METHODS

STARD checklist for reporting studies of diagnostic accuracy[1,2]

Section & Topic	No	Item
Title or abstract		
	1	Identification as a study of diagnostic accuracy using at least one measure of accuracy (such as sensitivity, specificity, predictive values, or area under the curve)
Abstract		
	2	Structured summary of study design, methods, results, and conclusions (for specific guidance, see STARD for Abstracts)
Introduction		
	3	Scientific and clinical background, including the intended use and clinical role of the index test
	4	Study objectives and hypotheses
Methods		
Study design	5	Whether data collection was planned before the index test and reference standard were performed (prospective study) or after (retrospective study)
Participants	6	Eligibility criteria
	7	On what basis potentially eligible participants were identified (such as symptoms, results from previous tests, inclusion in registry)
	8	Where and when potentially eligible participants were identified (setting, location and dates)
	9	Whether participants formed a consecutive, random or convenience series
Test methods	10a	Index test, in sufficient detail to allow replication
	10b	Reference standard, in sufficient detail to allow replication
	11	Rationale for choosing the reference standard (if alternatives exist)
	12a	Definition of and rationale for test positivity cutoffs or result categories of the index test, distinguishing prespecified from exploratory
	12b	Definition of and rationale for test positivity cutoffs or result categories of the reference standard, distinguishing prespecified from exploratory
	13a	Whether clinical information and reference standard results were available to the performers/readers of the index test
	13b	Whether clinical information and index test results were available to the assessors of the reference standard
Analysis	14	Methods for estimating or comparing measures of diagnostic accuracy
	15	How indeterminate index test or reference standard results were handled

	16	How missing data on the index test and reference standard were handled
	17	Any analyses of variability in diagnostic accuracy, distinguishing prespecified from exploratory
	18	Intended sample size and how it was determined
Results		
Participants	19	Flow of participants, using a diagram
	20	Baseline demographic and clinical characteristics of participants
	21a	Distribution of severity of disease in those with the target condition
	21b	Distribution of alternative diagnoses in those without the target condition
	22	Time interval and any clinical interventions between index test and reference standard
Test results	23	Cross tabulation of the index test results (or their distribution) by the results of the reference standard
	24	Estimates of diagnostic accuracy and their precision (such as 95% confidence intervals)
	25	Any adverse events from performing the index test or the reference standard
Discussion		
	26	Study limitations, including sources of potential bias, statistical uncertainty, and generalisability
	27	Implications for practice, including the intended use and clinical role of the index test
Other information		
	28	Registration number and name of registry
	29	Where the full study protocol can be accessed
	30	Sources of funding and other support; role of funders

Use of local conventional cardiac troponin (cTn) values for adjudication of final diagnoses

For the Roche cTnT fourth generation assay, the 10% coefficient of variation (CV) level is 0.035 ug/L. The laboratories of the participating sites reported only two decimals; therefore 0.04 ug/L was used as a cutoff for myocardial necrosis. In order to fulfil the criteria of a significant change (30% of 99th percentile or 10% CV level), a patient would eg need to have a level of < 0.01 ug/L at presentation and 0.04 ug/L at 6 h. A patient would also qualify if the first level is 0.02 ug/l and the second 0.04 ug/L. A patient would not fulfil the criteria if the first level is 0.03 ug/L and the second is 0.04 ug/L. If the first level is 0.04 ug/l, the second level needs to be at least 0.06 ug/L.

For the Abbott AxsymcTnI ADV, the 10% CV level is 0.16 ug/L. A patient having 0.16 ug/l at presentation would meet the criteria for significant change if the second was ≥ 0.21 ug/L. A patient having < 0.12 ug/L at presentation (limit of detection) would qualify if the second is > 0.16 ug/L.

For the Beckmann Coulter AccucTnI, the 10% CV level is 0.06 ug/L. A patient having 0.06 ug/L at presentation would qualify if the second is ≥ 0.08 ug/L. A patient having 0.05 at presentation would qualify if the second is 0.07 ug/L, but not 0.06 ug/L. A patient having undetectable cTnI (cTnI < 0.01 ug/L) at presentation would qualify if the second is ≥ 0.06 ug/L.

Use of hs-cTnT for adjudication of final diagnoses

In order to identify additional patients with small acute myocardial infarctions that were missed by the adjudication using the less sensitive conventional cTn assays a second adjudication using hs-cTnT was performed in all nonacute myocardial infarction patients according to the first adjudication. Two reasons led in 2009 to the inclusion of hs-cTnT into the APACE protocol for adjudication of diagnoses: First, hs-cTnT was the first and only hs-cTn assay available at that time. Second, previous work from several groups including ours[3] had shown that hs-cTnT has higher diagnostic accuracy for AMI compared with conventional cTn assays.

