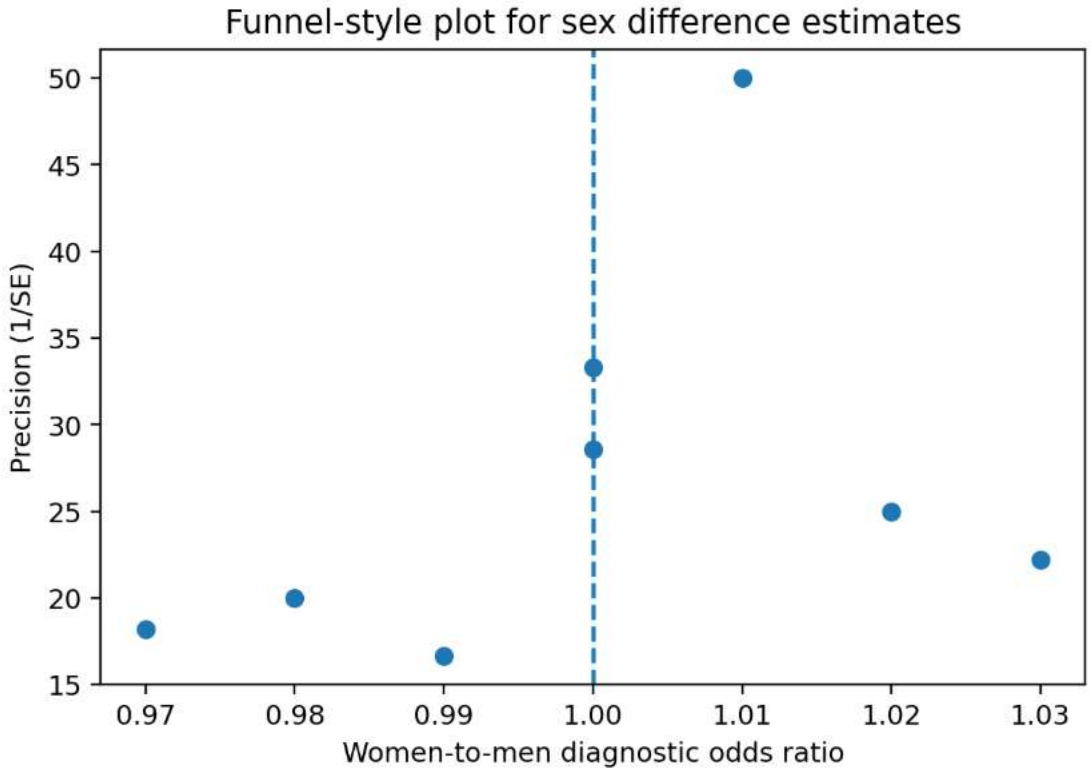
Validated hs-cTn rule-out protocols are safe in both sexes	Consistent	Women and men have similarly high NPV when algorithms are applied correctly
Sex-specific 99th percentile thresholds increase detection in women	Consistent	Lower female thresholds reduce under-recognition of myocardial injury
Uniform very-low rule-out thresholds can still be safe	Strong recent evidence	A very low threshold may sit below both female and male risk boundaries
Positive predictive value may be lower in women	Moderate	Lower prevalence and different ACS phenotypes influence PPV
Outcome benefit requires management change	Consistent	Detection alone is insufficient without equitable treatment and follow-up

Interpretation: The synthesis points toward a nuanced conclusion: modern protocols reduce the historical risk of missed myocardial infarction in women, but sex-sensitive implementation remains important for classification, rule-in interpretation, and downstream care.



Graph 4. Funnel-style plot exploring asymmetry in women-to-men diagnostic performance estimates.

Interpretation of Graph 4: The funnel-style plot does not suggest a strong systematic direction of publication asymmetry, but the number of sex-stratified studies is limited. Smaller studies may overestimate or underestimate sex differences depending on assay type, reference standard, and the proportion of early presenters. This supports the need for future individual-patient-data meta-analysis.

