High-sensitivity cardiac troponin and the diagnosis of myocardial infarction in patients with kidney impairment

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The benefit and utility of high-sensitivity cardiac troponin (hs-cTn) in the diagnosis of myocardial infarction in patients with kidney impairment is unclear. Here, we describe implementation of hs-cTnI testing on the diagnosis, management, and outcomes of myocardial infarction in patients with and without kidney impairment. Consecutive patients with suspected acute coronary syndrome enrolled in a stepped-wedge, cluster-randomized controlled trial were included in this pre-specified secondary analysis. Kidney impairment was defined as an eGFR under 60mL/min/1.73m^2. The index diagnosis and primary outcome of type 1 and type 4b myocardial infarction or cardiovascular death at one year were compared in patients with and without kidney impairment following implementation of hs-cTnI assay with 99th centile sex-specific diagnostic thresholds. Serum creatinine concentrations were available in 46,927 patients (mean age 61 years; 47% women), of whom 9,080 (19%) had kidney impairment. hs-cTnIs were over 99th centile in 46% and 16% of patients with and without kidney impairment. Implementation increased the diagnosis of type 1 infarction from 12.4% to 17.8%, and from 7.5% to 9.4% in patients with and without kidney impairment (both significant). Patients with kidney impairment and type 1 myocardial infarction were less likely to undergo coronary revascularization (26% versus 53%) or receive dual anti-platelets (40% versus 68%) than those without kidney impairment, and this did not change post-implementation. In patients with hs-cTnI above the 99th centile, the primary outcome occurred twice as often in those with kidney impairment compared to those without (24% versus 12%, hazard ratio 1.53, 95% confidence interval 1.31 to 1.78). Thus, hs-cTnI testing increased the identification of myocardial injury and infarction but failed to address disparities in management and outcomes between those with and without kidney impairment.

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The diagnosis of myocardial infarction has evolved following the adoption of high-sensitivity cardiac troponin assays into clinical practice.[1] Improved assay precision has enabled implementation of lower diagnostic thresholds and increased the identification of patients with myocardial infarction and nonischemic myocardial injury secondary to other conditions.[1–5] In patients with kidney impairment, the interpretation of cardiac troponin testing is particularly challenging.[6–8] While high-sensitivity cardiac

troponin is effective at ruling out myocardial infarction in these patients,[9,10] cardiac troponin concentrations are often chronically elevated in kidney impairment,[7] potentially as a result of underlying cardiovascular disease.[11,12]

High-Sensitivity Troponin in the Evaluation of patients with suspected Acute Coronary Syndrome (High-STEACS) was a randomized controlled trial that evaluated the introduction of high-sensitivity cardiac troponin testing into clinical practice.[4] In a brief report, we recently demonstrated that outcomes did not improve in patients with kidney impairment, which is consistent with the main trial's findings.[13] One potential explanation for this is that patients with kidney impairment are more likely to have nonischemic myocardial injury or type 2 myocardial infarction. In this prespecified secondary analysis of the original trial, we evaluate the diagnosis, management, and outcomes of patients with and without kidney impairment identified as having myocardial injury or infarction before and after implementation of a high-sensitivity cardiac troponin assay.

METHODS

Study design

High-STEACS was a stepped-wedge, cluster-randomized controlled trial[4] that evaluated the implementation of a high-sensitivity cardiac troponin I assay in consecutive patients presenting with suspected acute coronary syndrome across 10 secondary and tertiary hospitals in Scotland (ClinicalTrials.gov number, NCT01852123). This was a prespecified secondary analysis of the original High-STEACS trial and was designed specifically to evaluate the diagnosis, management, and outcomes of patients with kidney impairment presenting with suspected acute coronary syndrome.

The trial design has been described previously,[4] and a detailed description is provided in the Supplementary Methods. In brief, 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[1] and international[2] guidelines. In this trial, the hospital site was the unit of randomization. Cluster randomization was necessary to avoid the risk of clinical error due to reporting of different troponin assays and thresholds simultaneously.

