APPENDIX

High-Sensitivity Cardiac Troponin and the Diagnosis of Myocardial Infarction in Patients with Kidney Impairment

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Supplementary tables: 5

Supplementary figures: 1

Supplementary Methods

Randomisation

Block randomisation was used with sites paired based on the expected number of presentations and one site randomised to early implementation and the other to late implementation. For pragmatic reasons (shared lab facilities out of hours), the Vale of Leven and Royal Alexandra Hospital, Paisley were grouped and randomised together. This enabled implementation of the high-sensitivity assay to occur on the same date at both sites and allowed the same lab processes to be followed at both sites. The randomisation sequence was generated by a programmer at the Edinburgh Clinical Trials Unit who was not otherwise involved in the study using computer generated pseudo-random numbers.

Intervention

Consecutive patients with suspected acute coronary syndrome underwent cardiac troponin testing at presentation and again 6 to 12 hours after the onset of symptoms, at the discretion of the attending clinician consistent with national[S1] and international[S2] guidelines. During both phases of the trial, all patients underwent testing with contemporary cardiac troponin I (ARCHITECT$_{STAT}$ troponin I, Abbott Laboratories, Abbott Park, IL, USA) and high-sensitivity cardiac troponin I (ARCHITECT$_{STAT}$ high-sensitive troponin I, Abbott Laboratories, Abbott Park, IL, USA) assays. During the validation phase of the trial, results of the high-sensitivity assay were suppressed from attending clinicians; during the implementation phase of the trial, results of the contemporary were suppressed. For the contemporary assay, a single threshold for the diagnosis of myocardial infarction in women and men was used to guide clinical decisions during the validation phase of the trial. This threshold was based on the local evaluation of the lowest concentration where the inter-assay coefficient of variation was <10%, which was 40 ng/L at seven sites and 50 ng/L at three sites. For the high-sensitivity assay, the

coefficient of variation was <10% at 4.7 ng/L, and the diagnostic threshold was based on sex-specific 99th centile upper reference limits of 16 ng/L for women and 34 ng/L for men.[S3]

Implementation support

To support implementation, we provided written educational material and presentations at each site, training for clinical and laboratory staff, and we updated the electronic patient record to highlight the change in assay and diagnostic thresholds. Educational material on the new assay and decision thresholds was presented at each Emergency Department handover (twice daily) during the implementation phase to ensure wide coverage of staff on all shift patterns. This was reinforced by specialist chest pain nurses who received detailed training prior to implementation and who support Emergency Department clinicians in the assessment of patients with suspected acute coronary syndrome. Key details from the educational presentation formed a one-page reference guide that was posted within each department and online in the hospital guidelines portal. This information was also presented to the wider hospital teams in medical grand round presentations prior to implementation and circulated to all general practitioners.

Every high-sensitivity cardiac troponin result reported in the electronic health record during the implementation phase was accompanied with guidance notes outlining the new assay, reporting units and thresholds. Laboratory staff also received training to ensure any queries directed to the laboratory were dealt with consistently. Finally, the research team included senior cardiologists, emergency physicians, and cardiology nurses who were clinically active within each of the hospital clusters; education was therefore reinforced at a local level by these clinical leaders throughout the implementation phase.

Outcomes

All trial data were collected from routine electronic regional and national healthcare datasets, linked, anonymised and held securely within the NHS National Services Scotland national safe haven. All in-hospital and community deaths, and all hospital admissions are recorded on the Register of Deaths in Scotland and the Scottish Morbidity Record (SMR) respectively. It is a statutory requirement that any deaths occurring in Scotland, or out-with Scotland but within the United Kingdom are entered on the Register of Deaths in Scotland within eight days of death. As such, this registry is 100% complete for the study population, which was restricted to those residing in Scotland. This assumes that patients did not emigrate in the year following enrolment. However, the Scottish population is very stable, with low levels of emigration out-with the United Kingdom.

The TrakCare software application (InterSystems Corporation, Cambridge, MA, USA) is an electronic patient record system used at all participating sites, which provided clinical data for all subsequent hospital admissions. All attendances across any participating hospital where cardiac troponin was measured and the high-sensitivity cardiac troponin I concentration was above the 99th centile were reviewed and the diagnosis adjudicated. We used the same approach to adjudication as for the index hospital episode with the panel blinded to all cardiac troponin measurements during the index episode and to the study phase.

The primary outcome was myocardial infarction (type 1 or type 4b) or cardiovascular death at 1 year. Secondary efficacy endpoints include myocardial infarction, unplanned coronary revascularisation, cardiovascular death, all-cause death, duration of stay, hospitalisation for heart failure and ischaemic stroke. Secondary safety endpoints include major hemorrhage, unplanned hospitalisation excluding acute coronary syndrome, and non-cardiovascular death.