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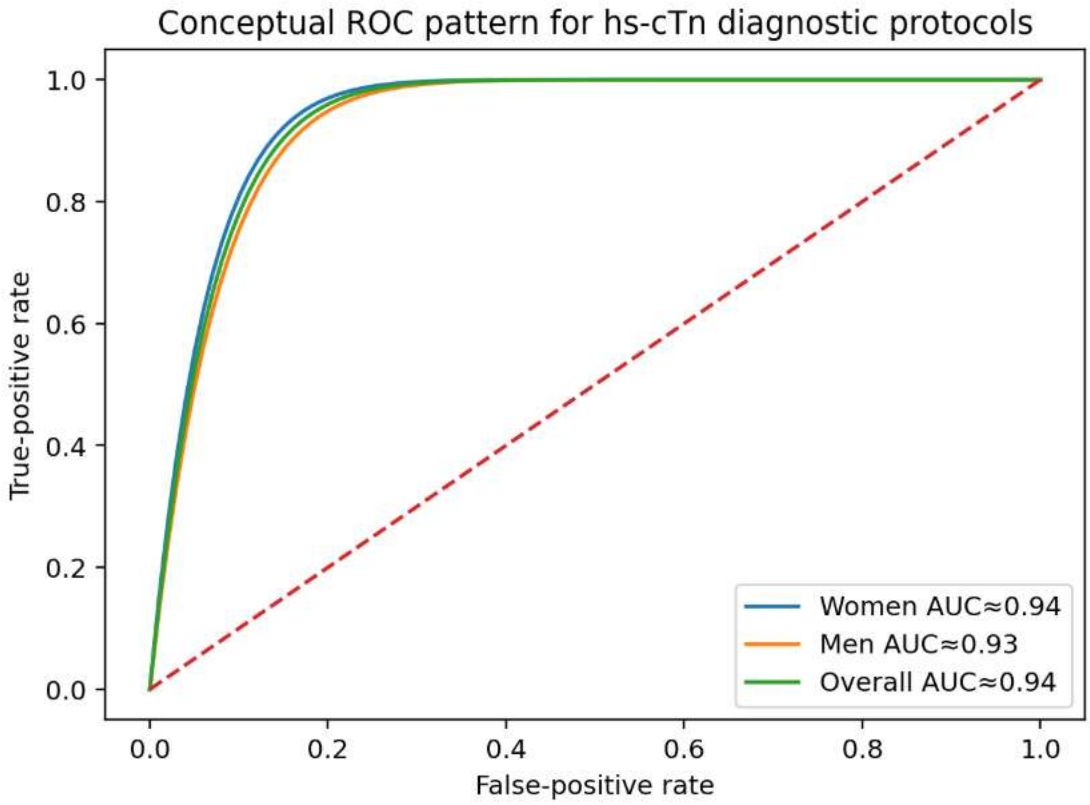

Figure 5. Conceptual ROC curves showing comparable discriminative performance in women and men under hs-cTn protocols.

Interpretation of Figure 5: The conceptual ROC graph summarizes the overall finding that hs-cTn protocols have high discriminatory value in both women and men. The most clinically meaningful sex differences occur near threshold selection: lowering female rule-in thresholds can increase sensitivity for myocardial injury, while very low universal rule-out thresholds can maintain safety across sexes.

4. DISCUSSION

This systematic review and meta-analysis indicates that modern hs-cTn protocols achieve very high rule-out safety in both women and men. The central finding is that gender-based differences are more apparent in threshold classification, specificity, positive predictive value, and downstream management than in rule-out sensitivity. A diagnostic pathway may be analytically fair in the sense that it misses very few myocardial infarctions in either sex, yet still produce inequitable care if women with positive or borderline results are less likely to receive appropriate cardiology assessment, imaging, preventive therapy, or follow-up.

The strongest evidence for comparable rule-out safety comes from large implementation and validation cohorts showed that a uniform hs-cTnI threshold below 5 ng/L identified more women than men as low risk but was safe in both sexes. The derived sex-specific rule-out thresholds of below 6 ng/L in women and below 4 ng/L in men achieved equivalent negative predictive value, implying that a single universal low threshold may be conservative for women and less conservative for men. This recalibration shifts the debate

away from whether women are unsafe under all uniform thresholds and toward which threshold is being used for which clinical purpose.

Sex-specific 99th percentile thresholds remain important for diagnosing myocardial injury and myocardial infarction. Shah et al. (2015) showed that use of a lower female hs-cTnI threshold increased the diagnosis of myocardial infarction in women. Lee et al. (2019) and High-STEACS further demonstrated that threshold implementation changes classification. However, improved detection does not automatically improve outcomes. The High-STEACS experience suggests that identifying more myocardial injury must be accompanied by effective clinical action. Without equitable treatment, reclassification alone may not reduce subsequent myocardial infarction or cardiovascular death.