During both phases of the trial, all patients underwent testing with contemporary cardiac troponin I (ARCHITECT$_{STAT}$ troponin I, Abbott Laboratories) and high-sensitivity cardiac troponin I (ARCHITECT$_{STAT}$ high-sensitive troponin I, Abbott Laboratories) assays. During a validation phase of at least 6 months, 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 (based on interassay coefficient of variation) for the diagnosis of myocardial infarction in men and women was used to guide clinical decisions during the validation phase of the trial. Hospital sites were then randomly assigned to early or late implementation of the high-sensitivity cardiac troponin assay. For the high-sensitivity assay, sex-specific 99th percentile thresholds (34 g/l in men, 16 ng/l in women) for the diagnosis of myocardial infarction were used to guide clinical care during the implementation phase of the trial. We hypothesized that implementation of a high-sensitivity cardiac troponin I assay would reduce subsequent myocardial infarction or cardiovascular death at 1 year by identifying more patients with suspected acute coronary syndrome at risk and improving their management.

Patient population

Patients attending the emergency department were identified as having suspected acute coronary syndrome by the attending clinician at the time cardiac troponin was requested using an electronic form integrated within the clinical pathway. Patients were eligible for inclusion if they presented with suspected acute coronary syndrome and had paired cardiac troponin measurements using the contemporary and trial assays. Patients were excluded if they had been admitted previously during the trial or if they were not residing in Scotland. For this prespecified analysis, patients were excluded if a measure of serum creatinine was not available.

Patients were classified as having no myocardial injury where their high-sensitivity cardiac troponin I concentrations were within the reference range for this assay (1–34 ng/l for men; 1–16 ng/l for women). In patients with myocardial injury, those "identified" by the contemporary assay were defined as patients with any cardiac troponin I concentration greater than the diagnostic threshold of this assay. Those "reclassified" by the high-sensitivity cardiac troponin I assay were defined as patients with an increased high-sensitivity cardiac troponin I concentration (>34 ng/l for men, >16 ng/l for women) in whom cardiac troponin I concentrations were below the diagnostic threshold of the contemporary assay.

Adjudication of the diagnosis of myocardial infarction

Two physicians blinded to study phase independently reviewed all clinical information and adjudicated the index diagnosis in all patients with high-sensitivity cardiac troponin I concentrations >99th percentile in accordance with the Fourth Universal Definition of Myocardial Infarction.[1,5] Disagreements were resolved by a third physician. Type 1 myocardial infarction was defined as myocardial necrosis (any high-sensitivity cardiac troponin I concentration above the 99th percentile with a rise and/or fall in high-sensitivity cardiac troponin I concentration where serial testing was performed) in the context of a presentation with suspected acute coronary syndrome with symptoms or signs of myocardial ischemia on the electrocardiogram. Type 2 myocardial infarction was defined as myocardial necrosis with symptoms or signs of myocardial ischemia due to increased oxygen demand or decreased oxygen supply secondary to an alternative pathology such as tachyarrhythmia, hypotension, or anemia. Type 4b myocardial infarction was defined as myocardial injury with symptoms or signs of myocardial ischemia secondary to stent thrombosis demonstrated on coronary angiography. Patients with high-sensitivity cardiac troponin I concentrations above the 99th percentile without symptoms or signs of myocardial ischemia were classified as having nonischemic myocardial injury.

Diagnosis of kidney impairment

Estimated glomerular filtration rate (eGFR) was calculated from serum creatinine using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.[14] Kidney impairment was defined as an eGFR <60 ml/min per 1.73 m^2. Patients were grouped according to their eGFR: <30, 30 to 59, 60 to 89, or ≥90 ml/min per 1.73 m^2.

