Patient selection for high sensitivity cardiac troponin testing and diagnosis of myocardial infarction

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RESEARCH

Patient selection for high sensitivity cardiac troponin testing and diagnosis of myocardial infarction: prospective cohort study

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Abstract

Objective To evaluate how selection of patients for high sensitivity cardiac troponin testing affects the diagnosis of myocardial infarction across different healthcare settings.

Design Prospective study of three independent consecutive patient populations presenting to emergency departments.

Setting Secondary and tertiary care hospitals in the United Kingdom and United States.

Participants High sensitivity cardiac troponin I concentrations were measured in 8500 consecutive patients presenting to emergency departments: unselected patients in the UK (n=1054) and two selected populations of patients in whom troponin testing was requested by the attending clinician in the UK (n=5815) and the US (n=1631). The final diagnosis of type 1 or type 2 myocardial infarction or myocardial injury was independently adjudicated.

Main outcome measures Positive predictive value of an elevated cardiac troponin concentration for a diagnosis of type 1 myocardial infarction.

Results Cardiac troponin concentrations were elevated in 13.7% (144/1054) of unselected patients, with a prevalence of 1.6% (17/1054) for type 1 myocardial infarction and a positive predictive value of 11.8% (95% confidence interval 7.0% to 18.2%). In selected patients, in whom troponin testing was guided by the attending clinician, the prevalence and positive predictive value were 14.5% (843/5815) and 59.7% (57.0% to 62.2%) in the UK and 4.2% (68/1631) and 16.4% (13.0% to 20.3%) in the US. Across both selected patient populations, the positive predictive value was highest in patients with chest pain, with ischaemia on the electrocardiogram, and with a history of ischaemic heart disease.

Conclusions When high sensitivity cardiac troponin testing is performed widely or without previous clinical assessment, elevated troponin concentrations are common and predominantly reflect myocardial injury rather than myocardial infarction. These observations highlight how selection of patients for cardiac troponin testing varies across healthcare settings and markedly influences the positive predictive value for a diagnosis of myocardial infarction.

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Introduction

Cardiac troponin is integral to the diagnosis of myocardial infarction,[1] but troponin concentrations are often elevated in patients who do not have acute coronary syndrome. The universal definition now classifies myocardial infarction as spontaneous or type 1, due to plaque rupture and coronary thrombosis, and secondary or type 2 due to myocardial oxygen supply-demand imbalance.[2-5] Patients with elevated cardiac troponin concentrations in the absence of myocardial ischaemia are classified as having myocardial injury.[6] Although patients with type 2 myocardial infarction or myocardial injury are increasingly recognised in clinical practice,[2-10] they represent a heterogeneous group with overt or covert major illness for whom no evidence base exists to guide optimal cardiac investigation or treatment.

We have shown that lowering the diagnostic threshold by using a more sensitive cardiac troponin assay reduced recurrent myocardial infarction or death in patients redefined as having type 1 myocardial infarction.[11] However, use of these lower diagnostic thresholds more than doubled the number of patients with type 2 myocardial infarction or myocardial injury with no improvement in their outcome despite undergoing additional cardiac investigation.[2] The introduction of high sensitivity cardiac troponin assays may further increase the frequency of type 2 myocardial infarction or myocardial injury,[6 7] potentially leading to diagnostic uncertainty and unnecessary investigation of patients without acute coronary syndrome.[12-14]

Patients attending the emergency department often have simultaneous testing for both cardiac and non-cardiac conditions,[15] to facilitate early diagnosis or discharge. In this context, a non-selective approach to high sensitivity cardiac troponin testing may contribute to diagnostic uncertainty.[16] Our aim was to evaluate how selection of patients for high sensitivity cardiac troponin testing affects the diagnosis of myocardial infarction across different healthcare settings.

Methods

Study populations

This prospective observational study used three populations of consecutive patients in the United Kingdom and the United States. In an unselected patient population, we identified all patients (n=1054) presenting to the emergency department at the Royal Infirmary of Edinburgh, UK, in whom the attending clinician did blood sampling irrespective of their clinical presentation (fig 1⇓). In a second, independent, selected patient population (n=5815), we identified all patients presenting to secondary and tertiary care hospitals in the UK in whom the attending clinician requested a cardiac troponin for suspected acute coronary syndrome (fig 1⇓).[17 18] In a third, selected patient population (n=1631), we identified all patients in whom serial cardiac troponin measurements were ordered by the attending clinician for suspected acute coronary syndrome at the Hennepin County Medical Center (Minneapolis, MN, USA).[19] Patients in the selected US population had to have a baseline cardiac troponin measurement at presentation and at least one additional measurement within 24 hours of presentation, before discharge. Across all three populations, we excluded patients if they had ST segment elevation myocardial infarction or a previous presentation during the study period. We obtained baseline clinical characteristics and investigations from a standardised electronic patient record as previously described.[2-19] We used regional and national registries to follow up all patients for death from any cause.[20] This method allowed capture of all deaths in hospital and in the community, ensuring complete follow-up.

All three patient populations included consecutive patients with approval from the regional or national research ethics committee and in accordance with the Declaration of Helsinki. To ensure that every eligible patient was included and avoid selection bias, consent was not sought from patients. All results and associated data were anonymised and linked.

Cardiac troponin I assay

In all three populations, cardiac troponin testing was done at the discretion of the attending physician by using a contemporary cardiac troponin I assay (Abbott Laboratories, Abbott Park, IL, USA). Plasma surplus to clinical requirements was used to measure cardiac troponin I concentration with the ARCHITECT$_{STAT}$ high-sensitive troponin I assay (Abbott Laboratories). In the unselected population, plasma was available from the sample obtained at presentation only, whereas in both selected populations high sensitivity cardiac troponin was measured in parallel with the contemporary assay at presentation and in all serial samples. The high sensitivity assay has an inter-assay coefficient of variation less than 10% at 4.7 ng/L. The 99th centile upper reference limit is 34 ng/L in men and 16 ng/L in women.[18 21] Clinicians were blinded to the results of the high sensitivity assay. Across all three populations, only results from the contemporary assay, where requested by the attending clinician, were used to guide patient care.

Classification of myocardial injury and infarction

The diagnosis was adjudicated according to the universal definition of myocardial infarction,[22] using the high sensitivity cardiac troponin I assay. Two physicians independently reviewed all clinical information, including non-invasive and invasive investigations and outcomes from presentation to 30 days.[2-23] Any discrepancies were resolved by the adjudication of a third independent reviewer. Type 1 myocardial infarction was defined as myocardial necrosis in the context of a presentation with suspected acute coronary syndrome with symptoms or signs of myocardial ischaemia on the electrocardiogram (supplementary table A). Patients with symptoms or signs of myocardial ischaemia due to increased oxygen demand or decreased supply (for example, tachyarrhythmia, hypotension, or anaemia) secondary to an alternative pathology and myocardial necrosis were classified as type 2 myocardial infarction. Myocardial injury was defined as evidence of myocardial necrosis in the absence of any clinical features of myocardial ischaemia (supplementary table A).

Patient and public involvement

Both patients and lay representatives are members of the trial steering committee for the High-STEACS clinical trial and all related studies (NCT01852123) and were involved in the design and conduct of this study. Lay summaries of the results, alongside access to the published article, will be available from the University of Edinburgh and the clinical trial website (https://highsteacs.com/).

