Clinical implications of sex-specific upper reference limits for high-sensitivity cardiac troponin I in myocardial infarction diagnosis

Supplementary data

Table 1 of the supplementary data. STARD checklist for studies of diagnostic accuracy[1]

Section & topic	No.	Item	Reported on page #
Ttitle or abstract			
	1	Identification as a study of diagnostic accuracy using at least 1 measure of accuracy (such as sensitivity, specificity, predictive values, or AUC).	3, 6-7, Online Suppl. page 8-9
Abstract			
	2	Structured summary of study design, methods, results, and conclusions (for specific guidance, see STARD for Abstracts).	3
Introduction			
	3	Scientific and clinical background, including the intended use and clinical role of the index test.	5-7
	4	Study objectives and hypotheses.	5, Online Suppl. pp. 3, 7-9
Methods			
Study design	5	Whether data collection was planned before the index test and reference standard were performed (prospective study) or after (retrospective study).	5, Online Suppl. pp. 3, 7-9
Participants	6	Eligibility criteria.	5, Online Suppl. pp. 3 Online Suppl. Suppl. Figure 2
	7	On what basis potentially eligible participants were identified (such as symptoms, results from previous tests, inclusion in registry).	5, Online Suppl. pp. 3 Online Suppl. Suppl. Figure 2

	8	Where and when potentially eligible participants were identified (setting, location and dates).	5, Online Suppl. pp. 3 Online Suppl. Suppl. Figure 2
	9	Whether participants formed a consecutive, random or convenience series.	5, Online Suppl. pp. 3 Online Suppl. Figure 2
.Test methods	10a	Index test, in sufficient detail to allow replication.	5-97 and Online Suppl. Methods
	10b	Reference standard, in sufficient detail to allow replication.	5-7 and Online Suppl. Methods
	11	Rationale for choosing the reference standard (if alternatives exist).	5-7 and Online Suppl. Methods
	12a	Definition of and rationale for test positivity cutoffs or result categories of the index test, distinguishing prespecified from exploratory.	5-7 and Online Suppl. Methods
	12b	Definition of and rationale for test positivity cutoffs or result categories of the reference standard, distinguishing prespecified from exploratory.	5-7 and Online Suppl. Methods
	13a	Whether clinical information and reference standard results were available to the performers/readers of the index test.	5-7 and Online Suppl. Methods
	13b	Whether clinical information and index test results were available to the assessors of the reference standard.	5-7 and Online Suppl. Methods
Analysis	14	Methods for estimating or comparing measures of diagnostic accuracy.	7 and Online Suppl. page 8-9
	15	How indeterminate index test or reference standard results were handled.	7 and Online Suppl. page 8-9
	16	How missing data on the index test and reference standard were handled.	7 and Online Suppl. page 8-9
	17	Any analyses of variability in diagnostic accuracy, distinguishing prespecified from exploratory.	7 and Online Suppl. page 8-9
	18	Intended sample size and how it was determined.	n/a
Results			
Participants	19	Flow of participants, using a diagram.	Suppl. Figure 2
	20	Baseline demographic and clinical characteristics of participants.	8, Table 1, Suppl. Table 2, Suppl. Table 6+7
	21a	Distribution of severity of disease in those with the target condition.	8, Table 1, Suppl. Table 2, Suppl. Table 6+7

	21b	Distribution of alternative diagnoses in those without the target condition.	8 and Online Suppl. page 17
	22	Time interval and any clinical interventions between index test and reference standard.	n/a
Test results	23	Cross tabulation of the index test results (or their distribution) by the results of the reference standard.	8-12
	24	Estimates of diagnostic accuracy and their precision (such as 95% confidence intervals).	8-12
	25	Any adverse events from performing the index test or the reference standard.	Online Suppl. page 23
Discussion			
	26	Study limitations, including sources of potential bias, statistical uncertainty, and generalizability.	15-16
	27	Implications for practice, including the intended use and clinical role of the index test.	13-16
Other information			
	28	Registration number and name of registry.	4
	29	Where the full study protocol can be accessed.	4
	30	Sources of funding and other support; role of funders.	17

Methods of the supplementary data

Routine clinical assessment

Patients underwent routine clinical assessment that included medical history, physical examination, standard blood tests including local serial measurements of (hs)-cTn, 12-lead electrocardiogram, chest radiography, continuous ECG rhythm monitoring, and pulse oximetry. Management of patients was left to the discretion of the attending physician.