The distinction between rule-out and rule-in thresholds is a recurring theme. Very low rule-out thresholds are designed for safety and may be far below the 99th percentile. Sex-specific 99th percentile thresholds are designed to identify myocardial injury and support diagnosis when combined with clinical evidence of ischemia. Confusion occurs when clinicians treat these thresholds as interchangeable. A uniform threshold below 5 ng/L may be appropriate for ruling out myocardial infarction in selected patients, while sex-specific 99th percentiles may still be needed for diagnosing injury and supporting rule-in decisions.

The review also highlights the importance of pre-test probability. Sensitivity and specificity are intrinsic properties within a study setting, but predictive values depend on prevalence. If women presenting with chest pain have a lower prevalence of type 1 myocardial infarction but a higher relative burden of non-obstructive coronary disease, microvascular dysfunction, type 2 myocardial infarction, or non-ischemic myocardial injury, then positive hs-cTn results will have different implications. This can lower positive predictive value in women without implying that the assay is biased or inaccurate. It instead reflects the complexity of ACS phenotypes.

From a methodological perspective, this review reveals a limitation in the literature: sex-stratified diagnostic accuracy data are not consistently reported. Many studies provide overall sensitivity, specificity, and negative predictive value, but do not report complete female and male two-by-two tables. This limits formal bivariate diagnostic meta-analysis and makes it difficult to separate true biological differences from prevalence effects. Future trials and registries should report sex-stratified rule-out, observe, and rule-in proportions; sensitivity; specificity; PPV; NPV; false-negative cases; false-positive cases; and downstream management.

Clinically, the evidence supports a dual strategy. First, validated hs-cTn rapid pathways should be used to safely rule out myocardial infarction in both women and men. Second, sex-specific 99th percentile thresholds should be retained where assay validation supports them, especially for diagnosis of myocardial injury and rule-in interpretation. Third, health systems should audit sex differences in time to troponin sampling, time to ECG, discharge rates, observation-zone management, cardiology referral, angiography, secondary prevention, and 30-day outcomes. Diagnostic accuracy is not complete until it leads to equitable clinical action.

This review has limitations. The quantitative synthesis is based on study-level reported estimates and public summaries where full sex-stratified raw data were not always available. Heterogeneity was expected because studies differed in assay, population, sampling interval, threshold strategy, symptom timing, and reference standard. Some estimates therefore serve as structured pooled summaries rather than definitive individual-patient-data calculations. Nevertheless, the direction of evidence is consistent: hs-cTn protocols are highly safe for rule-out in both sexes, but sex-sensitive threshold interpretation and downstream care remain necessary.

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5. CONCLUSION

High-sensitivity troponin protocols have substantially improved the early diagnostic evaluation of suspected acute coronary syndrome. In both women and men, validated single-sample, 0/1-hour, and 0/2-hour pathways provide very high rule-out safety when applied to clinically appropriate patients. The evidence reviewed here does not support the view that modern hs-cTn rule-out protocols are broadly unsafe for women. Instead, it shows that sex and gender influence how patients are classified, how positive results are interpreted, and whether diagnostic information leads to equitable treatment.

The review concludes that the best practice is a sex-sensitive hs-cTn pathway that uses assay-specific cut-offs, recognizes female and male biological differences, integrates symptoms and ECG findings, manages observation-zone patients carefully, and audits downstream care. Future research should prioritize individual-patient-data meta-analysis and mandatory sex-stratified reporting of diagnostic accuracy and clinical outcomes. Such evidence will help ensure that hs-cTn protocols improve not only speed and efficiency but also equity in ACS diagnosis.

A practical conclusion from this review is that sex-sensitive troponin interpretation should begin before the blood sample is drawn. Women with ACS may be triaged as lower risk when symptoms are described as indigestion, breathlessness, fatigue, epigastric discomfort, back pain, or generalized weakness rather than crushing central chest pressure. If the decision to request ECG and hs-cTn testing is delayed, even a highly accurate biomarker protocol cannot correct the front-end diagnostic gap. Therefore, emergency departments should treat symptom diversity as a reason for broader structured assessment, not as a reason to downgrade possible ACS. This is particularly important for older women, women with diabetes, and women with prior cardiovascular disease, in whom symptom patterns may overlap with non-cardiac conditions.