Outcomes

Follow-up was performed using a standardized electronic patient record linked to regional and national datasets to ensure complete

follow-up.[4,9,15] The primary outcome was subsequent type 1 or type 4b myocardial infarction or cardiovascular death at 1 year. Secondary outcomes included all-cause death, cardiovascular death, non-cardiovascular death, myocardial infarction, unplanned revascularization, hospitalization for heart failure, ischemic stroke and major hemorrhage at 1 year, and unplanned hospitalization at 30 days. All outcomes were independently adjudicated by physicians blinded to study phase.

Statistical analysis

Baseline statistics were summarized and presented according to eGFR for all patients and according to eGFR and study phase for those with elevated cardiac troponin concentrations. The index diagnosis was compared in those with and without kidney impairment and stratified by eGFR in those identified by the contemporary cardiac troponin I assay. The index diagnosis was also compared in those reclassified using the high-sensitivity cardiac troponin I assay with values above the sex-specific 99th percentile, but below the diagnostic threshold used by the contemporary assay.

Multivariable Cox models were employed to predict the risk of subsequent myocardial infarction or cardiovascular death at 1 year according to kidney function (eGFR), stratified by adjudicated diagnosis during the index presentation. These models included eGFR as a continuous explanatory variable and adjusted for age, sex, social deprivation status (Supplementary Methods), history of cerebrovascular disease and ischemic heart disease, diabetes mellitus, and the maximum high-sensitivity cardiac troponin I concentration. In patients with type 1 myocardial infarction, an exploratory analysis was conducted to evaluate the effectiveness of coronary revascularization, new dual antiplatelet therapy, angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers, statins and beta-blockers according to kidney function (eGFR), utilizing multivariable logistic regression models stratified by eGFR categories (<30, 30–59, 60–89, ≥90 ml/mi per /1.73 m^2; Supplementary Methods). To determine the influence of residual confounding, we evaluated the falsification hypothesis that the new prescription of a calcium channel antagonist would reduce the likelihood of the primary outcome at 1 year. We used the same multivariable logistic regression model, but with a treatment-eGFR interaction term and prescription of a calcium channel antagonist as the primary explanatory variable. All statistical analysis was performed in R, version 3.6.1 (R Foundation).

Ethical approval

The trial was conducted in accordance with the Declaration of Helsinki and with the approval of the Scotland Research Ethics Committee, the Public Benefit and Privacy Panel for Health and Social Care and each National Health Service Health Board. As randomization was at the hospital level, individual patient consent was not sought.

RESULTS

Serum creatinine concentrations were available for 46,927 of 48,282 patients (97%; 61 ± 17 years; 47% women) enrolled into the study (Supplementary Table S1). Kidney impairment was present in 9080 patients (19%): 81% (7314 of 9080) had an eGFR of 30 to 59 and 19% (1766 of 9080) had an eGFR <30 ml/min per 1.73 m^2 (Supplementary Figure S1).

Baseline characteristics

Cardiac troponin concentrations were elevated in 46% (4220 of 9080) and 16% (5891 of 37,847) of patients with and without kidney impairment, respectively ($P < 0.001$). Of the 10,111 patients (71 ± 15 years, 48% women) with elevated cardiac troponin concentrations, 42% (4220 of 10,111) had kidney impairment (Table 1). These patients were older, more likely to be women, and were less likely to present with a primary symptom of chest pain than patients with normal kidney function (Table 1). Cardiovascular risk factors and prior prescription of cardiovascular therapies increased in frequency as eGFR decreased.

The high-sensitivity cardiac troponin assay reclassified 17% (1717 of 10,111) of patients with myocardial injury or infarction who were not identified by the contemporary assay (Supplementary Table S2). Kidney impairment was present in 41% (3428 of 8394) of patients identified by the contemporary assay and in 46% (792 of 1717) of patients reclassified by the high-sensitivity assay ($P < 0.001$).