Analytical details of the three hs-cTnT/I assays

The hs-cTnT assay was measured on the Elecsys 2010 (Roche Diagnostics). The limit of blank (LoB) and limit of detection (LoD) were determined to be 3 ng/L and 5 ng/L respectively. The 99th-percentile of a healthy reference population was reported at 14 ng/L with an imprecision corresponding to 10% CV at 13 ng/L.[4]

The Abbott hs-cTnI assay used was the Architect High Sensitive *STAT* Troponin I (hsTnI) assay (Abbott Laboratories, Abbott Park, IL). Samples were thawed, mixed, and centrifuged (for 30 minutes at 3 000 RCF and 4°C for serum samples or for 10 minutes, twice, at 3 000 RCF for plasma samples)

prior to analysis and according to manufacturer's instructions. The hs-cTnI assay has a 99th percentile concentration of 26.2 ng/L with a corresponding CV of < 5% and a LoD of 1.9 ng/L.[5]

According to the manufacturer, the hs-cTnI-Centaur assay (ADVIA Centaur TNIH, Siemens Healthcare, Tarrytown, NY, USA) has a uniform 99th percentile concentration of 47 ng/L with a corresponding CV of < 5%. LoB, LoD, and limit of quantification (LoQ) have been determined to be 0.9 ng/L, 2.2 ng/L, and 2.5 ng/L. The assay is a dual-capture sandwich immunoassay using magnetic latex particles and a proprietary acridinium ester for chemiluminescence detection. The detection reagent is a recombinant sheep Fab antibody covalently linked to a tri-sulfo propyl acridinium ester (TSPAE)-BSA conjugate. TSPAE is a new generation of high-yield acridinium esters developed for enhanced chemiluminescent detection. Simultaneous addition of solid-phase reagent and detection reagent to the sample forms a classic sandwich immune complex, which is subsequently washed. Chemiluminescence is initiated and measured. Relative light units are directly proportional to the cTnI concentration. The time to first result is 18 minutes.[6,7]

Calculation of the glomerular filtration rate was performed using the abbreviated Modification of Diet in Renal disease formula.[8]

RESULTS

Correlation between 0-1 h and 0-2 h among AMI type 1 and type 2

As shown in figure 2 of the supplementary data, findings in patients with AMI type 1 were comparable to the overall cohort with correlation coefficients ranging from 0.931 to 0.969 ($P < .001$ for all assays). Type 2 AMI patients showed similar correlation coefficients ranging from 0.982 to 0.997 ($P < .001$ for all assays; figure 3 of the supplementary data).

Correlation between 0-1 h and 0-3 h changes

As shown in figure 5 of the supplementary data, with all three assays changes between 0 h-1 h correlated strongly with changes between 0 h-3 h with correlation coefficients ranging from 0.940 to 0.969 ($P < .001$ for all assays), for AMI patients.

REFERENCES

1. Bossuyt PM, Reitsma JB, Bruns DE, et al. Towards complete and accurate reporting of studies of diagnostic accuracy: The STARD Initiative. *Ann Intern Med.* 2003;138:40-44.

2. Korevaar DA, Cohen JF, Reitsma JB, et al. Updating standards for reporting diagnostic accuracy: the development of STARD 2015. *Res Integr Peer Rev.* 2016;1:7.

3. Reichlin T, Hochholzer W, Bassetti S, et al. Early diagnosis of myocardial infarction with sensitive cardiac troponin assays. *N Engl J Med.* 2009;361:858-867.

4. Giannitsis E, Kurz K, Hallermayer K, Jarausch J, Jaffe AS, Katus HA. Analytical Validation of a High-Sensitivity Cardiac Troponin T Assay. *Clin Chem.* 2010;56:254-261.

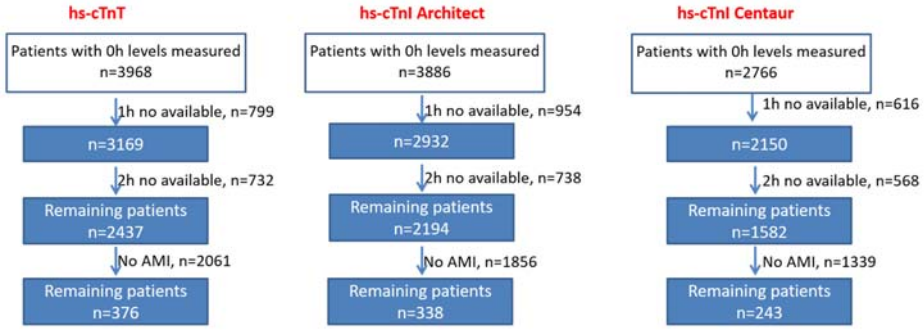
5. Koerbin G, Tate J, Potter JM, Cavanaugh J, Glasgow N, Hickman PE. Characterisation of a highly sensitive troponin I assay and its application to a cardio-healthy population. *Clin Chem Lab Med.* 2012;50:871-878.

