

Editorial

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High sensitivity cardiac troponin assays, rapid myocardial infarction rule-out algorithms, and assay performance

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High sensitivity (hs) assays for cardiac troponins (cTn) T and I have been introduced more than 10 years ago [1]. Until then rule-out of non-ST-elevation myocardial infarctions (NSTEMI) in the emergency room or chest pain-unit required determination of cTn upon arrival of the patient and then again after 6 h observation before NSTEMI could be ruled-out safely. In 2009 there were already studies showing that the observation period can be reduced to 3 h with more sensitive assays for cTn [2, 3]. In the following years studies were published showing that undetectable or very low cTn concentrations upon admission very reliably ruled out NSTEMI when hs-cTn assays were used. These data were further expanded by evaluation of the change in cTn concentration within 1 h or 2 h. The 2015 ESC guidelines for patients with suspected acute coronary syndromes presenting without persistent ST-segment elevation for the first time proposed rapid rule-out and rule-in strategies based on cTnT or cTnI measured upon arrival and after 1 h. At that time only two assays were validated for these algorithms [4]. In the current 2023 ESC Guidelines for the management of acute coronary syndromes a total of nine rapid rule-out and rule-in 0/1 h algorithms for nine different cTn assays are listed including two point of care assays [5].

Recently, several articles including two letters in *CCLM* appeared that analyzed the effect of random analytical variation or assay imprecision on the safety of rapid rule-out algorithms and in particular immediate/0 h rule-out [6–9]. Obviously, a potential problem would be misclassification of patients due to assay imprecision. Patients might be erroneously ruled-out or vice versa not ruled-out. Not surprisingly, the risk of misclassification is highest for patients with measured cTn concentrations close to the assay specific cutoff for rule-out. Similarly expected, greater

assay imprecision increases the rate of misclassification. While not ruling-out a patient who could be ruled-out only prolongs the stay of this patient in the emergency room and thus increases overall costs, falsely ruling-out may cause adverse outcomes for individual patients.

Interestingly, both author groups of the letters to *CCLM* conclude that even though the rate of misclassification is substantial for a CV of 10 % and cTn concentration close to the cutoff, the effect on the negative predictive value (NPV) is negligible [8, 9]. Even with 20 % CV the effect is still minor so that the calculated NPV remains >99 %. This is in line with the other studies on this subject [6, 7]. The current definition requires that the CV of a hs-cTn assay at the 99th percentile of the population distribution is less than 10 %. Since assay CV increases with decreasing cTn concentrations towards the limit of quantitation, CVs between 10 and 20 % at the low end of the measuring interval of high sensitivity cTn assays are not uncommon. At the limit of detection of an assay CVs are even higher [10, 11].

In summary, high assay imprecision compromises correct classification by every rule-out algorithm. Why does analytical variation have so little consequences on NPV and patient outcome? The answer to this question probably lies in the design of the studies on which the rapid rule-out algorithms are based. These studies were all clinical validations rather than technical validations. Going over the methodology they all have in common that the cutoffs for immediate rule-out, i.e. rule-out based on the cTn concentration at presentation (0 h cTn), were chosen as to achieve a predefined sensitivity and NPV, usually >99 %. For this purpose only assays were used which were approved for clinical use or were scheduled to be released shortly. These assays have known imprecision profiles which include the low end of their measuring interval. At concentrations below 5 ng/L CV is usually >10 % (Figure 1). None of the clinical studies tried to reduce random errors, e.g. by duplicate determination of cTn. Thus, the imprecision profile of an assay is so to speak tacitly priced into the determination of the cutoff for immediate rule-out. Accordingly, it is not surprising that even though a hypothetical CV of 10 % at the

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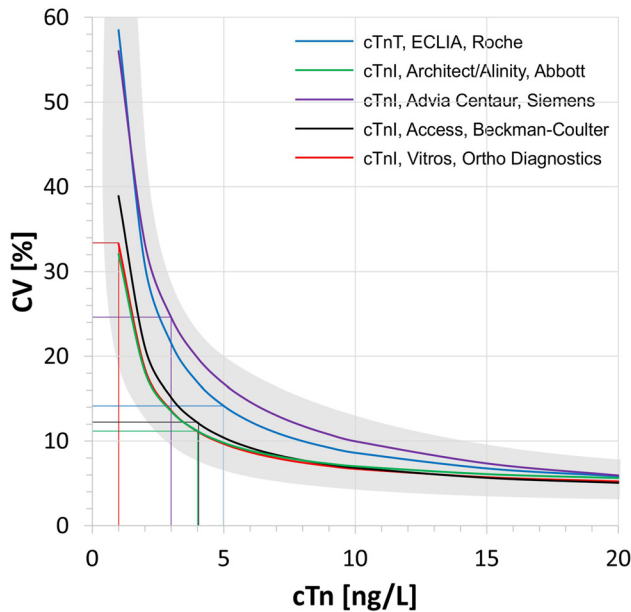


Figure 1: Imprecision profiles of five commonly used high sensitivity assays for cTn. The profiles were derived from published data [10, 12–14]. CV at the recommended cutoff for immediate rule-out is shown for each assay. The shaded area shall illustrate the approximate range of imprecisions for established hs-cTn assays. It does not show a confidence interval.

cutoff for immediate rule-out leads to substantial misclassification, this does not affect NPV. In fact, assay imprecision determines the “safety margin” required for the rule-out cutoff in order to achieve the desired sensitivity and NPV. Two caveats should be kept in mind: (1) most studies analyzed frozen patient samples in batch mode, i.e. with one lot of reagents and calibrators and one calibration. Accordingly the imprecision profile of these studies will be more favorable than under daily routine conditions. (2) There is no information on bias in most studies.

What are the consequences? Even though recent evidence suggests that even substantial increases in CV do not significantly compromise NPV [6–9] of rapid rule-out algorithms laboratories should ascertain that assay imprecision is within the known range of the respective cTn-assay around the relevant cutoff and bias is minimal. This should be regularly monitored by using control materials in the appropriate concentration range. The approximate CVs at the recommended cutoff for immediate rule-out can be estimated from Figure 1. Only few clinical studies reported assay imprecision in the low concentration range applied in rapid rule-out algorithms [15–18]. Even fewer reported regular monitoring of assay performance [15, 17]. However, assuming that assay imprecision in the clinical studies was similar to the known imprecision profile of the assay, similar

patient outcomes should be achieved, if the assay is properly performed and populations are comparable.

What would happen, if assay precision could be significantly improved? The effect on patient classification would probably be minor. However, improved precision would most likely permit to raise the respective cutoff without compromising NPV. This would mean that more patients could be ruled out with the 0 h cTn result. Similar considerations apply to the change of cTn concentration over one or 2 h.

In summary, the recent reports that moderately increased imprecision at the cutoff for immediate rule-out of myocardial infarction does not lead to clinically significant misclassification of patients confirm that the recommended 0/1 h algorithms are robust and represent an excellent example of value-based laboratory medicine.

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