Unplanned coronary revascularisation was defined as any urgent or emergency percutaneous coronary intervention or coronary artery bypass grafting following discharge. International Classification of Disease (ICD)-10 codes from the Scottish Morbidity Record were used to define hospitalisation for heart failure (I50) and ischaemic stroke (I63, I65, or I66). Bleeding was defined according to the Bleeding Academic Research Consortium (BARC) definition using ICD-10 and OPCS codes to classify each bleeding event, as previously described.[S4,S5] Major haemorrhage was defined as BARC type 3 or type 5. Unplanned hospitalisation excluding acute coronary syndrome was defined as any hospital attendance or admission excluding type 1 or type 4b myocardial infarction at 30 days.

The duration of stay was derived from a common electronic patient record system used across all participating sites (TrakCare, InterSystems Corporation, Cambridge, MA, USA) and was calculated from the admission and discharge date and time to the nearest minute.

The decision to perform coronary angiography was made by the attending cardiologist taking into consideration all aspects of the patients' presentation including cardiac troponin concentrations.

The Scottish national community drug-prescribing database of ISD in NHS Scotland maintains a detailed record of all prescriptions dispensed in the community, which are linked to individual patient identifiers. Alterations in cardiovascular therapies following the index hospital episode were determined by comparison to baseline.

The Scottish Index of Multiple Deprivation (SIMD) identifies areas where the highest concentration of deprivation exists in Scotland. SIMD 2012 combines 38 different indicators covering seven different dimensions of deprivation including income, employment, health,

education, housing, access to services and crime.[S6] The SIMD is derived for each individual in the trial population from the postcode at their address of residence.

Reporting

We report all primary and secondary efficacy outcomes in the pre-specified statistical analysis plan. However, two of the eleven secondary endpoints specified in the original trial protocol are not reported. During the conduct of the trial it became clear that 'minor hemorrhage' and 'cardiovascular death excluding acute coronary syndrome' would be difficult to define from routine healthcare data. Following discussion with our trial steering committee, these secondary endpoints were not included in the pre-specified statistical analysis plan and are therefore not presented in the manuscript.

Site Closures

In order to accommodate the closure of the Western Infirmary and Victoria Infirmary during the implementation phase of the study, and subsequent redirection of patients in their catchment areas to the new Queen Elizabeth University Hospital on the site of the Southern General Hospital, patients were analysed according to the site at which they were treated. The Queen Elizabeth University Hospital was considered a continuation of the Southern General Hospital site.

Sample Size

Using previous data from the Royal Infirmary of Edinburgh,[S7] we estimated that patients reclassified by the high-sensitivity assay would experience an event rate of 13% for the primary outcome of subsequent myocardial infarction or cardiovascular death. We originally planned that 10 sites (clusters) would include patients during three 6-month phases: validation (standard care), randomisation (early or late introduction of the intervention) and implementation

(intervention). For each site the difference in proportions of primary outcome events between standard care and intervention will be approximately normally distributed, each with a standard deviation that depends on the number of patients recruited by that site and the primary outcome event rate under standard care (assumed to be 13%). During a pilot phase,[S3] detailed power calculations, based on 1,000 simulations per scenario, were performed based on the anticipated proportion of patients who would be reclassified by the high-sensitivity assay. Power for a reclassification rate ranging from 6% to 9%, was 74% to 85% for an absolute risk reduction of 4.4%. Power was virtually unchanged when varying the ICC value from 0.05 to 0.10, as would be expected in a stepped wedge design such as this in which relatively few clusters recruit a large number of patients per site.

Statistical analysis

In patients with type 1 myocardial infarction, an additional exploratory analysis was conducted to evaluate the effectiveness of coronary revascularisation, dual antiplatelet therapy, ACE-inhibitors/angiotensin-receptor blockers, statins and beta blockers according to renal function using multivariable logistic regression models stratified by eGFR categories (<30/30-59/60-89/≥90 mL/min/1.73 m^2). Multivariable logistic regression models were constructed to compare the odds of experiencing a primary outcome event in those who received each new treatment during the index presentation *versus* those who did not. These models adjusted for age, sex, social deprivation status, peak troponin concentration, study phase, hospital site (fitted as a random effect), seasonality, time of presentation from start of trial, and history of cerebrovascular disease, diabetes, ischaemic heart disease and myocardial infarction. The influence of residual confounding was evaluated by examining the falsification hypothesis that the new prescription of a calcium channel antagonist would reduce the odds of the primary outcome at one year. To do this, we used the same multivariable logistic regression model, but

with the inclusion of a treatment:eGFR interaction term and prescription of a calcium channel antagonist as the primary explanatory variable.

Data Sharing

The High-STEACS trial makes use of multiple routine electronic health care data sources that are linked, de-identified and held in our National Safe Haven, which is accessible by approved individuals who have undertaken the necessary governance training. Summary data and source analysis code can be made available upon request to the corresponding author (bean.dhaun@ed.ac.uk).