Statistical analysis

We summarised baseline data for categorical variables as proportions and presented continuous data as mean and standard deviation or median and interquartile range as appropriate. Using the unselected patient population, we calculated the prevalence of the adjudicated diagnosis of type 1 myocardial infarction

(reference standard) and the subsequent positive predictive values for a range of pre-test probabilities, including that observed in this population. We used the binomial exact method to estimate confidence intervals for all proportions (see appendix for full statistical analysis plan). We evaluated agreement for the adjudication of diagnosis of type 1 myocardial infarction versus other causes of myocardial injury by using the κ statistic. Using the same method as in the unselected patient population, we determined the observed positive predictive value and the 95% confidence interval of an elevated cardiac troponin for the adjudicated diagnosis of type 1 myocardial infarction (reference standard) in the two selected populations from the UK and US. We determined the observed positive predictive value and specificity across pre-specified groups stratified by age, presenting symptoms, risk factors, presence of ischaemia on electrocardiogram, and previous history of ischaemic heart disease. This was a post hoc analysis of the previously published selected UK and US populations,[17-19] so no sample size calculations were done for this analysis. The sample size of the unselected patient population was based on the anticipated prevalence of type 1 myocardial infarction. We determined that we would need 1000 patients to estimate a prevalence of 2.5% with an upper 95% confidence limit of less than 5% at greater than 90% power with an α of 0.05. We used R version 3.2.3 for all analyses.

Results

During recruitment of the unselected patient population, 3619 visits to the emergency department were made, from which 1130 patients underwent blood sampling for their presenting complaint (fig 1⇓). Seventy six patients met our exclusion criteria, giving a final study population of 1054 patients with a mean age of 54 (SD 23) years (52.1% women) (table 1⇓). Cardiac troponin was requested by the attending physician in 3.8% (136/3619) of all visits and in 12.9% (136/1054) of the study population (supplementary table B). Of the patients for whom the attending clinician requested cardiac troponin, 6% (8/136; 7 female, 1 male) would have been reclassified using the high sensitivity, with two diagnosed as having type 1 myocardial infarction (supplementary table C). Most of the reclassified patients were women, reflecting the lower 99th centile upper reference limit in women (supplementary table C). More than half of all patients (609/1054; 57.8%) were admitted, of whom 15.9% (97/609) had troponin requested by the attending clinician (supplementary figure). Patients who had cardiac troponin requested by the attending physician were older and were more likely to be male, to have cardiovascular risk factors, to present with chest pain, and to have intermediate or high GRACE scores (supplementary table B).[24] The frequency of chest pain as the presenting complaint was 8.3% (75/906) in patients in whom the attending clinician did not request cardiac troponin.

In the selected population attending the emergency department in the UK, the attending clinician requested cardiac troponin in 5815 consecutive patients (mean age 64 (16) years; 43.9% female) (fig 1⇓ and table 1⇓). Patients selected for troponin testing were more likely to present with chest pain and had a higher prevalence of cardiovascular risk factors compared with unselected patients.

In the selected population attending the emergency department in the US, the attending clinician requested cardiac troponin in 1631 consecutive patients (mean age 57 (15) years; 44.1% female) (fig 1⇓ and table 1⇓). Patients selected for troponin testing in the US were less likely to present with chest pain compared with those selected for testing in the UK (51.2% *v* 83.0%). Agreement between adjudicating physicians for the diagnosis of type 1 myocardial infarction was good across both the UK and US cohorts (κ=0.86 (95% confidence interval 0.83 to 0.89) and 0.75 (0.65 to 0.86), respectively). Death at 30 days for all populations is reported in supplementary table D.

Prevalence of myocardial infarction and positive predictive value of cardiac troponin in unselected patients

In the unselected population attending the emergency department in the UK, 13.7% (144/1054) had high sensitivity cardiac troponin I concentrations above the 99th centile, with 17 (1.6%), 13 (1.2%), and 114 (10.8%) patients classified as having type 1 myocardial infarction, type 2 myocardial infarction, and myocardial injury, respectively. Of all patients with cardiac troponin concentrations above the 99th centile, chest pain (36/144; 25%), falls or collapse (40/144; 28%), and dyspnoea (13/144; 9%) were the most common presenting complaints (supplementary table E). The most common diagnoses were cardiac (35/144; 24%), respiratory (23/144; 16%), and infectious diseases (21/144; 15%). Overall, the prevalence of type 1 myocardial infarction was 1.6% (17/1054), with a positive predictive value for type 1 myocardial infarction of 11.8% (95% confidence interval 7.0% to 18.2%) (fig 2⇓, fig 3⇓, and table 2⇓).

Prevalence of myocardial infarction and positive predictive value of cardiac troponin in selected patients (UK)

In the selected population undergoing troponin testing in the UK, high sensitivity cardiac troponin was elevated in 24.1% (95% confidence interval 23.0% to 25.2%) (1403/5815) of all patients. Type 1 myocardial infarction adjudicated in 68 (4.2%) patients, with 102 (6.3%) and 245 (15.0%) patients classified as having type 2 myocardial infarction and myocardial injury, respectively (table 1⇓). The prevalence of type 1 myocardial infarction was 14.5% (843/5825) and the positive predictive value was 59.7% (57.0% to 62.2%) (fig 2⇓, fig 3⇓, and table 2⇓). The positive predictive value was highest in patients with chest pain (67.5%, 64.6% to 70.3%), evidence of myocardial ischaemia on electrocardiography (69.9%, 65.8% to 73.7%), or known ischaemic heart disease (68.1%, 64.1% to 72.0%) compared with those without (34.0% (29.0% to 39.4%), 57.5% (53.9% to 61.1%), and 55.1% (51.5% to 58.7%), respectively) (fig 4⇓ and supplementary table F). The positive predictive value was 83.2% (76.8% to 88.5%) in patients with all three of these clinical features.

Prevalence of myocardial infarction and positive predictive value of cardiac troponin in selected patients (US)

In the selected population undergoing serial troponin testing in the US, high sensitivity cardiac troponin was elevated in 25.4% (23.3% to 27.6%) (415/1631), with type 1 myocardial infarction adjudicated in 68 (4.2%) patients and 102 (6.3%) and 245 (15.0%), respectively, patients classified as having type 2 myocardial infarction and myocardial injury (table 1⇓). The prevalence of type 1 myocardial infarction was 4.2% (68/1631) and the positive predictive value was 16.4% (13.0% to 20.3%) (fig 2⇓, fig 3⇓, and table 2⇓). Similar to the selected population in the UK, the presence of chest pain, myocardial ischaemia on electrocardiography, and history of ischaemic heart disease improved the pre-test and post-test probability for a diagnosis

of type 1 myocardial infarction (fig 4⇓ and supplementary table G).

Discussion

We have evaluated the effect of selection of patients for high sensitivity cardiac troponin testing on the diagnosis of myocardial infarction in consecutive patients attending the emergency department in the UK and US, and we make several observations. Firstly, if testing is done in all patients without selection, elevated cardiac troponin concentrations are frequent, occurring in one in every eight patients. Most of these patients are admitted to hospital with an alternative primary diagnosis and are adjudicated as having type 2 myocardial infarction or myocardial injury. Testing without patient selection results in a very low prevalence of type 1 myocardial infarction (1.6%), and the positive predictive value of an elevated cardiac troponin concentration for type 1 myocardial infarction is low at 11.8%. Secondly, patient selection for cardiac troponin testing varies across healthcare settings and markedly influences the prevalence and positive predictive value for a diagnosis of myocardial infarction. In the UK, where the approach to testing is more conservative, the prevalence of type 1 myocardial infarction was 14.5% and the positive predictive value of high sensitivity cardiac troponin testing was 59.7%. However, in the US, where troponin testing is performed more widely, the prevalence and positive predictive value for type 1 myocardial infarction were much lower. Thirdly, across both healthcare settings, testing in those patients with a higher pre-test probability, such as those with chest pain, increases the positive predictive value of high sensitivity cardiac troponin threefold. These findings highlight the importance of the selection of patients for testing if we are to optimise the diagnostic utility of high sensitivity cardiac troponin.