6. Apple FS, Jaffe AS, Collinson P, et al. IFCC educational materials on selected analytical and clinical applications of high-sensitivity cardiac troponin assays. *Clin Biochem.* 2015;48:201-203.

7. Apple FS, Sandoval Y, Jaffe AS, Ordonez-Llanos J, Bio-Markers ITFoCAoC. Cardiac Troponin Assays: Guide to Understanding Analytical Characteristics and Their Impact on Clinical Care. *Clin Chem.* 2017;63:73-81.

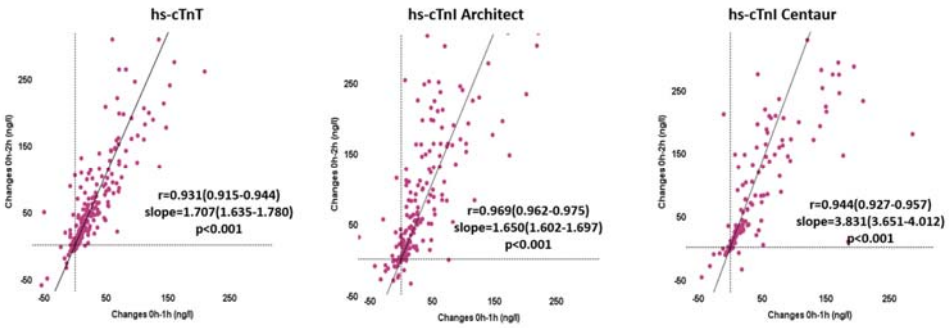
8. Levey AS, Coresh J, Greene T, et al. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. *Ann Intern Med.* 2006;145:247-254.

Figure 1 of the supplementary data. Patients flow diagram. Flowchart displaying number of consecutive AMI patients included in the final analyses



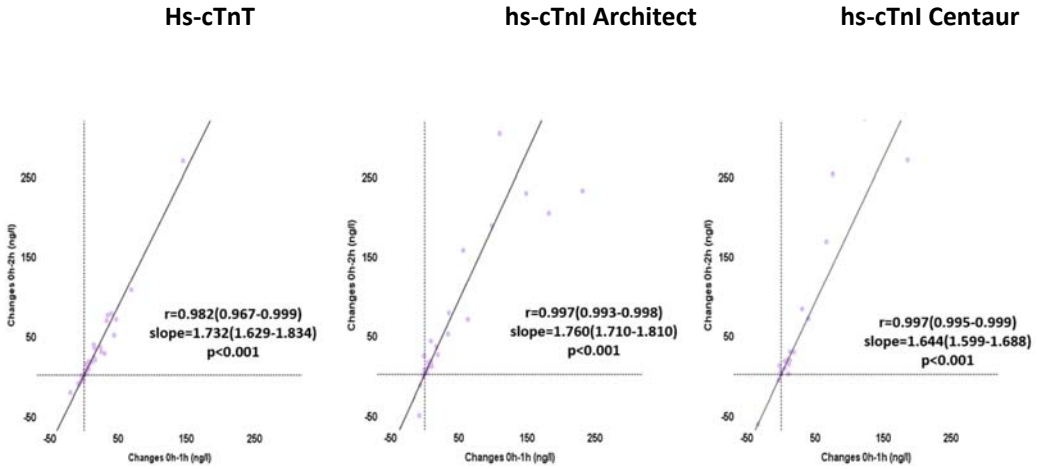
AMI, acute myocardial infarction; Hs-cTn, high-sensitivity cardiac troponin.

Figure 2 of the supplementary data. Correlation between 0- to 1-hour changes and 0- to 2-hour changes in patients with type 1 AMI. Scatter plots showing the association between Delta 0- to 1-hour and 0- to 1-hour hs-cTn.



AMI, acute myocardial infarction; Hs-cTn, high-sensitivity cardiac troponin.