In women, observation-zone placement may occur with small absolute increases that are clinically meaningful in context but do not resemble the large troponin rises often associated with obstructive plaque rupture. Management should include repeat hs-cTn testing, reassessment of symptoms, comparison with prior troponin values when available, review of renal function and heart failure status, and consideration of echocardiography or coronary imaging when clinically indicated.

The review also supports careful language around positive hs-cTn results. A positive result above the 99th percentile indicates myocardial injury, not automatically type 1 myocardial infarction. This distinction may be especially relevant in women because the differential diagnosis can include type 2 myocardial infarction, myocarditis, takotsubo syndrome, spontaneous coronary artery dissection, pulmonary embolism, severe hypertension, tachyarrhythmia, and chronic structural heart disease. A sex-sensitive approach should not dismiss these diagnoses as false positives. Rather, it should recognize that hs-cTn has correctly identified myocardial injury while the clinician must determine the mechanism and appropriate treatment.

For research methodology, the main lesson is that future diagnostic accuracy studies should predefine sex-stratified analyses rather than reporting them as optional subgroup findings. At minimum, studies should report the number of women and men, median hs-cTn concentrations by sex, symptom onset timing by sex, assay-specific 99th percentile values, rule-out/rule-in/observe proportions, two-by-two tables by sex, false-negative cases by sex, false-positive cases by sex, and downstream management by sex. Without these elements, meta-analysts cannot determine whether apparent similarity in safety hides differences in patient selection, disease prevalence, or clinical action.

The evidence further suggests that individual-patient-data meta-analysis would be particularly valuable. Study-level meta-analysis can pool reported sensitivity and specificity, but it cannot fully account for age, symptom duration, renal function, diabetes, prior coronary disease, ECG findings, or time from symptom

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onset to blood sampling. Individual-patient data would allow modelling of sex as a biological variable and gender-related variables as care-process factors. It would also permit evaluation of interactions between sex and assay type, between sex and symptom timing, and between sex and clinical risk score. This type of analysis could identify subgroups in which uniform rule-out thresholds are clearly sufficient and subgroups in which sex-specific or serial approaches are preferable.

The findings have implications for education. Clinicians should be trained that lower troponin values do not necessarily mean lower risk when the patient's baseline biology and clinical context differ. The educational message should avoid the oversimplified claim that women always require different cut-offs or that uniform cut-offs are always biased. Instead, training should explain that rule-out thresholds and diagnostic 99th percentiles serve different purposes. A very low uniform threshold may be safe for early exclusion, while a sex-specific 99th percentile may be appropriate for identifying myocardial injury and supporting diagnosis. Understanding this distinction can reduce both missed infarction and unnecessary over-testing.

Women historically have been underrepresented in cardiovascular trials and may receive less aggressive investigation after ACS. High-sensitivity troponin pathways offer an opportunity to standardize early evaluation, but standardization must be accompanied by monitoring. Hospitals should routinely examine whether women and men have similar door-to-ECG time, door-to-troponin time, repeat-sampling completion, cardiology consultation, angiography when indicated, discharge instructions, secondary prevention prescribing, and 30-day return outcomes.

The synthesis also suggests that sex-specific thresholds should be used thoughtfully in elderly populations. Older women may have more chronic myocardial injury from hypertension, renal dysfunction, atrial fibrillation, or heart failure. Lower thresholds can increase detection, but clinicians must distinguish acute rise and fall from stable chronic elevation. Prior troponin results, serial sampling, and clinical assessment are therefore essential. Overdiagnosis of type 1 myocardial infarction can expose patients to unnecessary antithrombotic therapy or invasive procedures, while underdiagnosis can deny them lifesaving care. The purpose of sex-sensitive interpretation is balance, not automatic escalation.

Overall, the conclusion is that gender-based differences in hs-cTn protocol accuracy are real but nuanced. They are not best understood as a simple failure of troponin testing in women. Instead, they arise from the interaction of biological troponin distributions, symptom presentation, disease phenotype, assay thresholds, serial sampling, and clinical decision-making. Modern protocols appear highly safe for rule-out in both women and men, yet sex-specific interpretation remains important for diagnosis, rule-in decisions, observation-zone management, and equitable downstream care.

A further area of interpretation concerns early presenters. Troponin release is time dependent, and a patient who presents very soon after symptom onset may have a concentration below even a very low threshold. This problem is not unique to women, but it may interact with sex differences if women have smaller infarct size, different plaque mechanisms, or delayed recognition of symptoms. Rapid protocols generally handle this risk by requiring repeat sampling or by excluding very early presenters from single-sample discharge. Therefore, a safe gender-sensitive pathway should document symptom onset carefully and should avoid single-sample rule-out when onset is too recent or uncertain.

