Clinical Chemistry

Exploring Sex-Specific High-Sensitivity Cardiac Troponin Thresholds for Rule-Out of Non-ST-Elevation Myocardial Infarction

Article:
Ingar Ziad Restan, Yong Yong Tew, Ole-Thomas Steiro, Ziwen Li, Hilde L Tjora, Jørund Langørgen, Torbjørn Omland, Paul Collinson, Rune Bjørneklett, Kjell Vikenes, Trude Steinsvik, Øyvind Skadberg, Øistein R Mjelva, Alf Inge Larsen, Vernon V S Bonarjee, Nicholas L Mills, Kristin M Aakre.
Exploring Sex-Specific High-Sensitivity Cardiac Troponin Thresholds for Rule-Out of Non-ST-Elevation Myocardial Infarction.
Clin Chem 2026; 72(8): 868–79. https://doi.org/10.1093/clinchem/hvag030

Guest: Dr. Ingar Ziad Restan is a cardiologist at Stavanger University Hospital in Stavanger, Norway.

Bob Barrett: This is a podcast from *Clinical Chemistry*, a production of the Association for Diagnostics & Laboratory Medicine. I am Bob Barrett.

Chest pain is one of the most common and challenging reasons patients come to the emergency department. The concern, of course, is myocardial infarction. But only a minority of these patients are actually having a heart attack. Emergency physicians need to make decisions quickly. Who needs treatment and further observation, and who can safely go home?

Current guideline-recommended single-sample rule-out thresholds are generally uniform within each assay, applied equally to females and males. That makes them simple to use. But does the same numerical threshold provide the same diagnostic safety margin, or could one threshold be too permissive in females and unnecessarily conservative in males?

A new research article in the August 2026 issue of *Clinical Chemistry* examines exactly these questions in two separate, large chest pain cohorts with samples tested on three commonly used instrument platforms.

Today we're joined by the article's lead author. Dr. Ingar Ziad Restan is a cardiologist at Stavanger University Hospital in Stavanger, Norway. His research focuses on accelerated diagnostic protocols and cardiac troponins in the setting of acute coronary syndromes.

So, Dr. Restan, your paper, in essence, asks the question: Should sex matter at the very low troponin concentrations used to rule out myocardial infarction? What prompted that question?

Ingar Ziad Restan: Thank you, Bob. There is, I believe, an increasing recognition that, in many areas of medicine, one size does not fit all. Individual or group-based characteristics have significance

when assessing a person for several pathologies, and biological sex might have been underestimated in this regard.

Sex-specific troponin cutoffs, meaning the 99-percentile upper reference limit, which is the main criterion for myocardial infarction (MI), have quite a bit of support amongst medical policy and guideline makers. However, in the emergency department, a lot of the clinical value of high-sensitivity troponin is at the other end of the scale, identifying patients with such low concentrations of troponin that MI can be ruled out early.

Due to that interesting biological fact, the European Society of Cardiology, the ESC, has recommendations for very low troponin levels that can be used to rule out MI with a very high degree of certainty. Our paper looked more closely at this set of very low cutoff levels that are proposed to rule out MI with only a single blood draw taken on arrival to the ED.

Our concern, however, is that if females generally have lower baseline troponin concentrations, such a single uniform low rule-out threshold may not give exactly the same safety margins in females and males.

In practical terms, the same number might represent a higher percentile for females and relatively lower for males. So, we hypothesized that uniform single-sample rule-out thresholds might be less sensitive in females while being unnecessarily conservative in males.

Bob Barrett: You evaluated this question in two independent patient cohorts and across three high-sensitivity troponin assays. For those who have not read the paper, could you just walk us through the design?

Ingar Ziad Restan: Certainly. What we did initially, we used nearly 2,000 patients from WESTCOR as the derivation cohort. That was a prospective observational study from two Norwegian hospitals, including adults presenting with symptoms suggestive of MI, in practical terms, mostly chest pain. We then externally validated our findings from WESTCOR into a substudy from the High-STEACS trial in Edinburgh, which had comparable size and similar patients.

A key point is that we looked at three widely used high-sensitivity troponin assays in parallel. Troponin T from Roche, troponin I on both an Abbotts platform and a Siemens platform.

The endpoint we used was type 1 MI at index presentation and we then assessed separately in females and males how the ESC-recommended uniform thresholds performed and

whether sex-specific thresholds could meet our predefined safety criteria, including a very high level of sensitivity for MI.