Strengths of study

Our study has several strengths. Firstly, we minimised selection bias by identifying all consecutive patients across all three study populations. As such, we have evaluated the performance of high sensitivity cardiac troponin testing as it is used in clinical practice. Secondly, we did not rely on the contemporary cardiac troponin assays for the diagnosis, but instead two cardiologists independently adjudicated the diagnosis in all patients by using the high sensitivity cardiac troponin I assay with sex specific thresholds as the reference standard.[47] Thirdly, we evaluated the effect of patient selection on the prevalence and positive predictive value of cardiac troponin for myocardial infarction across two healthcare settings with different approaches to testing.[13] Together these approaches ensure that our observations on the effect of patient selection for testing are generalisable and relevant for clinical practice across different healthcare settings.

Implications of findings

Our study has implications for the adoption of high sensitivity cardiac troponin assays, particularly in those regions, such as the US, where the frequency of testing is high.[13] The positive predictive value depends on the prevalence of type 1 myocardial infarction, which in turn depends on the selection of patients for testing, which differs widely across healthcare systems. In a representative sample of more than 44 000 patients attending more than 500 emergency departments in the US, 17% of all patients and 47% of those admitted to hospital had cardiac biomarkers tested,[5] compared with just 3% and 16% respectively in our selected population in the UK. Interestingly, in this analysis, less than a third of patients tested in the US presented with chest pain.[5] We acknowledge that patients with suspected acute coronary syndrome may present with atypical symptoms,[48] but this proportion is unlikely to differ between healthcare settings. We observed that chest pain was the presenting symptoms in 83% of patients selected for testing in the UK, compared with 51% in our US population. Differences in the proportion of patients presenting with chest pain probably reflect differences in the approach to clinical assessment before testing and to other factors that influence the clinicians' perception of risk and therefore the need to exclude acute coronary syndrome. The only other previous study of high sensitivity cardiac troponin I testing in a US emergency department reported a similar low prevalence of type 1 myocardial infarction of just 3.2%,[49] which we estimate would give a positive predictive value of 13.4% (fig 3⇓).

High sensitivity cardiac troponin assays are now being introduced worldwide, with the exception of the US where they have only recently been approved by the Food and Drug Administration.[50] Although cardiac troponin testing in undifferentiated patients may be justified when myocardial infarction is a possibility,[51 52] it is important that clinicians are aware that elevated cardiac troponin concentrations are not exclusive to type 1 myocardial infarction. Implementation of high sensitivity cardiac troponin testing should be accompanied by education of clinicians to guide patient selection and the interpretation of elevated troponin concentrations, and testing should be incorporated into evidence based pathways. If implemented without adoption of a considered approach, high sensitivity cardiac troponin assays may increase diagnostic uncertainty and increase the need for further invasive and non-invasive cardiac investigations with cost implications for the healthcare system.[14]

In the UK, where the approach to investigation is more conservative, we observed that troponin testing was performed in patients with a higher pre-test probability of myocardial infarction, and the positive predictive value of high sensitivity cardiac troponin was higher than in the US. Perhaps unsurprisingly, the positive predictive value across both populations was highest in patients with chest pain, myocardial ischaemia on the electrocardiogram, or known ischaemic heart disease, reflecting the higher prevalence of myocardial infarction in patients with these features. Interestingly, the presence of other established risk factors, such as hypertension and diabetes mellitus, did not increase the positive predictive value for a diagnosis of myocardial infarction in either population. Patients with hypertension and diabetes mellitus are clearly at higher risk of myocardial infarction and have a higher prevalence in both populations, but they are also more likely to have myocardial injury due to their comorbidities, which increases the number of false positives and reduces specificity. Therefore, the overall diagnostic performance of high sensitivity cardiac troponin is influenced by both patient selection (prevalence) and the presence of comorbid conditions (specificity), and clinicians need to be aware of both when selecting patients for testing and interpreting elevated cardiac troponin concentrations in their practice.

What is the optimal positive predictive value for high sensitivity cardiac troponin testing in this setting? Most studies report a positive predictive value of between 45% and 65% (fig 3⇓), but as yet no consensus exists on the optimal value. The ideal test would identify only those patients with myocardial infarction, but given that many causes of myocardial injury other than acute coronary syndrome exist, even with careful clinical assessment and selection of patients for testing, the positive predictive value

is always going to be below 100%. In this context, a test that identified more patients with the condition than without might be acceptable. It is important that clinicians are aware of the predictive value of testing and use the results to inform subsequent investigations rather than starting treatment for myocardial infarction in all patients with elevated cardiac troponin concentrations.

Although a more selective approach to testing clearly improves the positive predictive value, could this potentially lead to clinicians missing patients with myocardial infarction? Among the 1054 unselected patients, a total of 17 patients had type 1 myocardial infarction and 13 patients had type 2 myocardial infarction. Of these 30 patients, five (two with type 1 myocardial infarction and three with type 2 myocardial infarction) did not have cardiac troponin requested by the attending clinician. Four patients were managed appropriately for their primary presenting condition without the need for troponin testing, and one patient was discharged with atypical chest pain in whom testing would have been informative (supplementary table H). Interestingly, the approach to testing does not influence the negative predictive value of our previously defined risk stratification threshold to rule out myocardial infarction at presentation.[17] Across both the selected UK and US cohorts, the safety and efficacy of rule-out strategies using high sensitivity troponin assays remained comparable.[17]

Although elevated cardiac troponin concentrations without acute coronary syndrome may be challenging to interpret, they convey potentially important clinical information. Nearly all of these patients were already recognised by their attending physician as being acutely unwell and were admitted to hospital. Cardiac troponin is a powerful prognostic marker in patients with type 2 myocardial infarction or myocardial injury,[2] but no guidance exists on how to investigate these patients, including the role of cardiac monitoring, and as yet no evidence is available to suggest that cardiovascular treatments will improve outcomes.[2] Further studies are now needed to systematically evaluate patients with type 2 myocardial infarction and myocardial injury, to determine the underlying mechanisms, and to inform the optimal management of these patients.

Limitations of study

Our study has some limitations that merit discussion. Firstly, we did not do serial cardiac troponin testing or systematically do coronary investigations in our population of unselected patients. As a result, we may have underestimated the prevalence of type 1 myocardial infarction and, despite our careful attempt to classify patients, we accept that some patients may have been misclassified. Reassuringly, the relation between prevalence of myocardial infarction and positive predictive value was consistent in our US population, where all patients had up to four serial high sensitivity cardiac troponin tests, suggesting the lack of serial testing in our unselected patients has not compromised our analysis. In our practice, we advocate serial testing in all patients with myocardial injury to clarify the mechanism of injury and to document whether a rise and/or fall in cardiac troponin has occurred to support the diagnosis of myocardial infarction. Secondly, we acknowledge that although most troponin tests in the emergency department are intended to evaluate patients with suspected acute coronary syndrome, guidelines recommend testing for cardiac biomarkers in other acute presentations including pulmonary embolus and acute heart failure.[53 54] Although we have shown how high sensitivity cardiac troponin testing without consideration of pre-test probability affects the positive predictive value for type 1 myocardial infarction, we accept that cardiac troponin testing is not used exclusively to evaluate patients with suspected acute coronary syndrome. Thirdly, cardiac troponin is integral to the diagnosis of myocardial infarction, and the absence of an independent reference standard is a limitation of all diagnostic studies evaluating high sensitivity cardiac troponin testing.[18 55] However, this limitation does not affect the validity of our study of the prevalence and effect of patient selection on the positive predictive value of an elevated cardiac troponin concentration.