Adjudication of final diagnoses

MI was defined and cTn levels interpreted as recommended in current guidelines.[2, 3] In brief, MI was diagnosed when there was evidence of myocardial necrosis with a significant rise and/or fall in a clinical setting consistent with myocardial ischemia. Therefore, it is possible to have hs-cTn values above the 99th percentile without having an acute MI, such as in a patient

with chronically elevated hs-cTn values due to heart failure presenting with unstable angina, if the criteria for significant rise and/or fall are not fulfilled.

Patients with MI were further subdivided into type 1 MI (primary coronary events) and type 2 MI (ischemia due to increased demand or decreased supply, for example tachyarrhythmia or hypertensive crisis). [2, 4] All other patients were classified into categories of unstable angina (UA), cardiac but noncoronary disease (eg, tachyarrhythmia, perimyocarditis), noncardiac chest pain (NCCP) and symptoms of unknown origin with normal hs-cTn concentrations.

The adjudication of final diagnoses was performed centrally in the core lab (University Hospital Basel) in all patients with concentrations of hs-cTnI-Architect measured twice (first with the uniform 99th percentile and second with the sex-specific 99th percentile). More specifically, two independent cardiologists not directly involved in patient care reviewed all available medical records (including patient history, physical examination, results of laboratory testing including hs-cTn levels, radiologic testing, ECG, echocardiography, cardiac exercise test, lesion severity, and morphology in coronary angiography, discharge summary) pertaining to the patient from the time of emergency department (ED) presentation to 90 days of follow-up. In general, serial sampling was performed until at least 3 to 6 hours after presentation to the ED or the onset of chest pain. In situations of diagnostic disagreement, cases were reviewed and adjudicated in conjunction with a third cardiologist. While discharge diagnoses were often correct and in agreement with the final adjudicated diagnosis, there were also cases in which the discharge diagnosis needed to be revised, most often because more information became available from medical testing during early follow-up, and more rarely, because the discharge diagnosis was not in agreement with the universal definition of acute MI.

The hs-cTnI 99th percentile (uniform: 26.2 ng/L; sex-specific for women 15.6 ng/L and for men 34.2 ng/L) [5] was used as the cutoff for myocardial necrosis. Figure 1S. Absolute cTn changes were used to determine significant changes based on the diagnostic superiority of absolute over relative changes.[6-8] Based on studies of the biological variation of cTn [9, 10] as well as on data from previous chest pain cohort studies, [6, 11] a significant absolute

change was defined as a rise or fall of at least 10 ng/L within 6 hours, or, assuming linearity, as an absolute change of 6 ng/L within 3 hours. [12]

Follow-up

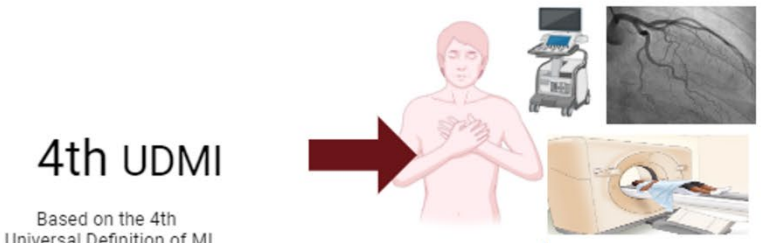
Patients were contacted 3, 12 and 24 months after discharge by telephone calls or in written form. We obtained information on death during follow-up from the patient's hospital notes, the family physician's records, and the national mortality registry.

