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Implementing rapid algorithms for high sensitivity troponin – economic benefits and caveat emptor.

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Corresponding Author:	Paul Collinson St George's Hospital London, UNITED KINGDOM
Corresponding Author Secondary Information:	
Corresponding Author's Institution:	St George's Hospital
Corresponding Author's Secondary Institution:	
First Author:	Paul Collinson
First Author Secondary Information:	
Order of Authors:	Paul Collinson
Order of Authors Secondary Information:	

Implementing rapid algorithms for high sensitivity troponin – economic benefits and caveat emptor.

Running head Commentary on Economic analysis

Paul Collinson[1]

[1]Departments of Clinical Blood Sciences and Cardiology, St George's University Hospitals NHS Foundation Trust and St George's University of London, Cranmer Terrace London SW17 0QT, UK

Corresponding author: Professor Paul Collinson[1], email: paul.collinson@stgeorges.nhs.uk

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High sensitivity cardiac troponin (hs cTn) assays are now available world-wide. The aim of the diagnostics industry as a whole is to provide and support the implementation of hs cTn. Provision of the previous generation assays will occur only until regulatory approval is obtained for the high sensitivity version in the relevant geographic area, with the objective of phasing out the previous generation assays (personal communication). In Europe there is almost complete conversion to hs cTn(1) although in the United States conversion has been slower due to regulatory delays.

The merits of switching to hs cTn assays have been debated. Earlier fears of increased resource utilisation arising from greater diagnostic sensitivity have not even born out in clinical practice(2-4). However, enthusiastic over requesting in the Emergency Department (ED) can often produce inappropraite cardiac referrals where cardiac troponin (cTn) elevation is not due to acute coronary syndromes (ACS). Indeed, ACS is now the minority cause of elevated cTn in the unselected ED population(4, 5).

The current hs cTn assays can achieve very low imprecision (the variation between repeated measurements of the same sample) at low absolute values of cTn, those values within the lower 25% of the reference interval. This property has been exploited in a number of clinical studies that have shown that measurements of cTn made on admission(6, 7) or in the 1-2 hours following admission(8) can be used to predict the subsequent risk of myocardial infarction as defined by the conventional 99th percentile threshold(9). Although often described as diagnostic algorithms these are in fact predictive algorithms, something which

should always be remembered. They are risk stratification tools based on the troponin and the result they provide should be combined with clinical findings and the electrocardiogram. An admission level that is very low or low but does not significantly change predicts a low risk. Conversely, an initially high value or one within the reference interval which significantly changes predicates admission to the coronary care unit. This predictive risk stratification approach has been endorsed both following evidence based review by the UK National Institute of health and Care Excellence (NICE)(10, 11) and by the European Society of Cardiology (ESC) (12).

Are these algorithms likely to be clinically useful and improve resource utilisation? Although the appeal of rapid emptying of the ED of patients who do not need to be there is apparently self-evident, there is a lack of real world studies to address this point. Although the switch to hs cTn in Europe is near universal, uptake of rapid diagnosis is less so(1). The recent paper by Cohen and colleagues in this issue of the Journal is therefore timely in supporting the introduction of rapid diagnostic algorithms by providing an assessment of both the clinical and economic benefits.

The authors undertook an audit of test requesting practices and clinical decisions over a 58 month period for patients presenting with suspected non-ST elevation myocardial infarction (NSTEMI) to the ED. During this period, all patients had cardiac troponin T (cTnT) measured by a high sensitivity assay (hs cTnT) but patients were managed according to the local diagnostic protocol which utilised the 99th percentile and pre-test probability for significant coronary artery disease for management decisions. The reason for this was although the assay has high sensitivity characteristics, only results above 13 ng/L were reported numerically and available to the clinicians managing the patient. The authors

therefore had the opportunity to compare actual management based on, effectively, the 99th percentile (14 ng/L) and clinical judgement with what might have happened if management had occurred according to ESC recommendations. They then undertook operational and financial modelling to assess the impact on resource utilisation. The unique aspect of the study is that it reviews real world data in a real world decision making environment with the clinicians blinded to the hs cTn results. The authors identified a cohort of 3775 out of 11477 consecutive patients who were triaged and met the ESC rapid rule out criteria but were nevertheless admitted. Only 0.32% of the patients had a primary outcome of index myocardial infarction or all cause death within 30 days. For those patients with a cTnT value <5 ng/L there was zero 30 day mortality. More than half of the patients who presented had cTnT values that met the rule out criteria but approximately one third underwent further clinical investigation. The prognosis in this group was statistically indistinguishable to those patients who met ESC rule out criteria and were discharged from the ED. The admitted patients used significant health care resources including ED stay, hospital stay and the use of invasive and non-invasive cardiac tests but did not have clinical findings requiring revascularisation.

The study therefore confirms the findings from other large studies that a very low troponin either at or close to the limit of detection of the assay defines a very low risk group of individuals who do not need hospital admission and intensive investigation(13). Indeed, they were able to identify a cohort where no benefits of further investigations were demonstrated. Numeric results below 14 ng/L were not available to the attending physicians who therefore managed patients based on clinical assessment. The net result was inappropriate and significant use of health care resources. The study therefore provides strong support for the economic benefit of shifting from diagnosis based on the 99th percentile plus clinical assessment to using rapid predictive algorithms plus clinical assessment(14). The overall

conclusion is therefore that rapid rule out of patients based on low troponin values is both safe and cost-effective.

The study also sheds light on requesting patterns in cTn testing. First, only approximately one third of troponin tests were part of investigation of suspected ACS. Second, of those patients evaluated 38.2% had a cTnT between 5-14 ng/L but did not have a repeat test performed as recommended by current guidelines. This is consistent with other studies where rapid diagnostic algorithms have been implemented(15).

There is an interesting caveat to this study. The study was only possible as the product labelling reported that the limit of quantitation of the assay, usually considered to be the lowest reportable numeric values of the assay, to be 13 ng/L. This may well have contributed to the unnecessary repeat testing occurred in patients with cTnT values <5 ng/L. Closer reading of the current package insert for the hs cTnT assay shows that this is indeed the wording used but applies to the 10% coefficient of variation (CV) of the assay. Limit of quantitation is usually considered to represent a CV of 20%. The assay performance reported by the manufacturer on the International Federation of Clinical Chemists cardiac biomarkers webpage is consistent with the ESC recommendations for cTnT with a 20% CV of 1-3 ng/L. (https://www.ifcc.org/media/479435/high-sensitivity-cardiac-troponin-i-and-t-assay-analytical-characteristics-designated-by-manufacturer-v052022.pdf). The study laboratory confirmed that the analytical performance of the assay was consistent with high sensitivity criteria. The company website supports the use of the ESC guideline. It is important that information supplied by manufacturers is consistent across electronic data sources and package inserts (instructions for use, IFU) and reflects accepted scientific publications and current guidelines. Caveat emptor indeed.

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Conflict of Interest form (one for each author)