Conclusions

When high sensitivity cardiac troponin testing is performed widely or without previous clinical assessment, elevated troponin concentrations are common and predominantly reflect myocardial injury rather than type 1 myocardial infarction. Our observations highlight how selection of patients for cardiac troponin testing varies across healthcare settings and markedly influences the positive predictive value for a diagnosis of myocardial infarction.

Contributors: ASVS and NLM designed the study and carried out the initial acquisition, analysis, or interpretation of data. All authors were involved in drafting and revising the manuscript and have given final approval of the version to be published. ASVS is the guarantor.

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Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: support for the submitted work as described above; NLM has acted as a consultant for Abbott Diagnostics, Roche Diagnostics, and Singulex; ASVS has acted as a consultant for Abbott Diagnostics; AC has received speaker fees from Abbott Diagnostics; FSA has acted as a consultant to Metanomics Healthcare, an advisor to Instrumentation Laboratory and Abbott Diagnostics, and on the Board of Directors of HyTest Ltd; YS has acted as an advisor for Roche Diagnostics; no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: All three patient populations in this study included consecutive patients with approval from the regional or national research ethics committee and in accordance with the Declaration of Helsinki. For the unselected patient population, approval to obtain plasma surplus to clinical requirement was granted by the National Research Scotland BioResource and Tissue Governance Unit. For the selected patient populations in the UK and US, approval was granted by the Scotland A Regional Ethics Committee and the Human Subjects Research Committee of Hennepin County Medical Center respectively.

Data sharing: Patient level data and statistical code will be available from the corresponding author following publication of the primary study (HighSTEACS: NCT01852123). Participants' consent to share data was not obtained, but the presented data are anonymised and risk of identification is low.

Transparency declaration: The lead author (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

1 Shah AS, Newby DE, Mills NL. High sensitivity cardiac troponin in patients with chest pain. *BMJ* 2013;359:f4222. doi:10.1136/bmj.f4222 pmid:23878152.

What is already known on this topic

High sensitivity cardiac troponin assays may improve the diagnosis of myocardial infarction but increase the detection of myocardial injury in patients without acute coronary syndrome

Lower diagnostic thresholds disproportionately increase the number of patients with troponin elevations who do not have acute coronary syndrome

What this study adds

High sensitivity cardiac troponin testing in all patients results in elevated troponin concentrations in one in eight patients, most of whom do not have type 1 myocardial infarction

Patient selection for cardiac troponin testing varies across healthcare settings in the UK and US, markedly influencing the prevalence and positive predictive value for a diagnosis of myocardial infarction

Selection of patients with a higher pre-test probability based on simple clinical features improved the positive predictive value