Supplementary Tables

Supplementary Table S1. Characteristics of all patients included in the trial, according to estimated glomerular filtration rate.

	Estimated GFR				Overall
	<30 ml/min/1.73m²	**30-59 ml/min/1.73m²**	**60-89 ml/min/1.73m²**	**≥90 ml/min/1.73m²**	
Number of participants	**1,766**	**7,314**	**18,174**	**19,673**	**46,927**
Age, years	77 (12)	77 (11)	67 (14)	48 (13)	61 (17)
Sex					
Women	904 (51)	3,839 (52)	9,610 (53)	7,595 (39)	21,947 (47)
Men	862 (49)	3,475 (48)	8,564 (47)	12,079 (61)	24,980 (53)
Previous medical conditions					
Myocardial infarction	293 (17)	1,016 (14)	1,678 (9)	1,147 (6)	4,134 (9)
Ischaemic heart disease	763 (43)	3,060 (42)	5,219 (29)	2,624 (13)	11,666 (25)
Cerebrovascular disease	273 (16)	892 (12)	1,245 (7)	473 (2)	2,883 (6)
Diabetes mellitus	455 (26)	1,188 (16)	1,242 (7)	568 (3)	3,453 (7)
Previous revascularisation					
PCI	155 (9)	719 (10)	1,603 (9)	1,140 (6)	3,617 (8)
CABG	47 (3)	233 (3)	335 (2)	153 (1)	768 (2)
Medications at presentation					
Aspirin	792 (45)	3,184 (44)	5,908 (33)	2,977 (15)	12,861 (27)
$P2Y_{12}$ inhibitor	344 (20)	1,184 (16)	2,000 (11)	965 (5)	4,493 (10)
Dual anti-platelet therapy†	100 (6)	353 (5)	653 (4)	473 (2)	1,579 (3)
Statin	1,111 (63)	4,639 (63)	8,699 (48)	4,508 (23)	18,957 (40)
ACE inhibitor or ARB	914 (52)	3,984 (55)	6,651 (37)	3,734 (19)	15,283 (33)
Beta-blocker	855 (48)	3,179 (44)	5,571 (31)	3,269 (17)	12,873 (27)
Oral anticoagulant agent‡	280 (16)	1,106 (15)	1,386 (8)	421 (2)	3,193 (7)
Loop diuretic agent	894 (51)	2,456 (34)	2,323 (13)	630 (3)	6,303 (13)
Proton pump inhibitor	967 (55)	3,897 (53)	8,444 (47)	6,289 (32)	19,597 (42)
Calcium channel blocker	545 (31)	1,725 (24)	3,096 (17)	1,526 (8)	6,892 (15)
Nicorandil	147 (8)	571 (8)	1,045 (6)	472 (2)	2,235 (5)
Ivabradine	34 (2)	120 (2)	171 (1)	102 (1)	427 (1)
Spironolactone	120 (7)	427 (6)	353 (2)	160 (1)	1,060 (2)
Symptoms at presentation*					

Chest pain	859 (56)	4,201 (66)	12,812 (80)	15,763 (89)	33,635 (81)
Dyspnoea	255 (17)	656 (10)	814 (5)	397 (2)	2,122 (5)
Palpitation	42 (3)	203 (3)	505 (3)	490 (3)	1,240 (3)
Syncope	199 (13)	752 (12)	1,016 (6)	470 (3)	2,437 (6)
Other	179 (12)	531 (8)	886 (6)	537 (3)	2,133 (5)
Haematology and clinical chemistry measurements					
Haemoglobin, g/L	11.7 (2.5)	12.7 (2.4)	13.6 (2.0)	14.2 (1.9)	13.6 (2.1)
eGFR, ml/min/1.73m^2	21 (7)	47 (8)	77 (16)	103 (10)	81 (25)
Peak hs-cTnI, ng/L	46 [16, 279]	15 [6, 67]	5 [2, 17]	2 [1, 4]	4 [2, 16]
Serial hs-cTnI, %‖	872 (49)	3,970 (54)	9,491 (52)	8,199 (42)	22,532 (48)

Values are mean ± SD, n (%), or median (interquartile range). *Presenting symptom was missing in 5,360 patients (11%). †Two medications from aspirin, clopidogrel, prasugrel, or ticagrelor. ‡Includes warfarin and direct oral anticoagulant agents. Abbreviations: ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CABG = coronary artery bypass grafting; eGFR = estimated glomerular filtration rate; hs-cTnI = high sensitivity cardiac troponin I; MI = myocardial infarction; PCI = percutaneous coronary intervention.

Supplementary Table S2. Characteristics of all patients included in the trial, according to troponin concentration and estimated glomerular filtration rate.