Results of the supplementary data

Angiographical examinations

Coronary angiography was performed in 23.3% of all patients (18.1% of all women and 26.0% of all men). Among them, 18.2% had normal coronaries or coronary sclerosis, and the rest had coronary vessel disease (27.4% of women and 14.8% of men). Among those patients with no pathological findings in the coronary angiogram, 33.4% (30.6% of women and 35.4% of men) had hs-cTnI values above the uniform URL. Among these patients, the final diagnoses were cardiac noncoronary (57.3%), type 2 MI (26.7%), type 1 MI (10.0%), and noncardiac chest pain (5.0%).

Adjudication of final diagnoses

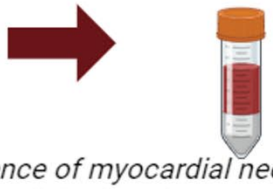


4th UDMI

Based on the 4th Universal Definition of MI

clinical work-up + study specific data*

12-lead ECG



s-cTn

MI *if evidence of myocardial necrosis with a significant rise and/or fall in a clinical setting consistent with myocardial ischemia*

The final diagnosis was centrally adjudicated by two independent cardiologists **twice:**

1

Uniform Adjudication

Using hs-cTnI **Uniform** URL

99th percentile

26.2 ng/l

2

Sex-specific Adjudication

Using hs-cTnI **sex-specific** URL

15.6ng/l

34.2ng/l

with uniform diagnosis of
a) UA or
b) "cardiac others"

+

hs-cTnI levels between 15.6 and 26.2 ng/l

-> **upgraded** to sex-specific diagnosis of T1MI or T2MI** or myocardial injury

with uniform diagnosis of
a) NSTEMI

+

hs-cTnI levels <34.2ng/l

-> **downgraded** to sex-specific diagnosis of UA***or cardiac others

*Included clinical presentation (medical history, physical examination), standard blood tests including serial measurements of local (hs)-cTn, 12-lead ECG, chest radiography, continuous ECG rhythm monitoring, pulse oximetry, cardiac imaging including transthoracic echocardiography, coronary angiography, myocardial perfusion scanning, and clinical follow-up.

**If also fulfilling, eg, the dynamic criteria.

Figure 1 of the supplementary data. Image displaying details of the adjudication of diagnoses with uniform and sex-specific cutoffs

UDMI, universal definition myocardial infarction; ECG, electrocardiogram; MI, myocardial infarction; hs-cTnI, high-sensitivity cardiac troponin I; UA, unstable angina; T1MI, type 1 myocardial infarction; UA; T2MI, type 2 myocardial infarction; NSTEMI, non–ST-segment elevation myocardial infarction