2 Shah AS, McAllister DA, Mills R, et al. Sensitive troponin assay and the classification of myocardial infarction. *Am J Med* 2015;359:493-501.e3. doi:10.1016/j.amjmed.2014.10.056 pmid:25436428.
3 Newby LK, Jesse RL, Babb JD, et al. ACCF 2012 expert consensus document on practical clinical considerations in the interpretation of troponin elevations: a report of the American College of Cardiology Foundation task force on Clinical Expert Consensus Documents. *J Am Coll Cardiol* 2012;359:2427-63. doi:10.1016/j.jacc.2012.08.969 pmid:23154053.
4 Saaby L, Poulsen TS, Hosbond S, et al. Classification of myocardial infarction: frequency and features of type 2 myocardial infarction. *Am J Med* 2013;359:789-97. doi:10.1016/j.amjmed.2013.02.029 pmid:23856021.
5 Saaby L, Poulsen TS, Diederichsen AC, et al. Mortality rate in type 2 myocardial infarction: observations from an unselected hospital cohort. *Am J Med* 2014;359:295-302. doi:10.1016/j.amjmed.2013.12.020 pmid:24457000.
6 Sandoval Y, Thygesen K. Myocardial Infarction Type 2 and Myocardial Injury. *Clin Chem* 2017;359:101-7. doi:10.1373/clinchem.2016.255521 pmid:28062614.
7 Sandoval Y, Smith SW, Thordsen SE, Apple FS. Supply/demand type 2 myocardial infarction: should we be paying more attention?*J Am Coll Cardiol* 2014;359:2079-87. doi:10.1016/j.jacc.2014.02.541 pmid:24632278.
8 Morrow DA, Wiviott SD, White HD, et al. Effect of the novel thienopyridine prasugrel compared with clopidogrel on spontaneous and procedural myocardial infarction in the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction 38: an application of the classification system from the universal definition of myocardial infarction. *Circulation* 2009;359:2758-64. doi:10.1161/CIRCULATIONAHA.108.833665 pmid:19451347.
9 Melberg T, Burman R, Dickstein K. The impact of the 2007 ESC-ACC-AHA-WHF Universal definition on the incidence and classification of acute myocardial infarction: a retrospective cohort study. *Int J Cardiol* 2010;359:228-33. doi:10.1016/j.ijcard.2008.10.021 pmid:19027971.
10 Stein GY, Herscovici G, Korenfeld R, et al. Type-II myocardial infarction--patient characteristics, management and outcomes. *PLoS One* 2014;359:e84285. doi:10.1371/journal.pone.0084285 pmid:24392121.
11 Mills NL, Churchhouse AM, Lee KK, et al. Implementation of a sensitive troponin I assay and risk of recurrent myocardial infarction and death in patients with suspected acute coronary syndrome. *JAMA* 2011;359:1210-6. doi:10.1001/jama.2011.338 pmid:21427373.
12 Melanson SE, Conrad MJ, Mosammaparast N, Jarolim P. Implementation of a highly sensitive cardiac troponin I assay: test volumes, positivity rates and interpretation of results. *Clin Chim Acta* 2008;359:57-61. doi:10.1016/j.cca.2008.05.007 pmid:18515084.
13 Makam AN, Nguyen OK. Use of cardiac biomarker testing in the emergency department. *JAMA Intern Med* 2015;359:67-75. doi:10.1001/jamainternmed.2014.5830 pmid:25401720.
14 Eggers KM, Lindahl B, Melki D, Jernberg T. Consequences of implementing a cardiac troponin assay with improved sensitivity at Swedish coronary care units: an analysis from the SWEDEHEART registry. *Eur Heart J* 2016;359:2417-24. doi:10.1093/eurheartj/ehw029 pmid:26916797.
15 Yiadom MY, Jarolim P, Jenkins C, Melanson SE, Conrad M, Kosowsky JM. Diagnostic implications of an elevated troponin in the emergency department. *Dis Markers* 2015;359:157812. doi:10.1155/2015/157812 pmid:25960590.
16 Baxi S, Lakin J, Stapleton S, Redberg R. High-sensitivity troponin: elevated without infarction, is the horse out of the barn?*Emerg Med J* 2014;359:354-5. doi:10.1136/emermed-2013-202796 pmid:23825057.
17 Shah AS, Anand A, Sandoval Y, et al. High-STEACS investigators. High-sensitivity cardiac troponin I at presentation in patients with suspected acute coronary syndrome: a cohort study. *Lancet* 2015;359:2481-8. doi:10.1016/S0140-6736(15)00391-8 pmid:26454362.
18 Shah AS, Griffiths M, Lee KK, et al. High sensitivity cardiac troponin and the under-diagnosis of myocardial infarction in women: prospective cohort study. *BMJ* 2015;359:g7873. doi:10.1136/bmj.g7873 pmid:25609052.
19 Sandoval Y, Smith SW, Shah AS, et al. Rapid Rule-Out of Acute Myocardial Injury Using a Single High-Sensitivity Cardiac Troponin I Measurement. *Clin Chem* 2017;359:369-76. doi:10.1373/clinchem.2016.264523 pmid:27811203.
20 Ford I, Murray H, Packard CJ, Shepherd J, Macfarlane PW, Cobbe SM. West of Scotland Coronary Prevention Study Group. Long-term follow-up of the West of Scotland Coronary Prevention Study. *N Engl J Med* 2007;359:1477-86. doi:10.1056/NEJMoa065994 pmid:17928595.
21 Shah ASV, Ferry AV, Mills NL. Cardiac Biomarkers and the Diagnosis of Myocardial Infarction in Women. *Curr Cardiol Rep* 2017;359:40. doi:10.1007/s11886-017-0839-9 pmid:28391559.
22 Thygesen K, Alpert JS, Jaffe AS, et al. Joint ESC/ACCF/AHA/WHF Task Force for the Universal Definition of Myocardial Infarction. Third universal definition of myocardial infarction. *Circulation* 2012;359:2020-35. doi:10.1161/CIR.0b013e31826e1058 pmid:22923432.
23 Sandoval Y, Smith SW, Love SA, Sexter A, Schulz K, Apple FS. Single High-Sensitivity Cardiac Troponin I to Rule Out Acute Myocardial Infarction. *Am J Med* 2017;359:1076-1083.e1. doi:10.1016/j.amjmed.2017.02.032 pmid:28344141.
24 Fox KA, Dabbous OH, Goldberg RJ, et al. Prediction of risk of death and myocardial infarction in the six months after presentation with acute coronary syndrome: prospective multinational observational study (GRACE). *BMJ* 2006;359:1091. doi:10.1136/bmj.38985.646481.55 pmid:17032691.
25 Invernizzi L, Doka M, Cappellini F, et al. Effectiveness of highly sensitive troponin T assay for early diagnosis of acute myocardial infarction (AMI). *Biochim Clin* 2013;359:36-9.
26 Lotze U, Lemm H, Heyer A, Müller K. Combined determination of highly sensitive troponin T and copeptin for early exclusion of acute myocardial infarction: first experience in an emergency department of a general hospital. *Vasc Health Risk Manag* 2011;359:509-15. doi:10.2147/VHRM.S21753 pmid:21915168.
27 Bahrmann P, Bahrmann A, Breithardt OA, et al. Additional diagnostic and prognostic value of copeptin ultra-sensitive for diagnosis of non-ST-elevation myocardial infarction in older patients presenting to the emergency department. *Clin Chem Lab Med* 2013;359:1307-19. doi:10.1515/cclm-2012-0401 pmid:23314553.
28 Bahrmann P, Christ M, Bahrmann A, et al. A 3-hour diagnostic algorithm for non-ST-elevation myocardial infarction using high-sensitivity cardiac troponin T in unselected older patients presenting to the emergency department. *J Am Med Dir Assoc* 2013;359:409-16. doi:10.1016/j.jamda.2012.12.005 pmid:23375478.
29 Hammerer-Lercher A, Ploner T, Neururer S, et al. High-sensitivity cardiac troponin T compared with standard troponin T testing on emergency department admission: how much does it add in everyday clinical practice?*J Am Heart Assoc* 2013;359:e000204. doi:10.1161/JAHA.113.000204 pmid:23735897.
30 Thelin J, Borna C, Erlinge D, Öhlin B. The combination of high sensitivity troponin T and copeptin facilitates early rule-out of ACS: a prospective observational study. *BMC Cardiovasc Disord* 2013;359:42. doi:10.1186/1471-2261-13-42 pmid:23777442.
31 Freund Y, Chenevier-Gobeaux C, Bonnet P, et al. High-sensitivity versus conventional troponin in the emergency department for the diagnosis of acute myocardial infarction. *Crit Care* 2011;359:R147. doi:10.1186/cc10270 pmid:21663627.
32 Santaló M, Martin A, Velilla J, et al. Using high-sensitivity troponin T: the importance of the proper gold standard. *Am J Med* 2013;359:709-17. doi:10.1016/j.amjmed.2013.03.003 pmid:23764266.
33 Hoeller R, Rubini Giménez M, Reichlin T, et al. Normal presenting levels of high-sensitivity troponin and myocardial infarction. *Heart* 2013;359:1567-72. doi:10.1136/heartjnl-2013-303643 pmid:23604180.
34 Body R, Carley S, McDowell G, et al. Rapid exclusion of acute myocardial infarction in patients with undetectable troponin using a high-sensitivity assay. *J Am Coll Cardiol* 2011;359:1332-9. doi:10.1016/j.jacc.2011.06.026 pmid:21920261.
35 Aldous SJ, Florkowski CM, Crozier IG, Than MP. The performance of high sensitivity troponin for the diagnosis of acute myocardial infarction is underestimated. *Clin Chem Lab Med* 2011;359:727-9.pmid:22505533.
36 Aldous SJ, Richards AM, Cullen L, Than MP. Early dynamic change in high-sensitivity cardiac troponin T in the investigation of acute myocardial infarction. *Clin Chem* 2011;359:1154-60. doi:10.1373/clinchem.2010.161166 pmid:21784766.
37 Christ M, Popp S, Pohlmann H, et al. Implementation of high sensitivity cardiac troponin T measurement in the emergency department. *Am J Med* 2010;359:1134-42. doi:10.1016/j.amjmed.2010.07.015 pmid:20932502.
38 Giannitsis E, Kehayova T, Vafaie M, Katus HA. Combined testing of high-sensitivity troponin T and copeptin on presentation at prespecified cutoffs improves rapid rule-out of non-ST-segment elevation myocardial infarction. *Clin Chem* 2011;359:1452-5. doi:10.1373/clinchem.2010.161265 pmid:21807867.
39 Collinson P, Goodacre S, Gaze D, Gray A. RATPAC Research Team. Very early diagnosis of chest pain by point-of-care testing: comparison of the diagnostic efficiency of a panel of cardiac biomarkers compared with troponin measurement alone in the RATPAC trial. *Heart* 2012;359:312-8. doi:10.1136/heartjnl-2011-300723 pmid:22076016.
40 Sebbane M, Lefebvre S, Kuster N, et al. Early rule out of acute myocardial infarction in ED patients: value of combined high-sensitivity cardiac troponin T and ultrasensitive copeptin assays at admission. *Am J Emerg Med* 2013;359:1302-8. doi:10.1016/j.ajem.2013.04.033 pmid:23816196.
41 Inoue K, Suwa S, Ohta H, et al. Heart fatty acid-binding protein offers similar diagnostic performance to high-sensitivity troponin T in emergency room patients presenting with chest pain. *Circ J* 2011;359:2813-20. doi:10.1253/circj.CJ-11-0598 pmid:21937835.
42 Eggers KM, Venge P, Lindahl B. High-sensitive cardiac troponin T outperforms novel diagnostic biomarkers in patients with acute chest pain. *Clin Chim Acta* 2012;359:1135-40. doi:10.1016/j.cca.2012.03.011 pmid:22456003.
43 Normann J, Mueller M, Biener M, Vafaie M, Katus HA, Giannitsis E. Effect of older age on diagnostic and prognostic performance of high-sensitivity troponin T in patients presenting to an emergency department. *Am Heart J* 2012;359:698-705.e4. doi:10.1016/j.ahj.2012.08.003 pmid:23137500.
44 Khan DA, Sharif MS, Khan FA. Diagnostic performance of high-sensitivity troponin T, myeloperoxidase, and pregnancy-associated plasma protein A assays for triage of patients with acute myocardial infarction. *Korean J Lab Med* 2011;359:172-8. doi:10.3343/kjlm.2011.31.3.172 pmid:21779191.
45 Keller T, Zeller T, Ojeda F, et al. Serial changes in highly sensitive troponin I assay and early diagnosis of myocardial infarction. *JAMA* 2011;359:2684-93. doi:10.1001/jama.2011.1896 pmid:22203537.
46 Zhelev Z, Hyde C, Youngman E, et al. 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* 2015;359:h15. doi: 10.1136/bmj.h15 pmid:25646632.
47 Apple FS. A new season for cardiac troponin assays: it's time to keep a scorecard. *Clin Chem* 2009;359:1303-6. doi:10.1373/clinchem.2009.128363 pmid:19478023.
48 Canto JG, Shlipak MG, Rogers WJ, et al. Prevalence, clinical characteristics, and mortality among patients with myocardial infarction presenting without chest pain. *JAMA* 2000;359:3223-9. doi:10.1001/jama.283.24.3223 pmid:10866870.
49 Korley FK, Schulman SP, Sokoll LJ, et al. Troponin elevations only detected with a high-sensitivity assay: clinical correlations and prognostic significance. *Acad Emerg Med* 2014;359:727-35. doi:10.1111/acem.12417 pmid:25112512.
50 United States Food and Drug Administration. 510(k) substantial equivalence determination decision summary assay only template. 2017. https://www.accessdata.fda.gov/cdrh_docs/reviews/K162895.pdf.
51 Jairam S, Jones P, Samaraie L, Chataline A, Davidson J, Stewart R. Clinical diagnosis and outcomes for Troponin T 'positive' patients assessed by a high sensitivity compared with a 4th generation assay. *Emerg Med Australas* 2011;359:490-501. doi:10.1111/j.1742-6723.2011.01446.x pmid:21824317.
52 Sherwood MW, Kristin Newby L. High-sensitivity troponin assays: evidence, indications, and reasonable use. *J Am Heart Assoc* 2014;359:e000403. doi:10.1161/JAHA.113.000403 pmid:24470520.
53 Konstantinides SV, Torbicki A, Agnelli G, et al. Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology (ESC). 2014 ESC guidelines on the diagnosis and management of acute pulmonary embolism. *Eur Heart J* 2014;359:3033-69, 3069a-3069k. doi:10.1093/eurheartj/ehu283 pmid:25173341.
54 Ponikowski P, Voors AA, Anker SD, et al. Authors/Task Force Members Document Reviewers. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail* 2016;359:891-975. doi:10.1002/ejhf.592 pmid:27207191.
55 Glasziou P, Irwig L, Deeks JJ. When should a new test become the current reference standard? *Ann Intern Med* 2008;359:816-22. doi:10.7326/0003-4819-149-11-200812020-00009 pmid:19047029.