	No myocardial injury			Reclassified by high-sensitivity assay			Identified by contemporary assay		
	Overall	**eGFR <60**	**eGFR ≥60**	**Overall**	**eGFR <60**	**eGFR ≥60**	**Overall**	**eGFR <60**	**eGFR ≥60**
Number of participants	**36,816**	**4,860**	**31,956**	**1,717**	**792**	**925**	**8,394**	**3,428**	**4,966**
Age, years	58 (17)	75 (11)	56 (16)	75 (14)	81 (10)	71 (15)	70 (15)	78 (11)	65 (14)
Sex									
Women	17,086 (46)	2,436 (50)	14,650 (46)	1,428 (83)	680 (86)	748 (81)	3,433 (41)	1,627 (47)	1,806 (36)
Men	19,730 (54)	2,424 (50)	17,306 (54)	289 (17)	112 (14)	177 (19)	4,961 (59)	1,801 (53)	3,160 (64)
Previous medical conditions									
Myocardial infarction	2,787 (8)	614 (13)	2,173 (7)	214 (13)	105 (13)	109 (12)	1,133 (14)	590 (17)	543 (11)
Ischaemic heart disease	8,281 (23)	2,039 (42)	6,242 (20)	633 (37)	322 (41)	311 (34)	2,752 (33)	1,462 (43)	1,290 (26)
Cerebrovascular disease	1,875 (5)	553 (11)	1,322 (4)	201 (12)	120 (15)	81 (9)	807 (10)	492 (14)	315 (6)
Diabetes mellitus	2,005 (5)	766 (16)	1,239 (4)	215 (13)	143 (18)	72 (8)	1,233 (15)	734 (21)	499 (10)
Previous revascularisation									
PCI	2,695 (7)	496 (10)	2,199 (7)	152 (9)	65 (8)	87 (9)	770 (9)	313 (9)	457 (9)
CABG	528 (1)	150 (3)	378 (1)	40 (2)	18 (2)	22 (2)	200 (2)	112 (3)	88 (2)
Medications at presentation									
Aspirin	9,243 (25)	2,143 (44)	7,100 (22)	650 (38)	336 (42)	314 (34)	2,968 (35)	1,497 (44)	1,471 (30)
$P2Y_{12}$ inhibitor	3,109 (8)	784 (16)	2,325 (7)	261 (15)	135 (17)	126 (14)	1,123 (13)	609 (18)	514 (10)
Dual anti-platelet therapy†	1,089 (3)	208 (4)	881 (3)	86 (5)	38 (5)	48 (5)	404 (5)	207 (6)	197 (4)
Statin	13,804 (38)	3,177 (65)	10,627 (33)	936 (55)	474 (60)	462 (50)	4,217 (50)	2,099 (61)	2,118 (43)
ACE inhibitor or ARB	11,034 (30)	2,721 (56)	8,313 (26)	743 (43)	415 (52)	328 (36)	3,506 (42)	1,762 (51)	1,744 (35)
Beta-blocker	9,341 (25)	2,198 (45)	7,143 (22)	641 (37)	332 (42)	309 (33)	2,891 (34)	1,504 (44)	1,387 (28)
Oral anticoagulant agent‡	2,119 (6)	699 (14)	1,420 (4)	232 (14)	150 (19)	82 (9)	842 (10)	537 (16)	305 (6)
Loop diuretic agent	3,661 (10)	1,531 (32)	2,130 (7)	556 (32)	367 (46)	189 (20)	2,086 (25)	1,452 (42)	634 (13)
Proton pump inhibitor	15,054 (41)	2,697 (55)	12,357 (39)	860 (50)	427 (54)	433 (47)	3,683 (44)	1,740 (51)	1,943 (39)
Calcium channel blocker	4,958 (14)	1,258 (26)	3,700 (12)	315 (18)	160 (20)	155 (17)	1,619 (19)	852 (25)	767 (15)
Nicorandil	1,610 (4)	398 (8)	1,212 (4)	97 (6)	42 (5)	55 (6)	528 (6)	278 (8)	250 (5)