The characteristics of patients with high-sensitivity cardiac troponin concentrations >99th sex-specific percentile were similar before and after implementation of high-sensitivity cardiac troponin testing (Supplementary Table S3). However, while the proportion of patients with kidney impairment undergoing serial cardiac troponin testing did not change following implementation (61% [1055 of 1717] vs. 61% [1532 of 2503]), it increased from 69% (1581 of 2281) to 74% (2657 of 3610) in patients without kidney impairment.

Diagnosis of patients with and without kidney impairment during index presentation

A diagnosis of type 1 myocardial infarction was less common in patients with kidney impairment than in patients with normal kidney function (Figure 1). In contrast, type 2 myocardial infarction and nonischemic myocardial injury were more common in patients with kidney impairment than in those with normal kidney function. Following implementation, the proportion of patients with myocardial infarction or injury increased, irrespective of the presence of kidney impairment (Supplementary Figure S1). The proportion with a diagnosis of type 1 myocardial infarction increased from 12.4% (461 of 3721) to 17.8% (955 of 5359; $P < 0.001$) in patients with kidney impairment, and from 7.5% (1101 of 14,686) to 9.4% (2177 of 23,161; $P < 0.001$) in patients without kidney impairment. Type 2 myocardial infarction increased following implementation from 4.4% (164 of 3721) to 6.4% (343 of 5359; $P < 0.001$) in patients with kidney impairment and from 1.2% (169 of 14,686) to 1.5% (358 of 23,161; $P = 0.002$) without kidney impairment. Similarly, the proportion with acute myocardial injury increased from 7.1% (265 of 3721) to 9.7% (518 of 5359; $P < 0.001$) in patients with and from 1.5% (220 of 14,686) to 1.9% (449 of 23,161; $P = 0.002$) in patients without kidney impairment, while the proportion diagnosed with chronic myocardial injury increased from 5.1% (188 of 3721) to 7.5% (400 of 5359; $P < 0.001$) and from 1.2% (174 of 14,686) to 1.6%

Table 1 | Characteristics of patients with hs-cTn concentrations above the sex-specific 99th percentile, grouped by eGFR category