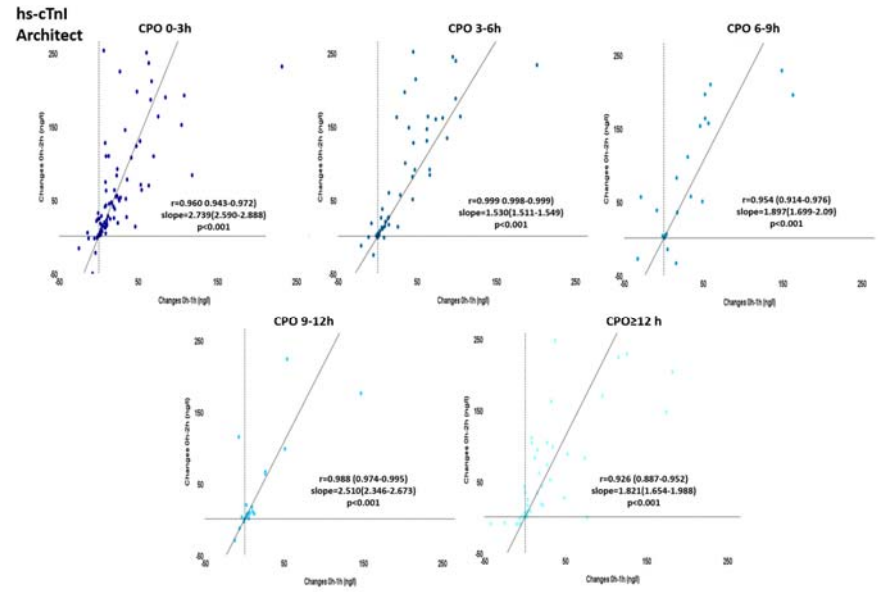
Figure 3 of the supplementary data. Correlation between 0 h-1 hour changes and 0- to 2-hour changes in patients with type 2 AMI. Scatter plots showing the association between Delta 0- to 1-hour and 0- to 2-hour hs-cTn.



AMI, acute myocardial infarction; Hs-cTn, high-sensitivity cardiac troponin.

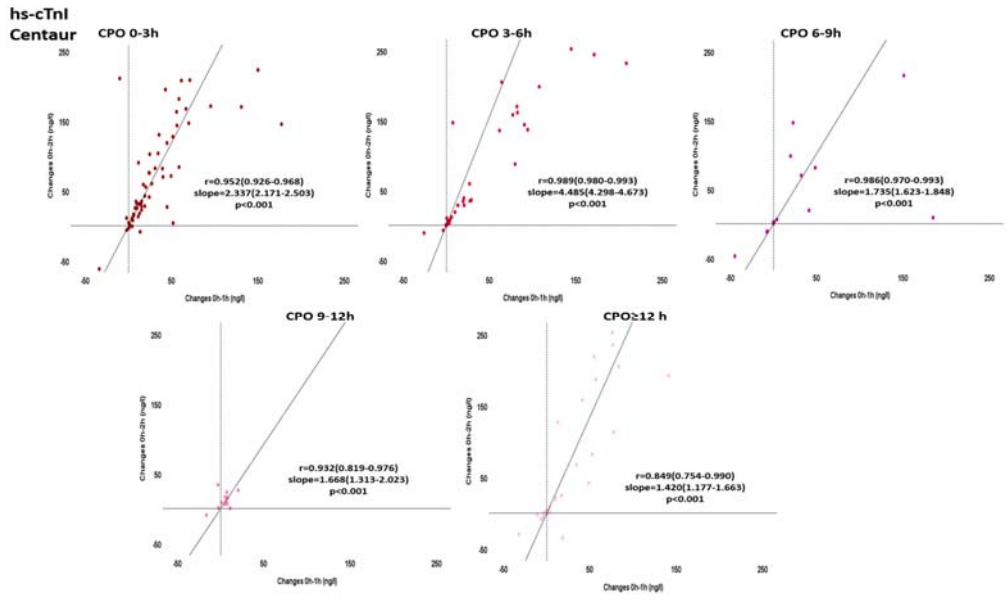
Figure 4 of the supplementary data. Correlation between 0- to 1-hour changes and 0- to 2-hour changes in AMI patients according to chest pain onset. Scatter plots showing the association between Delta 0- to 1-hour and 0- to 2-hour hs-cTn among AMI patients according to time since chest pain onset in AMI patients

A



CPO 0-<3h (n=115); CPO 3-<6h (n=78); CPO 6-<9h (n=39); CPO 9-<12h (n=26); CPO≥12h (n=80); missing data CPO (n=0)