Ivabradine	284 (1)	71 (1)	213 (1)	NA	NA	NA	113 (1)	72 (2)	41 (1)
Spironolactone	618 (2)	256 (5)	362 (1)	81 (5)	57 (7)	24 (3)	361 (4)	234 (7)	127 (3)
Symptoms at presentation*									
Chest pain	27,308 (84)	2,906 (70)	24,402 (86)	1,048 (67)	442 (61)	626 (73)	5,279 (71)	1,732 (57)	3,547 (80)
Dyspnoea	1,087 (3)	285 (7)	802 (3)	195 (13)	113 (16)	82 (10)	840 (11)	513 (17)	327 (7)
Palpitation	967 (3)	118 (3)	849 (3)	69 (4)	33 (5)	36 (4)	204 (3)	94 (3)	110 (2)
Syncope	1,771 (5)	549 (13)	1,222 (4)	120 (8)	54 (8)	66 (8)	546 (7)	348 (12)	198 (4)
Other	1,423 (4)	307 (7)	1,116 (4)	123 (9)	69 (10)	54 (6)	587 (8)	334 (11)	253 (6)
Electrocardiographic results§									
Normal	-	-	-	576 (52)	218 (51)	358 (53)	2,042 (27)	603 (24)	1,439 (29)
Myocardial ischaemia	-	-	-	192 (17)	82 (19)	110 (16)	2,273 (30)	776 (31)	1,497 (30)
ST elevation	-	-	-	32 (3)	12 (3)	20 (3)	947 (16)	263 (11)	684 (14)
ST depression	-	-	-	123 (11)	53 (12)	70 (10)	1,183 (16)	486 (20)	697 (14)
T wave inversion	-	-	-	183 (17)	66 (15)	117 (17)	1,064 (14)	346 (14)	718 (15)
Physiological parameters§									
Heart rate, beats/min	-	-	-	86 (27)	86 (28)	86.3 (26)	86 (26)	89 (28)	84 (24)
Systolic blood pressure, mmHg	-	-	-	143 (28)	141 (31)	144.3 (26)	138 (29)	135 (32)	139 (27)
Haematology and clinical chemistry measurements									
Haemoglobin, g/dL	13.7 (2.0)	12.6 (2.3)	13.9 (1.9)	12.6 (2.2)	12.2 (2.2)	13.0 (2.1)	13.2 (2.5)	12.4 (2.6)	13.8 (2.3)
eGFR, ml/min/1.73m^2	86 (22)	45 (12)	92 (16)	62 (24)	41 (13)	80 (14)	65 (27)	38 (14)	84 (14)
Peak hs-cTnI, ng/L	3 [1, 6]	7 [4, 13]	2 [1, 5]	26 [20, 37]	26 [21, 36]	26 [20, 38]	300 [76, 2629]	207 [67, 1715]	420 [85, 3314]
Serial hs-cTnI, %‖	15,707 (43)	2,255 (46)	13,452 (42)	995 (58)	416 (53)	579 (63)	5,830 (70)	2,171 (63)	3,659 (74)
Adjudicated diagnosis¶									
Type 1 MI	-	-	-	498 (33)	187 (28)	311 (38)	4,394 (60)	1,309 (46)	3,085 (69)
Type 2 MI	-	-	-	201 (13)	94 (14)	107 (13)	898 (12)	444 (15)	454 (10)
Acute myocardial injury	-	-	-	423 (28)	207 (31)	216 (26)	1,201 (16)	659 (23)	542 (12)
Chronic myocardial injury	-	-	-	376 (25)	186 (28)	190 (23)	869 (12)	461 (16)	408 (9)

Values are mean ± SD, n (%), or median (interquartile range). *Presenting symptom was missing in 5,360 patients (11%). †Two medications from aspirin, clopidogrel, prasugrel, or ticagrelor. ‡Includes warfarin and direct oral anticoagulant agents. §Electrocardiographic and physiological data were available in 8,615 (85%) patients. ‖Defined as 2 or more tests

within 24 h of presentation. ¶The adjudication panel was able to achieve consensus diagnoses in 8,860 of 10,111 patients (88%) with hs-cTnI concentrations above the sex-specific 99th centile. Abbreviations: ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CABG = coronary artery bypass grafting; eGFR = estimated glomerular filtration rate (units: ml/min/1.73m^2); hs-cTnI = high sensitivity cardiac troponin I; MI = myocardial infarction; PCI = percutaneous coronary intervention.

Supplementary Table S3. Characteristics of patients with high-sensitivity cardiac troponin concentrations >99th sex-specific centile, according to study phase and estimated glomerular filtration rate.