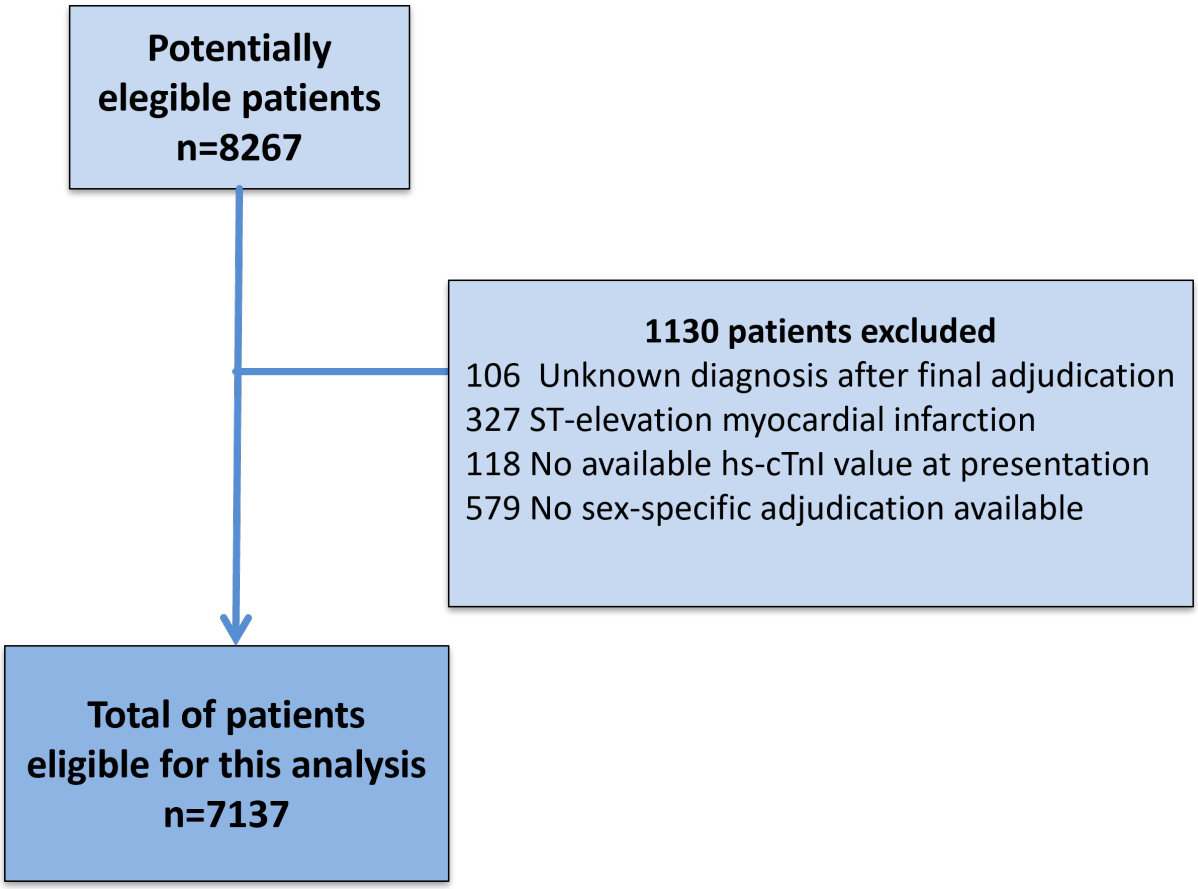


Figure 2 of the supplementary data: Flow-chart showing eligible patients

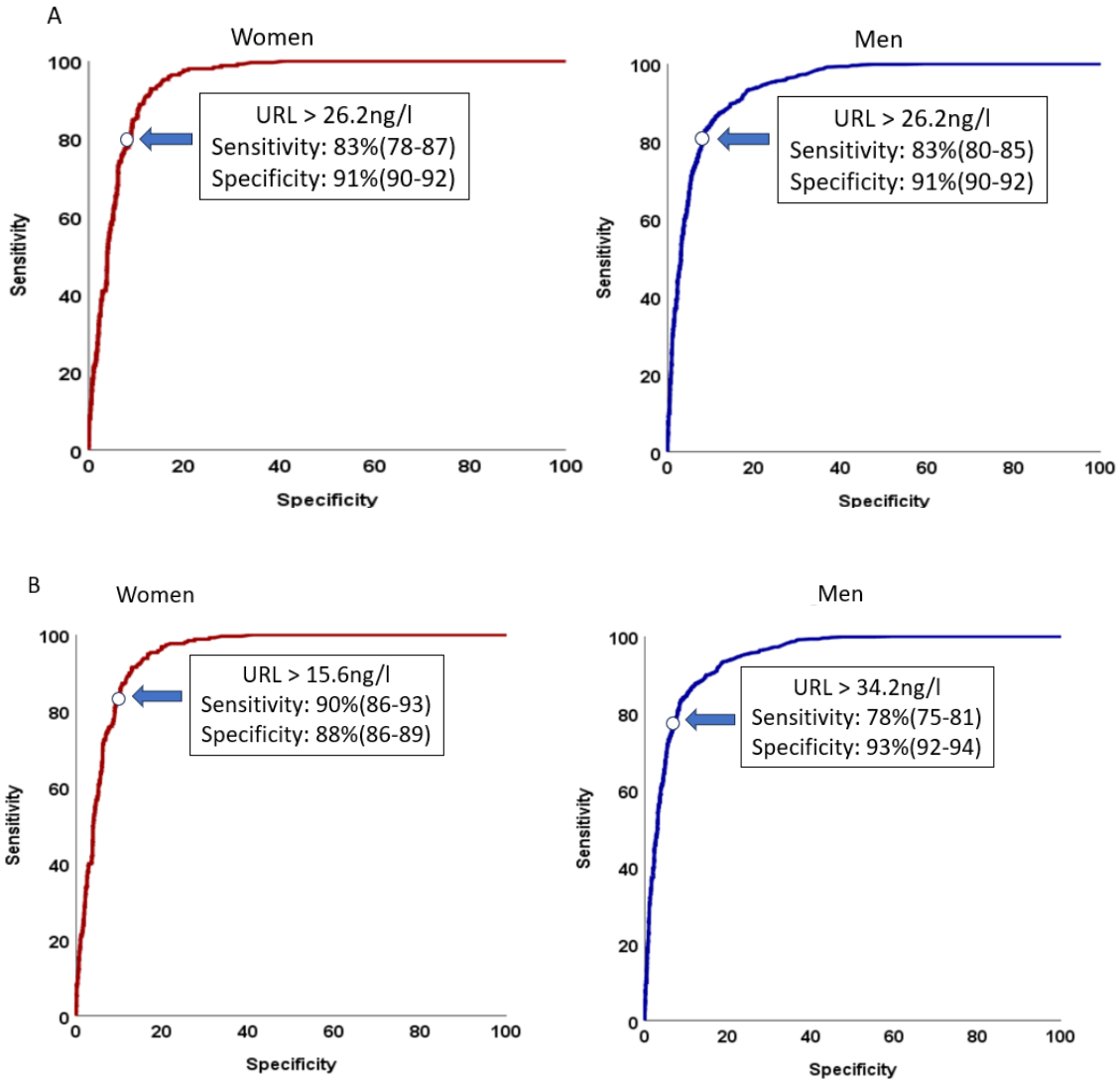


Figure 3 of the supplementary data. Diagnostic accuracy of uniform and sex-specific URLs for T1MI at presentation.

ROC curves displaying the diagnostic accuracy of 0h hs-cTnI using uniform (A) and sex-specific (B) URLs for myocardial infarction in men and women.