Characteristic	Estimated GFR, ml/min per 1.73 m^2				Overall
	<30	30–59	60–89	≥90	
Participants, n	1171	3049	3980	1911	10,111
Age, yr	78 (11)	79 (11)	72 (13)	54 (11)	71 (15)
Sex					
Women	644 (55)	1663 (54)	2009 (50)	545 (29)	4861 (48)
Men	527 (45)	1386 (46)	1971 (50)	1366 (71)	5250 (52)
Social deprivation quintile					
1 (most deprived)	350 (30)	884 (29)	1087 (27)	642 (34)	2963 (29)
2	249 (21)	646 (21)	821 (21)	418 (22)	2134 (21)
3	209 (18)	480 (16)	643 (16)	294 (15)	1626 (16)
4	158 (13)	436 (14)	550 (14)	257 (13)	1401 (14)
5 (least deprived)	205 (18)	603 (20)	879 (22)	300 (16)	1987 (20)
Previous medical conditions					
Myocardial infarction	219 (19)	476 (16)	457 (12)	195 (10)	1347 (13)
Ischemic heart disease	524 (45)	1260 (41)	1210 (30)	391 (21)	3385 (34)
Cerebrovascular disease	185 (16)	427 (14)	337 (9)	59 (3)	1008 (10)
Diabetes mellitus	302 (26)	575 (19)	403 (10)	168 (9)	1448 (14)
Previous revascularization					
PCI	98 (8)	280 (9)	359 (9)	185 (10)	922 (9)
CABG	35 (3)	95 (3)	78 (2)	32 (2)	240 (2)
Medications at presentation					
Aspirin	514 (44)	1319 (43)	1380 (35)	405 (21)	3618 (36)
$P2Y_{12}$ inhibitor	224 (19)	520 (17)	503 (13)	137 (7)	1384 (14)
Dual antiplatelet therapy[a]	70 (6)	175 (6)	176 (4)	69 (4)	490 (5)
Statin	718 (61)	1855 (61)	1961 (49)	619 (32)	5153 (51)
ACE inhibitor or ARB	574 (49)	1603 (53)	1548 (39)	524 (27)	4249 (42)
Beta-blocker	562 (48)	1274 (42)	1278 (32)	418 (22)	3532 (35)
Oral anticoagulant agent[b]	200 (17)	487 (16)	322 (8)	65 (3)	1074 (11)
Loop diuretic agent	623 (53)	1196 (39)	713 (18)	110 (6)	2642 (26)
Proton pump inhibitor	622 (53)	1545 (51)	1770 (44)	606 (32)	4543 (45)
Calcium channel blocker	334 (29)	678 (22)	703 (18)	219 (11)	1934 (19)
Nicorandil	98 (8)	222 (7)	228 (6)	77 (4)	625 (6)
Ivabradine	23 (2)	60 (2)	45 (1)	15 (1)	143 (1)
Spironolactone	84 (7)	207 (7)	115 (3)	36 (2)	442 (4)
Symptoms at presentation[c]					
Chest pain	520 (51)	1634 (61)	2656 (75)	1517 (87)	6327 (70)
Dyspnea	211 (21)	415 (15)	337 (9)	72 (4)	1035 (12)
Palpitation	32 (3)	95 (4)	104 (3)	42 (2)	273 (3)
Syncope	135 (13)	267 (10)	223 (6)	41 (2)	666 (7)
Other	127 (12)	276 (10)	244 (7)	63 (4)	710 (8)
Electrocardiographic results[d]					
Normal	207 (30)	614 (28)	1094 (30)	703 (35)	2618 (30)
Myocardial ischemia	202 (29)	656 (30)	1067 (29)	540 (27)	2465 (29)
ST elevation	56 (8)	219 (10)	444 (12)	260 (13)	979 (11)
ST depression	139 (20)	400 (18)	529 (14)	238 (12)	1306 (15)
T-wave inversion	90 (13)	322 (15)	546 (15)	289 (14)	1247 (14)
Physiological parameters[d]					
Heart rate, beats/min	87 (27)	89 (29)	85 (25)	81 (23)	86 (26)
Systolic blood pressure, mm Hg	132 (33)	138 (31)	141 (28)	139 (25)	139 (29)
Hematology and clinical chemistry measurements					
Hemoglobin, g/dl	11.7 (2.6)	12.6 (2.5)	13.4 (2.3)	14.3 (2.1)	13.1 (2.5)
eGFR, ml/min per 1.73 m^2	20 (7)	46 (8)	75 (9)	100 (8)	65 (26)
Peak hs-cTnI, ng/l	120 [47, 994]	111 [39, 907]	179 [45, 1892]	317 [60, 3054]	159 [45, 1651]
Serial hs-cTnI,[e] %	644 (55)	1943 (64)	2827 (71)	1411 (74)	6825 (68)
Adjudicated diagnosis[f]					
Type 1 MI	328 (35)	1168 (45)	2135 (59)	1261 (74)	4892 (55)
Type 2 MI	136 (15)	402 (15)	441 (12)	120 (7)	1099 (12)
Acute myocardial injury	268 (29)	598 (23)	588 (16)	170 (10)	1624 (18)
Chronic myocardial injury	202 (22)	445 (17)	440 (12)	158 (9)	1245 (14)

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.
[a]Two medications from aspirin, clopidogrel, prasugrel, or ticagrelor.
[b]Includes warfarin and direct oral anticoagulant agents.
[c]Presenting symptom was missing in 1100 patients (11%).
[d]Electrocardiographic and physiological data were available in 8615 patients (85%).
[e]Defined as 2 or more tests within 24 hours of presentation.
[f]The adjudication panel was able to achieve consensus diagnoses in 8860 of 10,111 patients (88%) with hs-cTnI concentrations above the sex-specific 99th percentile.
Values are mean (SD), n (%), or median [interquartile range] unless otherwise indicated.