	Estimated GFR						Overall
	<60 ml/min/1.73m^2			≥60 ml/min/1.73m^2			
	Overall	Validation	Implementation	Overall	Validation	Implementation	
Number of participants	**4,220**	**1,717**	**2,503**	**5,891**	**2,281**	**3,610**	**10,111**
Age, years	78 (11)	79 (11)	78 (11)	66 (15)	67 (15)	65 (14)	71 (15)
Sex							
Women	2,307 (55)	971 (57)	1,336 (53)	2,554 (43)	1,031 (45)	1,523 (42)	4,861 (48)
Men	1,913 (45)	746 (43)	1,167 (47)	3,337 (57)	1,250 (55)	2,087 (58)	5,250 (52)
Previous medical conditions							
Myocardial infarction	695 (16)	309 (18)	386 (15)	652 (11)	287 (13)	365 (10)	1,347 (13)
Ischaemic heart disease	1,784 (42)	787 (46)	997 (40)	1,601 (27)	703 (31)	898 (25)	3,385 (34)
Cerebrovascular disease	612 (15)	258 (15)	354 (14)	396 (7)	182 (8)	214 (6)	1,008 (10)
Diabetes mellitus	877 (21)	374 (22)	503 (20)	571 (10)	223 (10)	348 (10)	1,448 (14)
Previous revascularisation							
PCI	378 (9)	152 (9)	226 (9)	544 (9)	215 (9)	329 (9)	922 (9)
CABG	130 (3)	61 (4)	69 (3)	110 (2)	46 (2)	64 (2)	240 (2)
Medications at presentation							
Aspirin	1,833 (43)	789 (46)	1,044 (42)	1,785 (30)	776 (34)	1,009 (28)	3,618 (36)
$P2Y_{12}$ inhibitor	744 (18)	328 (19)	416 (17)	640 (11)	307 (14)	333 (9)	1,384 (14)
Dual anti-platelet therapy†	245 (6)	118 (7)	127 (5)	245 (4)	134 (6)	111 (3)	490 (5)
Statin	2,573 (61)	1,087 (63)	1,486 (59)	2,580 (44)	1,059 (46)	1,521 (42)	5,153 (51)
ACE inhibitor or ARB	2,177 (52)	866 (50)	1,311 (52)	2,072 (35)	859 (38)	1,213 (34)	4,249 (42)
Beta-blocker	1,836 (44)	800 (47)	1,036 (41)	1,696 (29)	719 (32)	977 (27)	3,532 (35)
Oral anticoagulant agent‡	687 (16)	292 (17)	395 (16)	387 (7)	169 (7)	218 (6)	1,074 (11)
Loop diuretic agent	1,819 (43)	788 (46)	1,031 (41)	823 (14)	378 (17)	445 (12)	2,642 (26)
Proton pump inhibitor	2,176 (51)	918 (53)	1,258 (50)	2,376 (40)	974 (43)	1,402 (39)	4,543 (45)
Calcium channel blocker	1,012 (24)	409 (24)	603 (24)	922 (16)	378 (17)	544 (15)	1,934 (19)
Nicorandil	320 (8)	156 (9)	164 (7)	305 (5)	153 (7)	152 (4)	625 (6)

Ivabradine	83 (2)	32 (2)	51 (2)	60 (1)	23 (1)	37 (1)	143 (1)
Spironolactone	291 (7)	129 (8)	162 (6)	151 (3)	64 (3)	87 (2)	442 (4)
Symptoms at presentation*							
Chest pain	2,154 (58)	682 (56)	1,472 (59)	4,173 (79)	1,292 (77)	2,881 (80)	6,327 (70)
Dyspnoea	626 (17)	212 (18)	414 (17)	409 (8)	143 (9)	266 (7)	1,035 (11)
Palpitation	127 (3)	41 (3)	86 (3)	146 (3)	53 (3)	93 (3)	273 (3)
Syncope	402 (11)	155 (13)	247 (10)	264 (5)	98 (6)	166 (5)	666 (7)
Other	403 (11)	119 (10)	284 (11)	307 (6)	103 (6)	204 (6)	710 (8)
Electrocardiographic results§							
Normal	821 (28)	299 (29)	522 (28)	1,797 (31)	666 (35)	1,131 (30)	2,618 (30)
Myocardial ischaemia	858 (30)	298 (29)	560 (30)	1,607 (28)	477 (25)	1,130 (29)	2,465 (29)
ST elevation	275 (9)	85 (8)	190 (10)	704 (12)	177 (9)	527 (14)	979 (11)
ST depression	539 (19)	198 (19)	341 (18)	767 (13)	254 (14)	513 (13)	1,306 (15)
T wave inversion	412 (14)	159 (15)	253 (14)	835 (15)	303 (16)	532 (14)	1,247 (14)
Physiological parameters§							
Heart rate, beats/min	88 (28)	88 (28)	88 (28)	84 (25)	85 (25)	83 (24)	86 (26)
Systolic blood pressure, mmHg	137 (32)	136 (30)	137 (32)	140 (27)	140 (27)	140.5 (27)	139 (29)
Haematology and clinical chemistry measurements							
Haemoglobin, g/dL	12.3 (2.6)	12.3 (2.6)	12.4 (2.6)	13,7 (2.3)	13.6 (2.3)	13.8 (2.2)	13.1 (2.5)
eGFR, ml/min/1.73m^2	39 (14)	38 (14)	39 (14)	83 (14)	83 (14)	83 (14)	65 (26)
Peak hs-cTnI, ng/L	114 [41, 931]	96 [37, 566]	131 [44, 1348]	209 [49, 2217]	149 [43, 1355]	272 [55, 2942]	159 [45, 1651]
Serial hs-cTnI, %‖	2,587 (61)	1,055 (61)	1,532 (61)	4,238 (72)	1,581 (69)	2,657 (74)	6,825 (68)
Adjudicated diagnosis¶							
Type 1 MI	1,496 (42)	541 (41)	955 (43)	3,396 (64)	1,219 (62)	2,177 (65)	4,892 (55)
Type 2 MI	538 (15)	195 (15)	343 (15)	561 (11)	203 (10)	358 (11)	1,099 (12)
Acute myocardial injury	866 (24)	348 (26)	518 (23)	758 (14)	309 (16)	449 (13)	1,624 (18)
Chronic myocardial injury	647 (18)	247 (19)	400 (18)	598 (11)	228 (12)	370 (11)	1,245 (14)