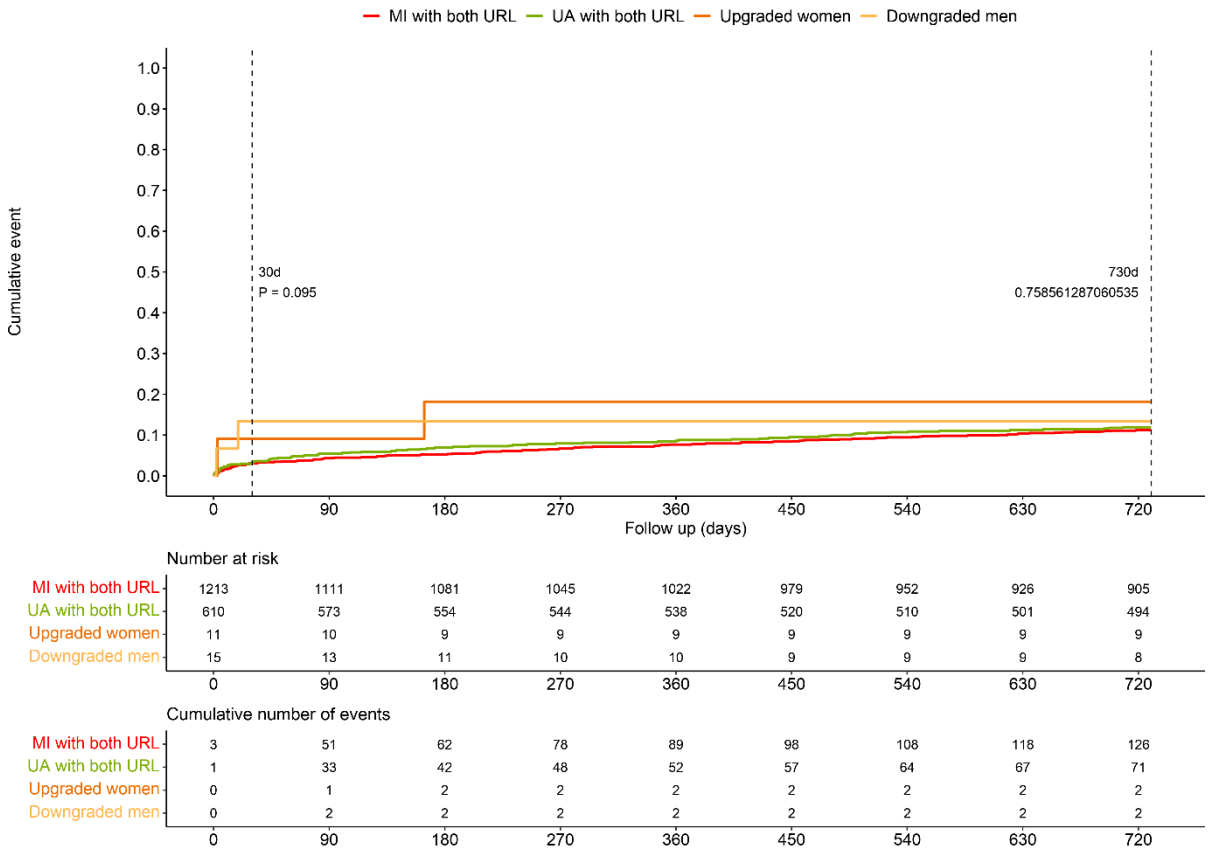


Figure 4 of the supplementary data. Reclassification and nonindex MI within 30 and 730 days.

Kaplan-Meier curves display time free of MI after 30 and 730 days among the different reclassification groups.

MI, Type 1 myocardial infarction; UA, unstable angina; URL, upper reference limit.