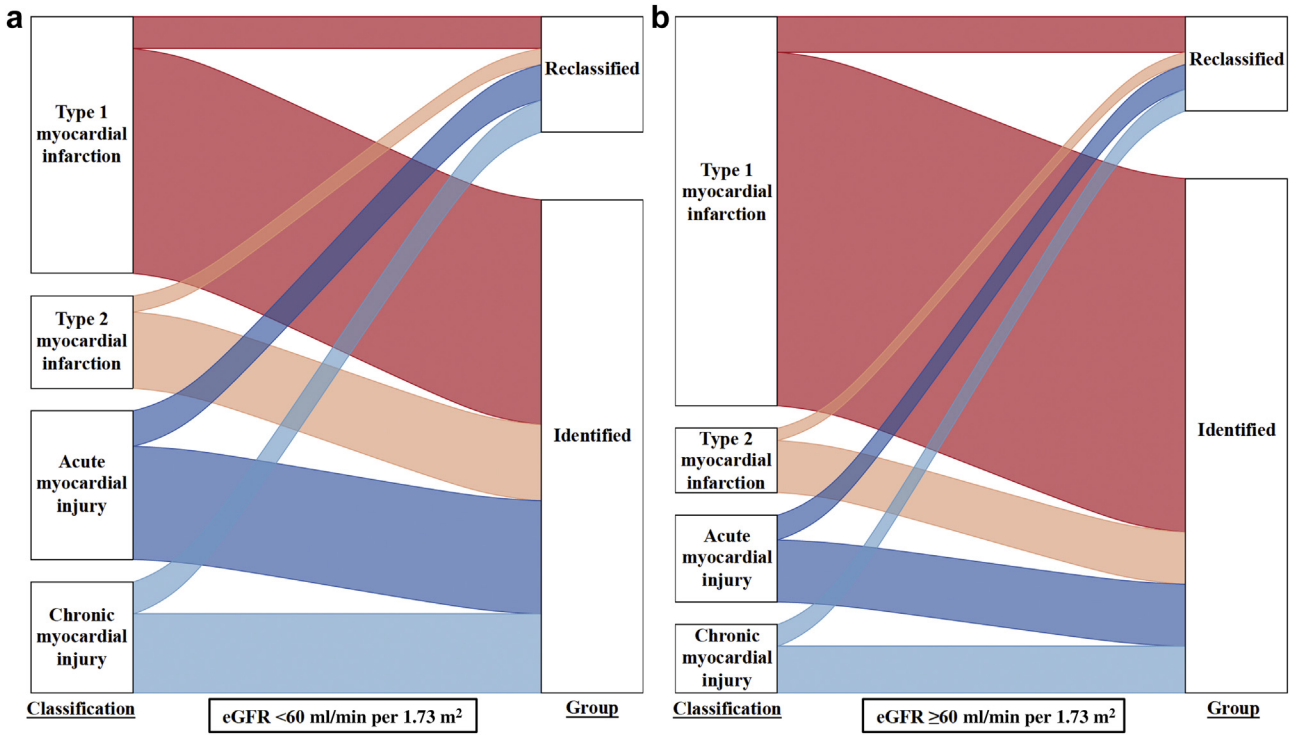

Figure 1 | Alluvial plot illustrating the proportions of adjudicated diagnoses according to patient group (reclassified or identified) in patients with (a) and without kidney impairment (b), in whom the adjudication panel was able to determine a consensus diagnosis (n = 8860). In patients with kidney impairment (**a**), 42% (1496 of 3547) had an adjudicated diagnosis of type 1 myocardial infarction (red band), while 13% (187 of 1496) were reclassified by the high-sensitivity assay. Across all patients with kidney impairment who were reclassified by the high-sensitivity assay, 28% (187 of 674) had an adjudicated diagnosis of type 1 myocardial infarction. By contrast, in patients without kidney impairment (**b**), 64% (3396 of 5313) had an adjudicated diagnosis of type 1 myocardial infarction (red band), while 9% (311 of 3396) were reclassified by the high-sensitivity assay. Across all patients without kidney impairment who were reclassified by the high-sensitivity assay, 38% (311 of 824) had an adjudicated diagnosis of type 1 myocardial infarction. Type 1 myocardial infarction (red); type 2 myocardial infarction (gold); acute myocardial injury (dark blue); and chronic myocardial injury (light blue). eGFR, estimated glomerular filtration rate.

(370 of 23,161; $P = 0.001$) in those with and without kidney impairment, respectively.

Management of patients with and without kidney impairment before and after implementation

Following implementation, length of stay increased in patients with kidney impairment and elevated cardiac troponin concentrations (Table 2). While management intensified in patients without kidney impairment following implementation, the proportion of patients with kidney impairment undergoing coronary angiography, undergoing revascularization, or receiving preventative therapies did not change, irrespective of whether they had an elevated cardiac troponin concentration (Table 2), had been diagnosed with type 1 myocardial infarction (Supplementary Table S4), or had been reclassified by the high-sensitivity cardiac troponin assay (Supplementary Table S5).

Management of patients with and without kidney impairment during index presentation