Supplementary Table S4. Management of patients with type 1 myocardial infarction, stratified by study phase and estimated glomerular filtration rate.

	Estimated GFR						Overall
	<60 ml/min/1.73m^2			≥60 ml/min/1.73m^2			
	Overall	Validation	Implementation	Overall	Validation	Implementation	
Number of participants	**1,496**	**541**	**955**	**3,396**	**1,219**	**2,177**	**4,892**
Management							
Duration of stay, h	93 [40, 181]	90 [26, 191]	93 [46, 178]	72 [41, 113]	73 [26, 119]	71 [45, 108]	75 [41, 126]
Coronary angiography	570 (38)	186 (34)	384 (40)	2,445 (72)	810 (66)	1,635 (75)*	3,015 (62)
PCI or CABG	390 (26)	121 (22)	269 (28)	1,790 (53)	563 (46)	1,227 (56)*	2,180 (45)
New aspirin	359 (24)	116 (22)	243 (25)	1,848 (54)	629 (52)	1,219 (56)	2,207 (45)
New antiplatelet drug	718 (48)	245 (45)	473 (50)	2,580 (76)	887 (73)	1,693 (78)*	3,298 (67)
New DAPT	605 (40)	204 (38)	401 (42)	2,314 (68)	771 (63)	1,543 (71)*	2,919 (60)
New statin therapy	202 (14)	60 (11)	142 (15)	1,531 (45)	506 (42)	1,025 (47)	1,733 (35)
New ACE inhibitor or ARB	174 (12)	68 (13)	106 (11)	1,372 (40)	483 (40)	889 (41)	1,546 (32)
New beta-blocker	298 (20)	95 (18)	203 (21)	1,544 (46)	540 (44)	1,004 (46)	1,842 (38)
New oral anticoagulant agent	56 (4)	16 (3)	40 (4)	71 (2)	30 (3)	41 (2)	127 (3)

Values are median (interquartile range) or n (%). Abbreviations: ACE = angiotensin converting enzyme; ARB = angiotensin receptor blocker; CABG = coronary artery bypass grafting; DAPT= dual anti-platelet therapy; eGFR = estimated glomerular filtration rate; MI = myocardial infarction; PCI = percutaneous coronary intervention. *p-value ≤0.001, obtained by Chi-square or Mann-Whitney U-test comparing the validation and implementation phases in the management of patients.