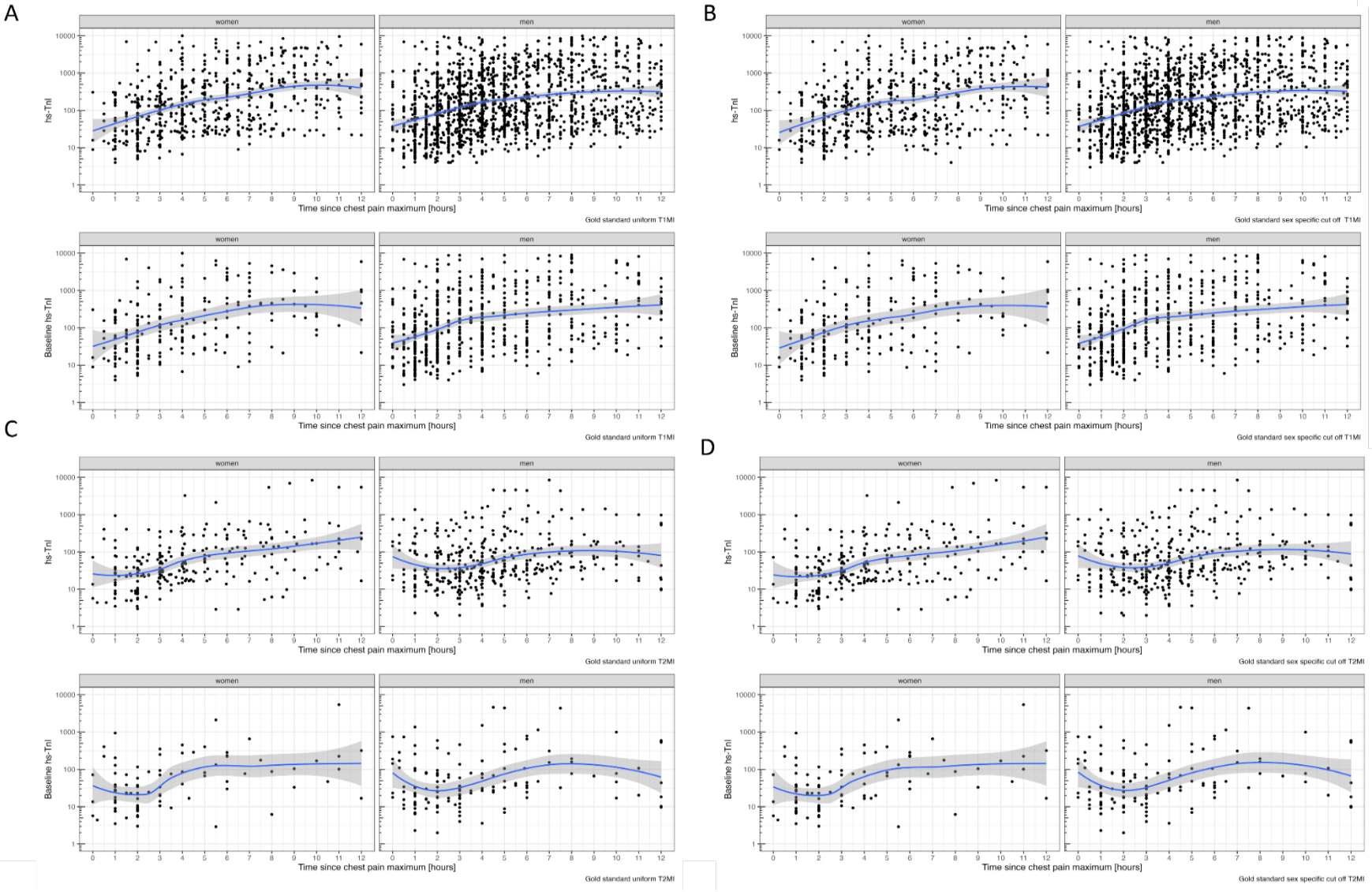

A
B
C
D
women
men
hs-TnI
Baseline hs-TnI
Time since chest pain maximum [hours]
Gold standard uniform T1MI
Gold standard sex specific cut off T1MI
Gold standard uniform T2MI
Gold standard sex specific cut off T2MI

Figure 5 of the supplementary data: hs-cTn kinetics in women and men.

Scatter plot displaying changes in hs-cTnI concentrations (serial sampling and baseline values) stratified by sex and time since maximum chest pain in patients with T1MI using uniform hs-cTnI values (A), T1MI using sex-specific values (B), T2MI using uniform hs-cTnI values (C), T2MI using sex-specific hs-cTnI values (D).