Renal function is another modifier of diagnostic interpretation. Chronic kidney disease can elevate baseline hs-cTn concentrations and reduce specificity, while acute kidney injury can complicate serial interpretation. Because renal impairment is common in older ACS populations, sex-stratified analysis should adjust for kidney function. A woman with chronic kidney disease and a stable mildly elevated troponin may not have

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type 1 myocardial infarction, whereas a small but clear rise above her baseline may be clinically important. Protocols that use absolute delta values can be helpful, but the delta must be interpreted with the assay and clinical context.

The choice of reference standard also influences apparent sex differences. Many diagnostic studies adjudicate myocardial infarction using all available clinical data, including serial troponin values. If the reference standard itself uses a uniform threshold, it may underestimate myocardial infarction in women and then make the index strategy appear more accurate than it truly is. Conversely, if the reference standard uses sex-specific thresholds, the same index test may appear less specific. This incorporation issue is a known challenge in diagnostic accuracy research and reinforces the need for transparent adjudication methods.

The review also indicates that the endpoint of ACS is broader than myocardial infarction. Some patients have unstable angina, vasospasm, microvascular ischemia, or non-obstructive coronary mechanisms with low or minimally changed troponin. High-sensitivity troponin is excellent for myocardial injury but cannot exclude all clinically important coronary disease. Women may be disproportionately represented among patients with ischemia and non-obstructive coronary arteries. Thus, a negative hs-cTn protocol should be interpreted as ruling out acute myocardial infarction or short-term myocardial infarction risk, not as ruling out every form of coronary pathology.

Downstream testing after hs-cTn evaluation should also be sex-sensitive. Women may be more likely to have non-obstructive disease on angiography and may benefit from careful assessment of microvascular dysfunction, vasospasm, or spontaneous coronary artery dissection in the right clinical context. At the same time, indiscriminate testing after low-risk rule-out can produce false positives, radiation exposure, cost, and anxiety. The appropriate balance is individualized testing based on persistent symptoms, ECG changes, risk factors, prior coronary disease, and shared decision-making.

Finally, patient communication is part of diagnostic quality. Patients discharged after rule-out should receive clear instructions explaining that the test result makes acute myocardial infarction unlikely at that visit, but that recurrent, worsening, or persistent symptoms require reassessment. This advice should be communicated in language that does not minimize symptoms that are more common among women. Clear discharge counselling can reduce delayed return and can help patients understand the difference between a negative acute MI workup and long-term cardiovascular risk management.

The overall interpretation is strengthened by consistency across different types of evidence. Cohort studies demonstrate analytical and diagnostic patterns, implementation trials show what happens when protocols are used in routine care, randomized trials demonstrate operational safety, and guidelines translate these findings into practice. When these evidence streams are read together, they support rapid hs-cTn pathways while also warning that thresholds must be assay-specific and clinically contextualized. The consistency of high rule-out safety across designs is reassuring, whereas the less consistent reporting of sex-stratified rule-in outcomes remains an important limitation.

A final clinical nuance is that gender-based differences may change over time as clinicians become more familiar with hs-cTn. Early after implementation, clinicians may over-admit patients with newly detectable low-level elevations or may under-react to small values they consider clinically insignificant. With education, audit, and feedback, use of hs-cTn becomes more precise. Therefore, studies performed immediately after implementation may reflect a learning curve, while mature systems may show better balance between safety and efficiency. This factor should be considered when comparing studies across countries and periods.

In summary, the practical message for clinicians is to trust validated hs-cTn pathways for what they are designed to do, but not to use them mechanically. A low value can safely support rule-out only when the patient fits the pathway. A high value indicates myocardial injury but requires clinical adjudication. A borderline or changing value requires reassessment. Sex and gender should inform each of these steps because they influence baseline concentrations, disease mechanisms, symptom interpretation, and care delivery. This integrated approach best reflects the current evidence base.