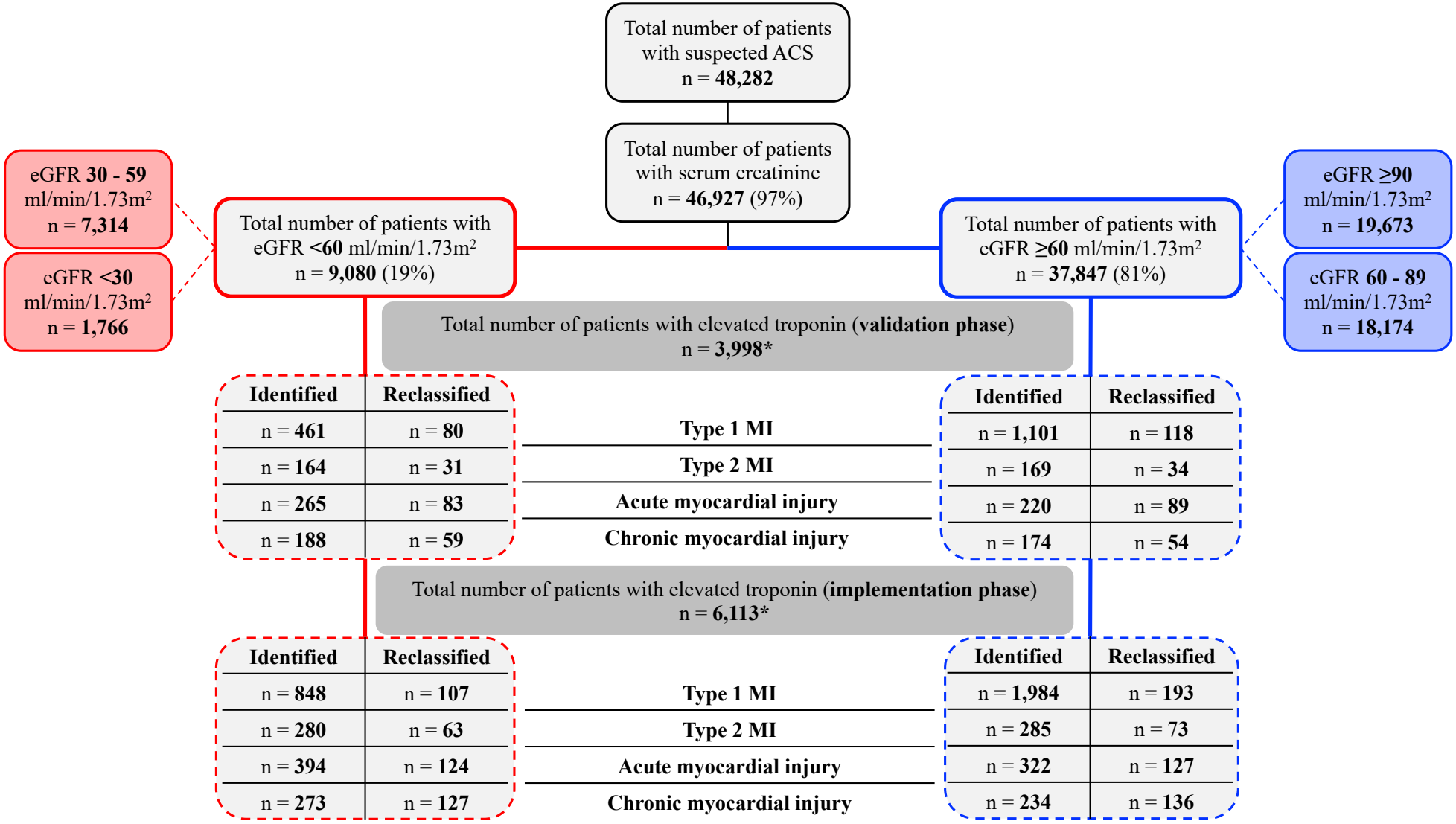
Supplementary Table S5. Management of patients reclassified by the high-sensitivity assay, stratified by study phase and estimated glomerular filtration rate.

	Estimated GFR						Overall
	<60 ml/min/1.73m^2			≥60 ml/min/1.73m^2			
	Overall	Validation	Implementation	Overall	Validation	Implementation	
Number of participants	**792**	**331**	**461**	**925**	**363**	**562**	**1,717**
Management							
Duration of stay, h	42 [7, 147]	24 [4, 117]	56 [19, 160]*	32 [12, 101]	20 [4, 85]	48 [21, 105]*	34 [9, 121]
Coronary angiography	35 (4)	10 (3)	25 (5)	99 (11)	18 (5)	81 (14)*	134 (8)
PCI or CABG	18 (2)	8 (2)	10 (2)	54 (6)	15 (4)	39 (7)	72 (4)
New aspirin	39 (5)	14 (4)	25 (5)	108 (12)	24 (7)	84 (15)*	147 (9)
New antiplatelet drug	82 (10)	24 (7)	58 (13)	170 (18)	40 (11)	130 (23)*	252 (15)
New DAPT	52 (7)	15 (5)	37 (8)	103 (11)	20 (6)	83 (15)*	155 (9)
New statin therapy	24 (3)	11 (3)	13 (3)	85 (9)	21 (6)	64 (11)	109 (6)
New ACE inhibitor or ARB	27 (3)	9 (3)	18 (4)	77 (8)	22 (6)	55 (10)	104 (6)
New beta-blocker	90 (11)	33 (10)	57 (12)	131 (14)	31 (9)	100 (18)*	221 (13)
New oral anticoagulant agent	57 (7)	22 (7)	35 (8)	66 (7)	18 (5)	48 (9)	123 (7)

Values are median (interquartile range) or n (%). Abbreviations: ACE = angiotensin converting enzyme; ARB = angiotensin receptor blocker; CABG = coronary artery bypass grafting; DAPT= dual anti-platelet therapy; eGFR = estimated glomerular filtration rate; PCI = percutaneous coronary intervention. *p-value ≤0.001, obtained by Chi-square or Mann-Whitney U-test comparing the validation and implementation phases in the management of patients.

Supplementary Figures

Supplementary Figure S1. Flow diagram of patients included in secondary analysis, according to eGFR (<60/≥60 ml/min/1.73m^2) category, study phase and adjudicated diagnosis.



*The adjudication panel achieved a consensus diagnosis in 83% (3,290/3,998) of patients in the validation phase and 91% (5,570/6,113) of patients in the implementation phase.

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