REFERENCES OF THE SUPPLEMENTARY DATA

1. Korevaar DA, Cohen JF, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig L, Moher D, de Vet HCW, Altman DG, Hooft L and Bossuyt PMM. Updating standards for reporting diagnostic accuracy: the development of STARD 2015. *Res Integr Peer Rev*. 2016;1:7.
2. Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, White HD and Group ESCSD. Fourth universal definition of myocardial infarction (2018). *Eur Heart J*. 2019;40:237-269.
3. Byrne RA, Rossello X, Coughlan JJ, Barbato E, Berry C, Chieffo A, Claeys MJ, Dan GA, Dweck MR, Galbraith M, Gilard M, Hinterbuchner L, Jankowska EA, Juni P, Kimura T, Kunadian V, Leosdottir M, Lorusso R, Pedretti RFE, Rigopoulos AG, Rubini Gimenez M, Thiele H, Vranckx P, Wassmann S, Wenger NK, Ibanez B and Group ESCSD. 2023 ESC Guidelines for the management of acute coronary syndromes. *Eur Heart J*. 2023;44:3720-3826.
4. Collet JP, Thiele H, Barbato E, Barthelemy O, Bauersachs J, Bhatt DL, Dendale P, Dorobantu M, Edvardsen T, Folliguet T, Gale CP, Gilard M, Jobs A, Juni P, Lambrinou E, Lewis BS, Mehilli J, Meliga E, Merkely B, Mueller C, Roffi M, Rutten FH, Sibbing D, Siontis GCM and Group ESCSD. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J*. 2020.
5. International Federation of Clinical Chemistry and Laboratory Medicine. High sensitivity cardiac troponin I and T assay analytical characteristics designated by manufacturer. 2022.
6. Reichlin T, Irfan A, Twerenbold R, Reiter M, Hochholzer W, Burkhalter H, Bassetti S, Steuer S, Winkler K, Peter F, Meissner J, Haaf P, Potocki M, Drexler B, Osswald S and Mueller C. Utility of absolute and relative changes in cardiac troponin concentrations in the early diagnosis of acute myocardial infarction. *Circulation*. 2011;124:136-45.
7. Irfan A, Reichlin T, Twerenbold R, Meister M, Moehring B, Wildi K, Bassetti S, Zellweger C, Gimenez MR, Hoeller R, Murray K, Sou SM, Mueller M, Mosimann T, Reiter M, Haaf P, Ziller R, Freidank H, Osswald S and Mueller C. Early Diagnosis of Myocardial Infarction Using Absolute and Relative Changes in Cardiac Troponin Concentrations. *Am J Med*. 2013.
8. Mueller M, Biener M, Vafaie M, Doerr S, Keller T, Blankenberg S, Katus HA and Giannitsis E. Absolute and relative kinetic changes of high-sensitivity cardiac troponin T in acute coronary syndrome and in patients with increased troponin in the absence of acute coronary syndrome. *Clin Chem*. 2012;58:209-18.
9. Vasile VC, Saenger AK, Kroning JM and Jaffe AS. Biological and analytical variability of a novel high-sensitivity cardiac troponin T assay. *Clin Chem*. 2010;56:1086-90.
10. Wu AH, Shea E, Lu QT, Minyard J, Bui K, Hsu JC, Agee SJ and Todd J. Short- and long-term cardiac troponin I analyte stability in plasma and serum from healthy volunteers by use of an ultrasensitive, single-molecule counting assay. *Clin Chem*. 2009;55:2057-9.
11. Hammarsten O, Fu ML, Sigurjonsdottir R, Petzold M, Said L, Landin-Wilhelmsen K, Widgren B, Larsson M and Johanson P. Troponin T percentiles from a random population sample, emergency room patients and patients with myocardial infarction. *Clin Chem*. 2012;58:628-37.
12. Rubini Gimenez M, Wildi K, Wussler D, Koechlin L, Boeddinghaus J, Nestelberger T, Badertscher P, Sedlmayer R, Puelacher C, Zimmermann T, du Fay de Lavallaz J, Lopez-Ayala P, Leu K, Rentsch K, Miro O, Lopez B, Martin-Sanchez FJ, Bustamante J, Kawecki D, Parenica J, Lohrmann J, Kloos W, Buser A, Keller DI, Reichlin T, Twerenbold R and Mueller C. Early kinetics of cardiac troponin in suspected acute myocardial infarction. *Rev Esp Cardiol (Engl Ed)*. 2021;74:502-509.