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Tables

Table 1| Baseline characteristics of unselected patients and patients selected for cardiac troponin testing in UK and US. Values are numbers (percentages) unless stated otherwise

Characteristics	Unselected patients (n=1054)	Selected patients (UK) (n=5815)	Selected patients (US) (n=1631)
Female sex	549/1054 (52.0)	2552 (43.9)	720/1631 (44.1)
Mean (SD) age, years	54 (23)	64 (16)	57 (15)
Chest pain	183/1042 (17.6)	4825/5813 (83.0)	835/1572 (51.2)
Risk factors			
Smoker	299/902 (33.1)	1105/3615 (30.6)	592/1631 (36.3)
Hypertension	337/1041 (32.4)	1969/5233 (37.6)	1074/1631 (65.9)
Hyperlipidaemia	299/1041 (28.7)	1611/5232 (30.8)	696/1631 (42.7)
Past medical history			
Ischaemic heart disease	193/1042 (18.5)	1846/5240 (35.2)	337/1631 (20.7)
Myocardial infarction	109/1041 (10.5)	1082/5235 (20.7)	190/1629 (11.7)
Cerebrovascular disease	99/1041 (9.5)	475/5340 (9.1)	153/1631 (9.4)
Diabetes mellitus	106/1047 (10.1)	842/5233 (16.1)	505/1631 (31.0)
PCI	52/1046 (5.0)	611/5233 (11.7)	150/1621 (9.2)
CABG	32/1046 (3.1)	330/5228 (6.3)	73/1620 (4.5)
Drugs at presentation			
Aspirin	180 (17.5)	1344 (33.7)	627 (38.4)
Clopidogrel	81 (7.9)	468 (11.8)	76 (4.7)
β blockers	149 (14.5)	1082 (27.2)	589 (36.1)
ACE-I/ARB	189 (18.3)	1311 (32.9)	578 (35.4)
Statin	249 (24.2)	1578 (39.6)	556 (34.1)
Warfarin	44 (4.3)	278 (7.0)	115 (7.1)
Haemodynamics			
Mean (SD) systolic blood pressure, mm Hg	130.5 (22.2)	137.5 (26.0)	143.7 (28.5)
Mean (SD) heart rate, beats/min	86.9 (22.3)	81.2 (22.9)	90.2 (34.3)
Killip class			
I	930/1037 (89.7)	4847/5336 (90.8)	-
II	85/1037 (8.2)	408/5336 (7.6)	-
III	15/1037 (1.4)	75/5336 (1.4)	-
IV	1/1037 (0.1)	6/5336 (0.1)	-
Baseline electrocardiography			
ST elevation*	13/656 (2.0)	218/5157 (4.2)	304/1631 (18.6)
ST depression	21/653 (3.2)	397/5156 (7.7)	212/1631 (13.0)
T wave inversion	58/653 (8.9)	726/5154 (14.1)	316/1631 (19.4)
Diagnosis			
Type 1 myocardial infarction	17/1054 (1.6)	843/5815 (14.5)	68/1631 (4.2)
Type 2 myocardial infarction	13/1054 (1.2)	229/5815 (3.9)	102/1631 (6.3)
Myocardial injury	114/1054 (10.8)	341/5815 (5.9)	245/1631 (15.0)

ACE-I/ARB=angiotensin converting enzyme inhibitor/angiotensin receptor blocker; CABG=coronary artery bypass grafting; PCI=percutaneous coronary intervention.
*In the selected US population, ST segment elevation was defined as an increase >0.5 mm in any lead.