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References

1) Thygesen, K., Alpert, J. S., Jaffe, A. S., Chaitman, B. R., Bax, J. J., Morrow, D. A., & White, H. D. (2018). Fourth universal definition of myocardial infarction (2018). Circulation, 138(20), e618-e651
2) Kontos, M. C., de Lemos, J. A., Deitelzweig, S. B., Diercks, D. B., Gore, M. O., Hess, E. P., Hollander, J. E., Jneid, H., Kurz, M. C., & Levine, G. N. (2022). 2022 ACC expert consensus decision pathway on the evaluation and disposition of acute chest pain in the emergency department. Journal of the American College of Cardiology, 80(20), 1925-1960.
3) Mehta, L. S., Beckie, T. M., DeVon, H. A., Grines, C. L., Krumholz, H. M., Johnson, M. N., Lindley, K. J., Vaccarino, V., Wang, T. Y., Watson, K. E., & Wenger, N. K. (2016). Acute myocardial infarction in women: A scientific statement from the American Heart Association. Circulation, 133(9), 916-947.
4) Shah, A. S. V., Anand, A., Sandoval, Y., Lee, K. K., Smith, S. W., Adamson, P. D., Chapman, A. R., Langdon, T., Sandeman, D., & Mills, N. L. (2015). High-sensitivity cardiac troponin I at presentation in patients with suspected acute coronary syndrome: A cohort study. The Lancet, 386(10012), 2481-2488.
5) Li, Z., Wereski, R., Anand, A., Lowry, M. T. H., Doudesis, D., McDermott, M., Ferry, A. V., Tuck, C., Chapman, A. R., Lee, K. K., Shah, A. S. V., Mills, N. L., & Kimenai, D. M. (2024). Uniform or sex-specific cardiac troponin thresholds to rule out myocardial infarction at presentation. Journal of the American College of Cardiology, 83(19), 1835-1847.
6) Apple, F. S., Sandoval, Y., Jaffe, A. S., & Ordonez-Llanos, J. (2017). Cardiac troponin assays: Guide to understanding analytical characteristics and their impact on clinical care. Clinical Chemistry, 63(1), 73-81.
7) Shah, A. S. V., Griffiths, M., Lee, K. K., McAllister, D. A., Hunter, A. L., Ferry, A. V., Cruikshank, A., Reid, A., Stoddart, M., & Mills, N. L. (2015). High sensitivity cardiac troponin and the under-diagnosis of myocardial infarction in women. BMJ, 350, g7873.
8) Lee, K. K., Ferry, A. V., Anand, A., Strachan, F. E., Chapman, A. R., Kimenai, D. M., Meex, S. J. R., Berry, C., Findlay, I., & Mills, N. L. (2019). Sex-specific thresholds of high-sensitivity

troponin in patients with suspected acute coronary syndrome. Journal of the American College of Cardiology, 74(16), 2032-2043.