Bob Barrett: Your paper reports that females more often had troponin concentrations below the uniform rule-out thresholds, yet those thresholds did not reach your sensitivity target in females. That sounds counterintuitive at first. What did you find?

Ingar Ziad Restan: I think the counterintuitive part is important. More females have very low troponin concentrations, so uniform thresholds rule out a larger proportion of females. But that does not automatically mean the threshold is equally safe.

In the derivation cohort, the WESTCOR, the guideline-recommended uniform thresholds did not achieve 99% sensitivity in females for any of the three assays.

In males, performance generally met safety criteria, but fewer males were ruled out, meaning the strategy was less efficient in males. When we derived sex-specific thresholds, the female thresholds were lower numerically and the male thresholds were higher. For instance, using Siemens troponin I as an example, for females the threshold was less than two nanograms per liter, and for males less than seven nanograms per liter. The ESC-recommended uniform threshold is below three nanograms per liter.

While this could seem like a trivial distinction of very small numbers, the numerically small sex-specific adjustments reduced the proportion of females ruled out while improving sensitivity, while in males it substantially increased the proportion eligible for single-sample rule-outs.

Bob Barrett: Well, just to follow up, can you give a practical example of what that means in the emergency department?

Ingar Ziad Restan: Certainly. Again, the Siemens assay could be a good example in this regard, particularly in the derivation cohort. When using the uniform threshold, only 17% of males were ruled out with this assay. With the sex-specific male threshold we derived, that increased to 54%, and that is potentially a very large difference in patient flow.

The trade-off, however, is that for females the threshold became more conservative, reducing early rule-out proportions. So, in the end, we can’ t say that sex-specific is better in every sense. Rather, the balance between safety and efficiency is shifted between the sexes using these sex-specific thresholds.

Bob Barrett: Doctor, some readers might skim this paper and wonder whether current rule-out pathways are unsafe, particularly for women. Is that the message of the paper?

Ingar Ziad Restan: Certainly not, Bob, and thank you for that good question. I would be very careful not to overstate our findings. The current diagnostic pathways have a very strong evidence base and are used safely in many settings. They do not rely on troponin alone. They include symptoms, EKG findings, and other criteria.

Our study focuses on one specific component of these diagnostic pathways, the very low single-sample rule-out threshold in patients presenting more than three hours after symptom onset.

What we have shown is that the performance of that component is not identical in females and males. So, the message is not that the current pathways should be abandoned, but perhaps that there are room for refinement, especially if the aim is to provide equivalent safety margins across sexes while also improving efficiency in emergency departments worldwide.

Bob Barrett: Well, finally, doctor, clinical laboratories and emergency departments both value simplicity, but sex-specific thresholds, especially across different assays, adds complexity. What do you think about that trade-off?

Ingar Ziad Restan: I think that's probably the central implementation question, Bob. A universal threshold is attractive because it's simple, but this simplicity can hide important variation. Our data suggests that both assay-specific and sex-specific behavior matter at these very low-troponin concentrations. If we ignore that, we might accept unequal safety and efficiency without realizing it.

The 2015 ESC guidelines recommended diagnostic algorithms for three different high-sensitivity troponin assays, while the 2023 revision included nine.

Currently, there's at least 30 different troponin assays that are commercially available, and additional platforms continue to emerge. And all these have distinct characteristics and thresholds, which already represents the complexity in the field. At the same time, I do not think the answer is to ask every clinician to memorize multiple new thresholds. If sex-specific rule-out thresholds are ever implemented, which I think they might, they should probably be built into the laboratory reporting systems and clinical decision support.

The report should state directly whether the value falls below the appropriate rule-out threshold for that patient, that

assay, and in a certain clinical context. That would preserve clinical usability while also allowing us a more nuanced interpretation.

So, before any sex-specific rule-out threshold should be implemented, I would prefer larger validation, ideally pooled across cohorts and healthcare systems, and then prospective evaluation of what the clinical implementation means. The ultimate question is whether sex-specific thresholds improve clinical practice, not just whether they look better in a retrospective diagnostic analysis.

Bob Barrett: That was Dr. Ingar Ziad Restan from Stavanger University Hospital in Stavanger, Norway. He wrote a research article in the August 2026 issue of *Clinical Chemistry* assessing sex-specific troponin thresholds for rule-out of myocardial infarction and was our guest in this podcast on that topic. I'm Bob Barrett. Thanks for listening.