Table 2| **Diagnosis of type 1 myocardial infarction using high sensitivity cardiac troponin**

	Type 1 myocardial infarction			Diagnostic parameter, % (95% CI)			
	Yes	No	Total	Sensitivity	Specificity	Negative predictive value	Positive predictive value
Unselected cohort (n=1054)							
High sensitivity cardiac troponin >99th centile:	-	-	-	100 (80.5 to 100)	87.7 (85.6 to 90.0)	100 (99.6 to 100)	11.8 (7.0 to 18.2)
Yes	17	127	144				
No	0	910	910				
Total	17	1037	1054				
Selected cohort, UK (n=5815)							
High sensitivity cardiac troponin >99th centile:	-	-	-	100 (99.6 to 100)	88.5 (87.6 to 89.4)	100 (99.9 to 100)	59.7 (57.0 to 62.2)
Yes	843	570	1413				
No	0	4402	4402				
Total	843	4972	5815				
Selected cohort, US (n=1631)							
High sensitivity cardiac troponin >99th centile:	-	-	-	100 (94.7 to 100)	77.8 (75.7 to 79.8)	100 (99.7 to 100)	16.4 (13.0 to 20.3)
Yes	68	347	415				
No	0	1216	1216				
Total	68	1563	1631				

Figures

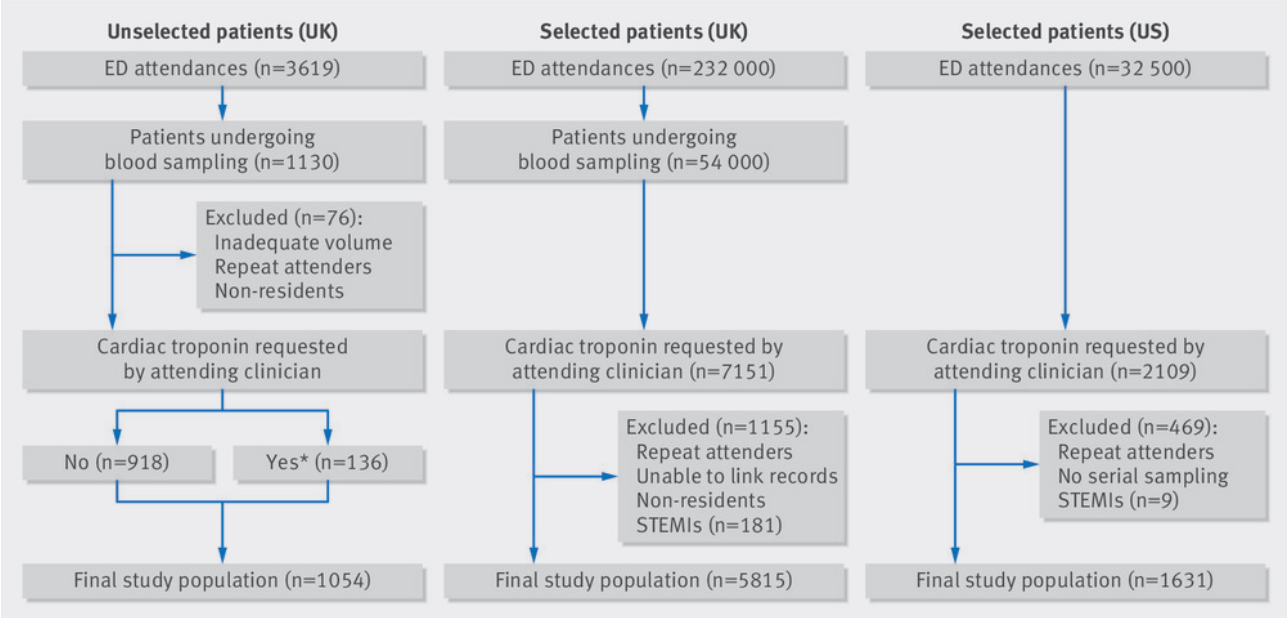

Fig 1 Flow diagram summarising enrolment of unselected patients and those selected for cardiac troponin testing in the UK and US. ED=emergency department; STEMI=ST segment elevation myocardial infarction. *Troponin used only to guide clinical care in patients with suspected acute coronary syndrome

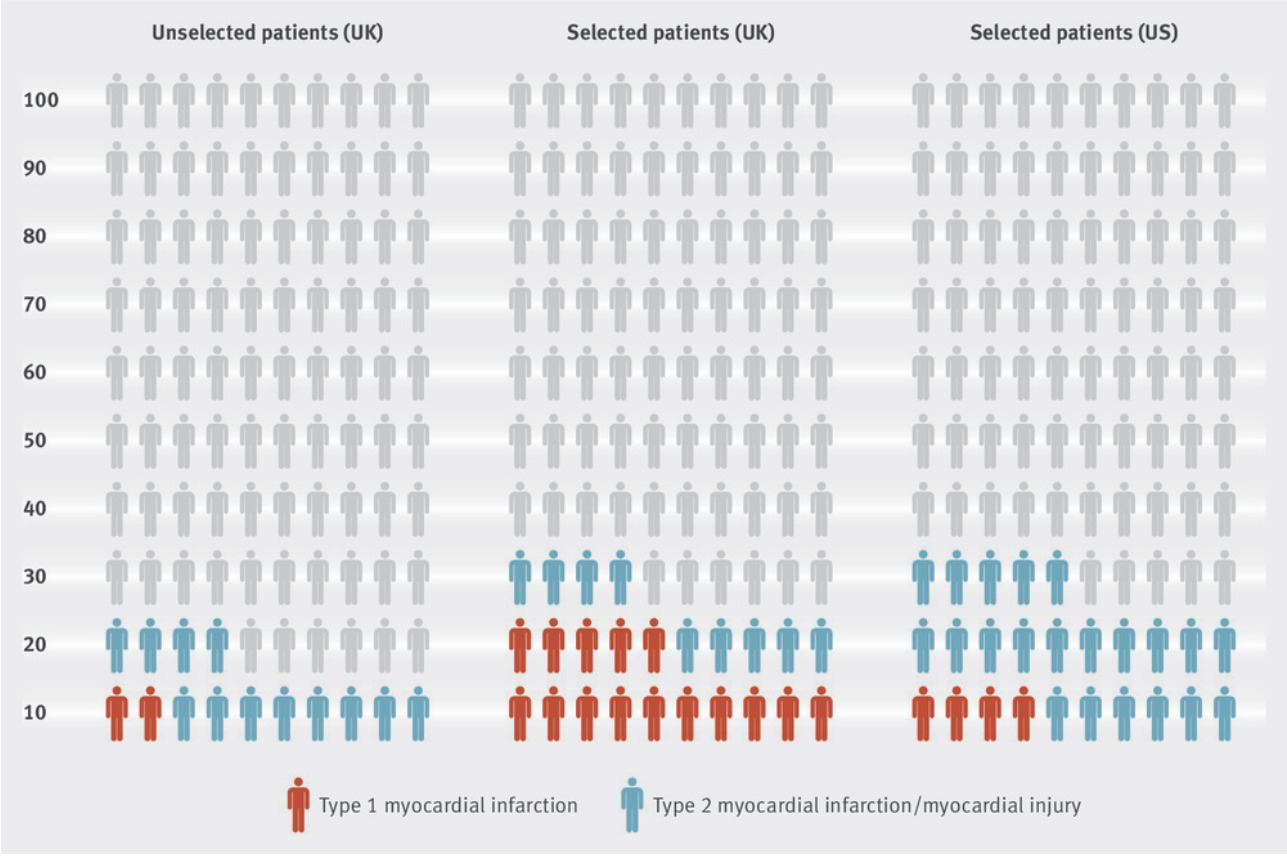

Fig 2 Prevalence of elevated high sensitivity cardiac troponin concentrations and type 1 myocardial infarction in unselected patients and those selected for cardiac troponin testing in the UK and US