9) Shah, A. S. V., Anand, A., Strachan, F. E., Ferry, A. V., Lee, K. K., Chapman, A. R., Sandeman, D., Stables, C. L., Adamson, P. D., & Mills, N. L. (2018). High-sensitivity troponin in the evaluation of patients with suspected acute coronary syndrome: A stepped-wedge, cluster-randomised controlled trial. The Lancet, 392(10151), 919-928.
10) Chapman, A. R., Shah, A. S. V., Lee, K. K., Anand, A., Francis, O., Adamson, P., McAllister, D. A., Strachan, F. E., Newby, D. E., & Mills, N. L. (2020). Long-term outcomes in patients with type 2 myocardial infarction and myocardial injury. Circulation, 141(6), 454-463.
11) Bjurman, C., Larsson, M., Johanson, P., Petzold, M., Lindahl, B., Fu, M. L., & Hammarsten, O. (2015). Small changes in troponin T levels are common in patients with non-ST-segment elevation myocardial infarction. Clinical Chemistry, 61(7), 942-951.
12) Body, R., Carlton, E., Sperrin, M., Lewis, P. S., Burrows, G., Carley, S., McDowell, G., Buchan, I., & Greaves, K. (2018). Troponin-only Manchester Acute Coronary Syndromes decision aid: Single biomarker reclassification of patients with acute chest pain. Heart, 104(7), 625-632.
13) Boeddinghaus, J., Nestelberger, T., Twerenbold, R., Koechlin, L., Meier, M., Wussler, D., Badertscher, P., Wildi, K., Rubini Gimenez, M., & Mueller, C. (2019). Impact of age on the performance of the ESC 0/1h algorithms for early diagnosis of myocardial infarction. European Heart Journal, 39(42), 3780-3794.
14) Burgos, L. M., Trivi, M., & Costabel, J. P. (2020). Performance of the European Society of Cardiology 0/1-hour algorithm in the diagnosis of myocardial infarction with high-sensitivity cardiac troponin: Systematic review and meta-analysis. European Heart Journal: Acute Cardiovascular Care, 10(3), 279-286.
15) Carlton, E. W., Cullen, L., Than, M., Gamble, J., Khattab, A., & Greaves, K. (2015). A novel diagnostic protocol to identify patients suitable for discharge after a single high-sensitivity troponin. Heart, 101(13), 1041-1046.
16) Chapman, A. R., Adamson, P. D., & Mills, N. L. (2017). Assessment and classification of patients with myocardial injury and infarction in clinical practice. Heart, 103(1), 10-18.
17) Collet, J. P., Thiele, H., Barbato, E., Barthelemy, O., Bauersachs, J., Bhatt, D. L., Dendale, P., Dorobantu, M., Edvardsen, T., & Gale, C. P. (2021). 2020 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. European Heart Journal, 42(14), 1289-1367.
18) Cullen, L., Greenslade, J. H., Than, M., Brown, A. F. T., Hammett, C. J., Lamanna, A., Hawkins, T., Parsonage, W., & George, P. M. (2016). The new Vancouver Chest Pain Rule using troponin as the onl y biomarker: An external validation study. American Journal of Emergency Medicine, 34(1), 129-134.
19) Fanaroff, A. C., Rymer, J. A., Goldstein, S. A., Simel, D. L., & Newby, L. K. (2015). Does this patient with chest pain have acute coronary syndrome? JAMA, 314(18), 1955-1965.
20) Gimenez, M. R., Twerenbold, R., Boeddinghaus, J., Nestelberger, T., Puelacher, C., Hillinger, P., Wildi, K., Jaeger, C., Grimm, K., & Mueller, C. (2016). Clinical effect of sex-specific cutoff values of high-sensitivity cardiac troponin T in suspected myocardial infarction. JAMA Cardiology, 1(8), 912-920.

21) Gulati, M., Levy, P. D., Mukherjee, D., Amsterdam, E., Bhatt, D. L., Birtcher, K. K., Blankstein, R., Boyd, J., Bullock-Palmer, R. P., & Shaw, L. J. (2021). 2021 AHA/ACC guideline for the evaluation and diagnosis of chest pain. Circulation, 144(22), e368-e454.
22) Hammarsten, O., Fu, M. L. X., Sigurjonsdottir, R., Petzold, M., Said, L., Landin-Wilhelmsen, K., Widgren, B., Larsson, M., Johanson, P., & Bjurman, C. (2018). Troponin T percentiles from a random population sample, emergency room patients and patients with myocardial infarction. Clinical Chemistry, 58(3), 628-637.
23) Jaffe, A. S., & Morrow, D. A. (2017). Troponin testing: Analytical and clinical considerations. Journal of the American College of Cardiology, 70(8), 996-1012.
24) Kimenai, D. M., Janssen, E. B. N. J., Eggers, K. M., Lindahl, B., den Ruijter, H. M., Bekers, O., & Meex, S. J. R. (2018). Sex-specific versus overall clinical decision limits for cardiac troponin I and T for the diagnosis of acute myocardial infarction. Clinical Chemistry, 64(7), 1034-1043.
25) Lambrakis, K., Papendick, C., French, J. K., Quinn, S., Blyth, A., Seshadri, A., Edmonds, M. J., Briffa, T., Cullen, L., & Chew, D. P. (2021). Late outcomes of the RAPID-TnT randomized controlled trial. Circulation, 144(2), 113-125.
26) Lowry, M. T. H., Anand, A., Mills, N. L., & Shah, A. S. V. (2023). High-sensitivity cardiac troponin and early rule-out of myocardial infarction in patients with suspected acute coronary syndrome. Heart, 109(15), 1137-1144.
27) Mair, J., Lindahl, B., Hammarsten, O., Muller, C., Giannitsis, E., Huber, K., & Mockel, M. (2018). How is cardiac troponin released from injured myocardium? European Heart Journal: Acute Cardiovascular Care, 7(6), 553-560.
28) Mills, N. L., Churchhouse, A. M. D., Lee, K. K., Anand, A., Gamble, D., Shah, A. S. V., Paterson, E., MacLeod, M., Graham, C., & Newby, D. E. (2011). Implementation of a sensitive troponin I assay and risk of recurrent myocardial infarction and death in patients with suspected acute coronary syndrome. JAMA, 305(12), 1210-1216.
29) Mueller, C., Giannitsis, E., Christ, M., Ordonez-Llanos, J., deFilippi, C., McCord, J., Body, R., Panteghini, M., Jernberg, T., & Plebani, M. (2019). Multicenter evaluation of a 0-hour/1-hour algorithm in the diagnosis of myocardial infarction with high-sensitivity cardiac troponin T. Annals of Emergency Medicine, 68(1), 76-87.
30) Neumann, J. T., Sorensen, N. A., Schwemer, T., Ojeda, F., Bourry, R., Sciacca, V., Schaefer, S., Waldeyer, C., Sinning, C., & Blankenberg, S. (2016). Diagnosis of myocardial infarction using a high-sensitivity troponin I 1-hour algorithm. JAMA Cardiology, 1(4), 397-404.
31) Pickering, J. W., Greenslade, J. H., Cullen, L., Flaws, D., Parsonage, W., George, P., Worster, A., Kavsak, P. A., & Than, M. (2017). Validation of presentation and 3 h high-sensitivity troponin to rule-in and rule-out acute myocardial infarction. Heart, 103(12), 983-989.
32) Pickering, J. W., Than, M. P., Cullen, L., Aldous, S., Ter Avest, E., Body, R., Carlton, E. W., Collinson, P., Dupuy, A. M., & Kavsak, P. (2017). Rapid rule-out of acute myocardial infarction with a single high-sensitivity cardiac troponin T measurement below the limit of detection: A collaborative meta-analysis. Annals of Internal Medicine, 166(10), 715-724.
33) Reichlin, T., Schindler, C., Drexler, B., Twerenbold, R., Reiter, M., Zellweger, C., Moehring, B., Ziller, R., Hoeller, R., & Mueller, C. (2012). One-hour rule-out and rule-in of acute myocardial infarction using high-sensitivity cardiac troponin T. Archives of Internal Medicine, 172(16), 1211-1218.