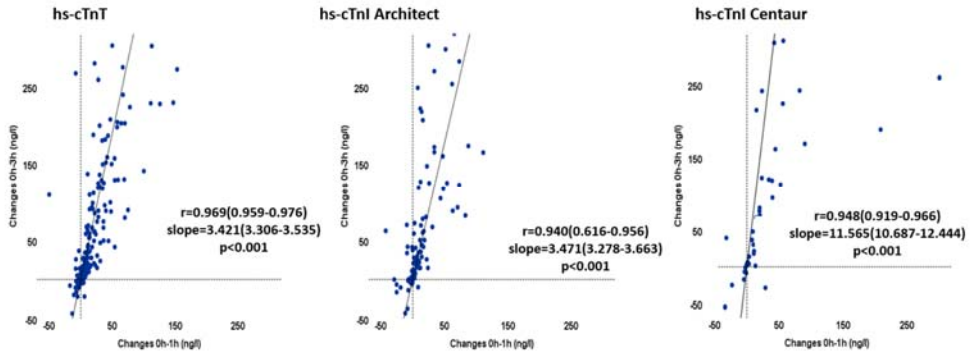
B



CPO 0-<3h (n=84); CPO 3-<6h (n=56); CPO 6-<9h (n=31); CPO 9-<12h (n=17); CPO≥12h (n=55); missing data CPO (n=1)

AMI, acute myocardial infarction; CPO, chest pain onset; Hs-cTn, high-sensitivity cardiac troponin.

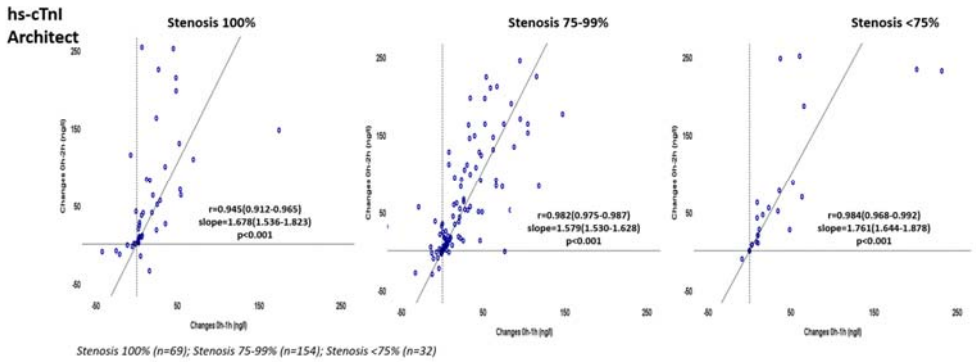
Figure 5 of the supplementary data. Correlation between 0- to 1-hour changes and 0- to 3-hour changes in AMI patients. Scatter plots showing the association between Delta 0- to 1-hour and 0- to 3-hour hs-cTn.



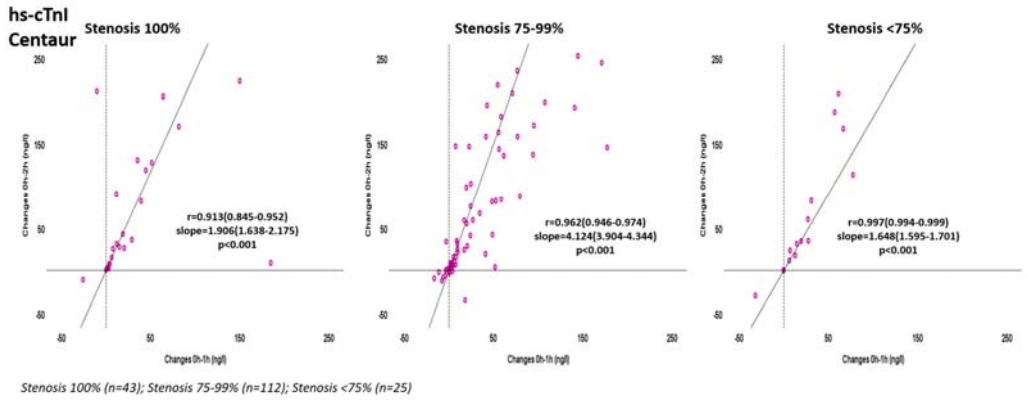
AMI, acute myocardial infarction; Hs-cTn, high-sensitivity cardiac troponin.

Figure 6 of the supplementary data. Correlation between 0- to 1-hour changes and 0- to 2-hour changes in AMI patients according to stenosis grade. Scatter plots showing the association between Delta 0- to 1-hour and 0- to 2-hour hs-cTn among AMI patients according to stenosis grade of the culprit lesion.

A



B



AMI, acute myocardial infarction; Hs-cTn, high-sensitivity cardiac troponin.