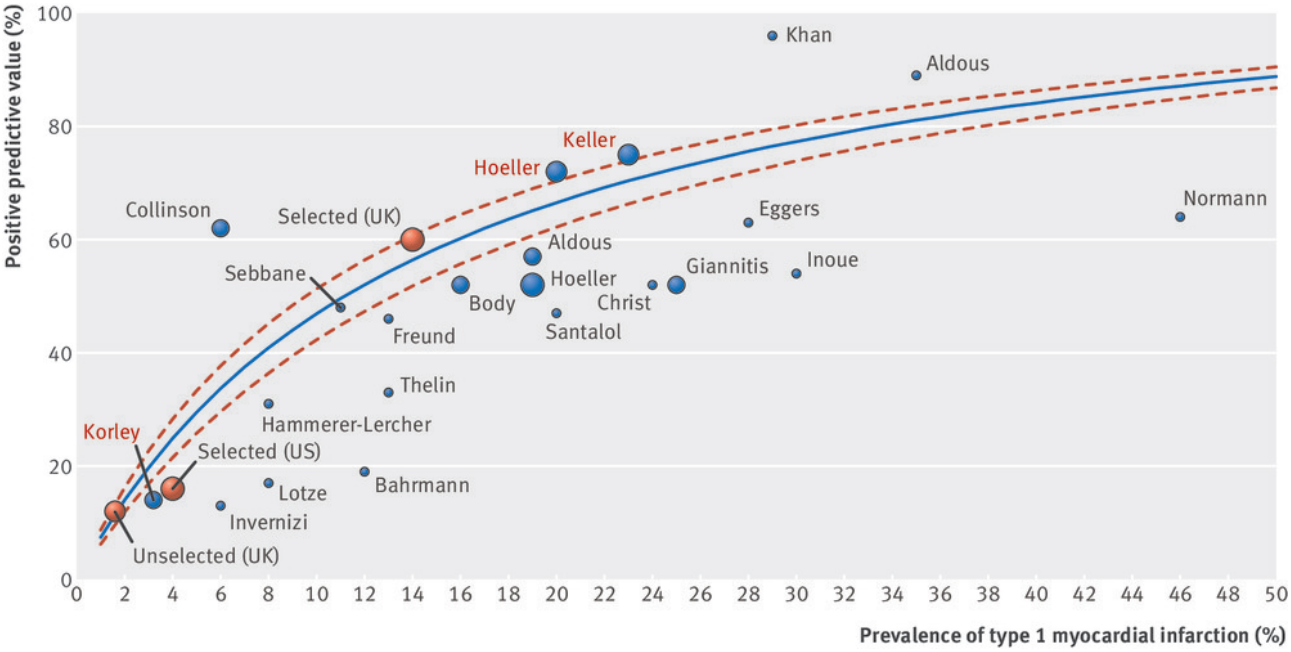

Fig 3 Influence of prevalence on positive predictive value of elevated high sensitivity cardiac troponin concentration for diagnosis of type 1 myocardial infarction. Red dots represent populations of unselected patients in the emergency department (n=1054) and selected patients in the UK (n=5815) and US (n=1631). Blue dots represent reported positive predictive values for high sensitivity cardiac troponin by prevalence of type 1 myocardial infarction in previously published cohorts using high sensitivity cardiac troponin T (blue) and high sensitivity cardiac troponin I (red) assays.[25-45] Data for positive predictive values for high sensitivity troponin T cohorts were extracted from a recent systematic review and meta-analysis published by Zhelev et al.[46] Dot size reflects number of patients in each cohort (small dot <500 patients, medium dot 500-1500 patients, large dot >1500 patients). Blue line represents central estimate of positive predictive value with 95% confidence interval (dashed red lines) derived from unselected emergency department population in the UK

Variable	Stratum	Prevalence (%) (95% CI)	Specificity (%) (95% CI)
Selected patients (UK)			
Age	<60	8.6 (7.5 to 9.8)	96.7 (95.8 to 97.4)
	≥60	18.3 (17.0 to 19.6)	82.7 (81.3 to 84.1)
Chest pain	Yes	15.1 (14.1 to 16.2)	91.4 (90.5 to 92.3)
	No	11.4 (9.5 to 13.6)	75.0 (72.0 to 77.8)
Ischaemic ECG	Yes	31.0 (28.4 to 33.7)	80.6 (77.8 to 83.3)
	No	11.0 (10.0 to 12.0)	90.9 (89.9 to 91.8)
Hypertension	Yes	19.1 (17.4 to 21.0)	84.5 (82.6 to 86.2)
	No	13.1 (11.9 to 14.3)	90.1 (89.0 to 91.2)
Diabetes	Yes	17.9 (15.4 to 20.7)	85.2 (82.4 to 87.8)
	No	14.8 (13.8 to 15.9)	88.7 (87.6 to 89.7)
Ischaemic heart disease	Yes	20.5 (18.7 to 22.4)	87.9 (86.2 to 89.6)
	No	12.6 (11.5 to 13.7)	88.3 (87.1 to 89.4)
Selected patients (US)			
Age	<60	3.4 (2.3 to 4.7)	83.2 (80.6 to 85.6)
	≥60	5.3 (3,7 to 7.2)	70.1 (66.4 to 73.6)
Chest pain	Yes	5.7 (4.3 to 7.5)	86.4 (83.8 to 88.7)
	No	1.9 (1.0 to 3.2)	69.7 (66.2 to 73.0)
Ischaemic ECG	Yes	18.3 (11.9 to 26.1)	66.0 (56.0 to 75.1)
	No	3.0 (2.2 to 4.0)	78.6 (76.4 to 80.7)
Hypertension	Yes	4.8 (3.6 to 6.3)	72.4 (68.1 to 76.3)
	No	2.9 (1.7 to 4.6)	80.2 (77.7 to 82.5)
Diabetes	Yes	5.3 (3.6 to 7.7)	74.0 (71.2 to 76.6)
	No	3.6 (2.6 to 4.9)	85.0 (81.7 to 87.9)
Ischaemic heart disease	Yes	13.4 (9.9 to 17.5)	70.5 (65.0 to 75.7)
	No	1.8 (1.1 to 2.7)	79.5 (77.1 to 81.7)

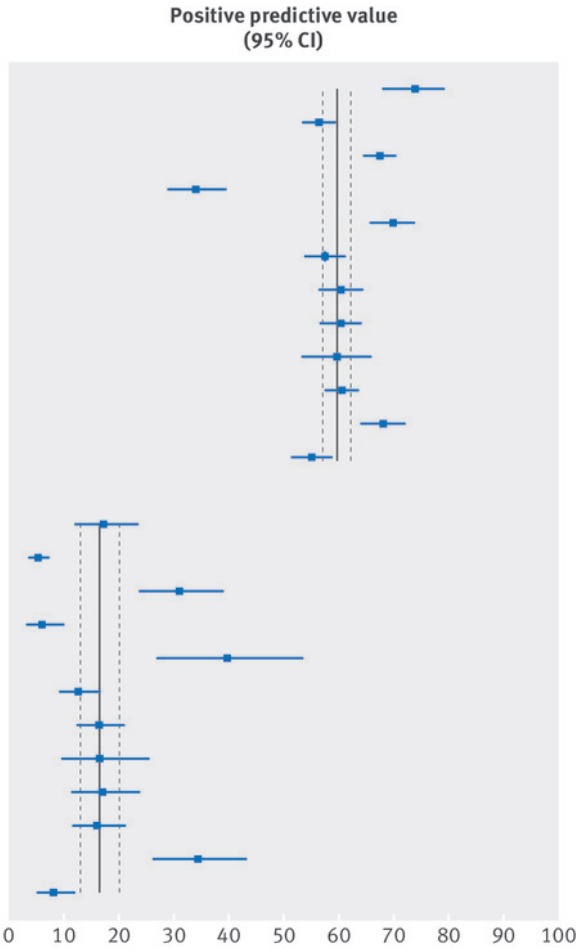

Fig 4 Influence of clinical characteristics on positive predictive value of elevated high sensitivity cardiac troponin for diagnosis of type 1 myocardial infarction in patients selected for troponin testing in the UK (top panel) and US (bottom panel). Solid line represents positive predictive value across whole population, with dashed lines representing 95% confidence intervals