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High-sensitivity cardiac troponin at 3 hours: is the cat amongst the pigeons?

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In November 2014 the National Institute for Health and Care Excellence (NICE) issued recommendations for the use of high-sensitivity cardiac troponin (hs-cTn) assays in the United Kingdom [1]. Two assays were evaluated: the Elecsys hs-cTnT assay (Roche Diagnostics) and the ARCHITECT hs-cTnI assay (Abbott Laboratories). On the basis of both clinical and economic evidence, NICE recommended that hs-cTn assays could be used to 'rule out' the diagnosis of non-ST elevation myocardial infarction (NSTEMI) within 4 hours of patients arriving in an Emergency Department (ED). NICE further stated that this would typically involve 'ruling out' NSTEMI in patients with hs-cTn concentrations below the 99th percentile upper reference limit when tested both on arrival in the ED and three hours later. This recommendation was based on the findings of a commissioned systematic review [2]. The systematic review had pooled existing evidence from 18 studies to define more granular 'optimal' testing strategies for each hs-cTn assay. However, diagnostic strategies based on such models may not perform as well when used in practice. In this issue of the Journal, two studies have made efficient use of existing data from large cohort studies to further evaluate the accuracy of those diagnostic strategies [3,4].

Pickering et al pooled data from five cohort studies to examine the diagnostic accuracy of hs-cTn measured on arrival and 3 hours later, using standard cardiac troponin testing as the reference standard [3]. Four of the five studies included had set out to evaluate hs-cTn measurement 2 hours after arrival. However, in practice a significant proportion of participants underwent hs-cTn testing between 3 and 4.5 hours after arrival and this group was included in the current analysis. The findings may come as a surprise. Using the 99th percentile cut-off, this 3-hour rule out strategy had a sensitivity of just 93.2% (95% CI 87.5 – 96.8%) with hs-cTnI and 94.8% (95% CI 89.6 – 97.9%) with hs-cTnT. The number of patients in each of the five individual cohorts was too small to allow meaningful direct comparisons that could help us to understand whether this may be partly

explained by different assays used as a reference standard or by differences in the proportion of patients presenting within a few hours of symptom onset.

Pickering et al conclude that pathways based exclusively on the 99th percentile should not be used to rule out NSTEMI in clinical practice and propose an alternative that combines a low threshold for risk stratification at presentation [5,6] and delta criteria to identify patients with rising cardiac troponin concentrations at 3 hours that remain below the 99th percentile. This approach would improve the sensitivity from 93.7% to 99.2% (1 false negative) for hs-cTnI and from 94.8% to 99.3% (1 false negative) for hs-cTnT. The pathway requires external validation, but the concept of harnessing the additional sensitivity these assays give in patients with troponin concentrations within the normal reference range is important. This approach will help risk stratify patients and identify the small number of patients who will continue to require testing at 6 hours, and will help to improve the safety and efficacy of early rule out pathways.

Parsonage et al also pooled data from three existing datasets to evaluate the optimal testing strategies for ruling out NSTEMI defined in the NICE systematic review [4]. This post-hoc analysis of observational data evaluated performance of the 'optimal' testing strategies used to model the clinical and cost-effectiveness of the hs-cTnI and hs-cTnT assays in the NICE technology appraisal. They observed that the hs-cTnI testing strategy had a higher false negative rate than the model (2.0% *versus* 0.4%), and the hs-cTnT pathway ruled out a smaller proportion of patients than anticipated by the model (53% versus 69%). There are some limitations that arise in pooling data from different cohorts. First, the diagnostic endpoint of acute myocardial infarction was adjudicated using a variety of assays. Whilst the hs-cTnI pathway ruled out the expected proportion of patients (80% *versus* 78%) the sensitivity was low at 89%. The majority of false negatives (37/51) were from the cohort of patients where a hs-cTnT assay was used to adjudicate the final diagnosis. It is likely

that the observed performance of the hs-cTnI assay at presentation and 3 hours would have been better if the index diagnosis was based on serial sampling over 6 hours with the same assay. Second, in two of the three cohorts included in this analysis the second blood sample was drawn after 2 hours (rather than 3 hours, as specified in the NICE recommendations). It is possible that this earlier sampling time may have reduced the observed sensitivity and negative predictive value.

However, based on their findings, Parsonage et al recommend that neither of the testing strategies using hs-cTnI and hs-cTnT should be used to rule out NSTEMI in clinical practice. This raises the question of what strategy should be used. The NICE review was a technology appraisal rather than a clinical guideline and, as such, recommended the general principle of using hs-cTn in an early rule out protocol rather than a specific pathway. It was based on an economic analysis showing that early rule out protocols are cost-effective compared to a standard cTn assay at 10-12 hours. Since delayed testing is more expensive than early testing the economic analysis may be best understood as showing that the additional cases detected by delayed testing do not justify the additional costs, as a general principle. The specific choice of which early rule out pathway to use depends upon clinical interpretation of the accuracy data. Systematic appraisal and the development of innovative testing strategies like those reported in this edition of the journal will help clinicians to maximise the potential of high-sensitivity cardiac troponins and improve the safety and effectiveness of our Emergency Departments.

The findings of these two papers should not lead us to conclude that the NICE recommendations, which focus on guiding the cost-effective use of NHS resources, are inappropriate. However, they do suggest that diagnostic accuracy may be lower than originally anticipated. This serves to emphasise the potential tension between cost-effectiveness and the clinical safety of rule out algorithms. It also highlights the need for future work to externally validate these findings, and to determine whether

additional clinical risk stratification (which was outside the scope of the NICE recommendations) will optimise the safety and effectiveness of the rule out strategies that NICE and the European Society of Cardiology currently recommend.

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