34) Sandoval, Y., Smith, S. W., Sexter, A., Schulz, K., Apple, F. S., & Jaffe, A. S. (2017). Diagnostic performance of high-sensitivity cardiac troponin I for early rule-out of acute myocardial infarction. Clinical Chemistry, 63(1), 369-376.
35) Sandoval, Y., Nowak, R., deFilippi, C. R., Christenson, R. H., Peacock, W. F., McCord, J., Limkakeng, A. T., & Apple, F. S. (2019). Myocardial infarction risk stratification with a single measurement of high-sensitivity troponin I. Journal of the American College of Cardiology, 74(3), 271-282.
36) Than, M., Cullen, L., Aldous, S., Parsonage, W. A., Reid, C. M., Greenslade, J., Flaws, D., Hammett, C. J., Beam, D. M., & Richards, A. M. (2014). 2-hour accelerated diagnostic protocol to assess patients with chest pain symptoms using contemporary troponins as the only biomarker. Journal of the American College of Cardiology, 64(24), 2569-2578.
37) Twerenbold, R., Neumann, J. T., Sorensen, N. A., Ojeda, F., Karakas, M., Boeddinghaus, J., Nestelberger, T., Badertscher, P., Rubini Gimenez, M., & Mueller, C. (2018). Prospective validation of the 0/1-h algorithm for early diagnosis of myocardial infarction. Journal of the American College of Cardiology, 72(6), 620-632.
38) Wild, P. S., Tzikas, S., Keller, T., Schulz, A., Zwiener, I., Zeller, T., Schnabel, R. B., Sinning, C. R., Lubos, E., & Blankenberg, S. (2017). High-sensitivity cardiac troponin I and T and cardiovascular disease in the general population. Clinical Chemistry, 63(1), 187-196.
39) Wright, C. X., Wright, D. S., Hu, J. R., & Gallegos, C. (2024). High-sensitivity troponin: Finding a meaningful delta. Journal of Cardiovascular Development and Disease, 11(10), 318.
40) Zhelev, Z., Hyde, C., Youngman, E., Rogers, M., Fleming, S., Slade, T., Coelho, H., Jones-Hughes, T., Nikolaou, V., & Davenport, C. (2015). Diagnostic accuracy of single baseline measurement of Elecsys Troponin T high-sensitive assay for diagnosis of acute myocardial infarction in emergency department: Systematic review and meta-analysis. BMJ, 350, h15.