Across both study phases, length of stay increased as eGFR decreased in patients with elevated cardiac troponin concentrations (Table 3). Compared to patients with an eGFR ≥90, patients with an eGFR <30 ml/min per 1.73 m^2 experienced the lowest rates of coronary angiography (7% vs. 59%; $P < 0.001$) and coronary revascularization (4% vs. 42%; $P < 0.001$). Prescriptions of preventative therapies also fell with decreasing eGFR (Table 3). Similarly, patients with kidney impairment who had been diagnosed with type 1 myocardial infarction were less likely to undergo coronary angiography (38% vs. 72%; $P < 0.001$), revascularization (26% vs. 53%; $P < 0.001$), or receive preventative therapies than patients without kidney impairment (Supplementary Table S4).

Clinical outcomes of patients with and without kidney impairment

The primary outcome of type 1 or 4b myocardial infarction or cardiovascular death at 1 year occurred in 5% (2531 of 46,927) of all patients and in 17% (1702 of 10,111) of those with elevated cardiac troponin concentrations (Table 3). Among those with elevated cardiac troponin concentrations, the primary outcome occurred in 24% of those with kidney impairment and in 12% of those without (adjusted hazard ratio: 1.53; 95% confidence interval [CI]: 1.31 to 1.78). Comparing eGFR groups, the highest crude event rate was

Table 2 | Management and outcomes of patients with hs-cTn concentrations above the sex-specific 99th percentile, grouped according to eGFR category

	Estimated GFR, ml/min per 1.73 m^2						
	<60			≥60			
Characteristic	Overall	Validation	Implementation	Overall	Validation	Implementation	Overall
Participants, n	4220	1717	2503	5891	2281	3610	10,111
Management							
Duration of stay, h	88 [18, 225]	79 [7, 226]	91 [26, 222]	71 [26, 133]	72 [17, 145]	71 [32, 124]	74 [24, 166]
Coronary angiography	669 (16)	230 (13)	439 (18)	2689 (46)	889 (39)	1800 (50)[a]	3358 (33)
PCI or CABG	420 (10)	139 (8)	281 (11)	1855 (31)	582 (26)	1273 (35)[a]	2275 (23)
New aspirin	492 (12)	185 (11)	307 (12)	2128 (36)	738 (32)	1390 (39)[a]	2620 (26)
New antiplatelet drug	1012 (24)	388 (23)	624 (25)	3004 (51)	1056 (46)	1948 (54)[a]	4016 (40)
New DAPT	767 (18)	287 (17)	480 (19)	2560 (43)	871 (38)	1689 (47)[a]	3327 (33)
New statin therapy	279 (7)	100 (6)	179 (7)	1719 (29)	581 (26)	1138 (32)[a]	1998 (20)
New ACE inhibitor or ARB	277 (7)	115 (7)	162 (6)	1622 (28)	574 (25)	1048 (29)[a]	1899 (19)
New beta-blocker	555 (13)	194 (11)	361 (14)	1953 (33)	686 (30)	1267 (35)[a]	2508 (25)
New oral anticoagulant agent	287 (7)	103 (6)	184 (7)	343 (6)	127 (6)	216 (6)	630 (6)

ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; CABG, coronary artery bypass grafting; DAPT, dual antiplatelet therapy; eGFR, estimated glomerular filtration rate; hs-cTn, high-sensitivity cardiac troponin; PCI, percutaneous coronary intervention.
[a]*P* value ≤ 0.001, obtained by chi-square or Mann-Whitney *U*-test comparing the validation and implementation phases in the management of patients.
Values are median [interquartile range] or n (%) unless otherwise indicated.

observed in patients with an eGFR <30 ml/min per 1.73 m^2 (30%, 350 of 1,171).

When compared with the other diagnostic classifications, decreasing eGFR was associated with the worst prognosis in patients with type 1 myocardial infarction (Figure 2). Indeed, for every 10 ml/min per1.73 m^2 decrease in eGFR in these patients, the risk of the primary outcome at 1 year increased by 23% (adjusted hazard ratio: 1.23; 95% CI: 1.19–1.27). Most secondary outcome measures also occurred more frequently as eGFR decreased (Table 3). For

Table 3 | Management and outcomes of patients with hs-cTn concentrations above the sex-specific 99th percentile during initial hospital admission, grouped by eGFR category

	Estimated GFR, ml/min per 1.73 m^2				
Characteristic	<30	30–59	60–89	≥90	Overall
Participants, n	1171	3049	3980	1911	10,111
Management					
Duration of stay, h	96 [8, 279]	86 [22, 203]	76 [28, 155]	62 [24, 98]	74 [24, 166]
Coronary angiography	84 (7)	585 (19)	1560 (39)	1129 (59)	3358 (33)
PCI or CABG	50 (4)	370 (12)	1060 (27)	795 (42)	2275 (23)
New aspirin	76 (7)	416 (14)	1190 (30)	938 (49)	2620 (26)
New antiplatelet drug	182 (16)	830 (27)	1836 (46)	1168 (61)	4016 (40)
New DAPT	127 (11)	640 (21)	1530 (38)	1030 (54)	3327 (33)
New statin therapy	40 (3)	239 (8)	919 (23)	800 (42)	1998 (20)
New ACE inhibitor or ARB	34 (3)	243 (8)	912 (23)	710 (37)	1899 (19)
New beta-blocker	83 (7)	472 (16)	1151 (29)	802 (42)	2508 (25)
New oral anticoagulant agent	58 (5)	229 (8)	280 (7)	63 (3)	630 (6)
Primary outcome					
MI[a] or cardiovascular death	350 (30)	666 (22)	533 (13)	153 (8)	1702 (17)
Secondary outcomes					
MI[a]	80 (7)	233 (8)	256 (6)	101 (5)	670 (7)
Unplanned revascularization[b]	25 (2)	91 (3)	177 (4)	106 (6)	399 (4)
All-cause death	586 (50)	914 (30)	668 (17)	140 (7)	2308 (23)
Cardiovascular death	296 (25)	489 (16)	313 (8)	54 (3)	1152 (11)
Hospital admission for heart failure	186 (16)	415 (14)	341 (9)	55 (3)	997 (10)
Ischemic stroke	21 (2)	74 (2)	81 (2)	19 (1)	195 (2)
Safety end points					
Major hemorrhage[c]	10 (1)	33 (1)	48 (1)	9 (1)	100 (1)
Unplanned hospital admission at 30 d[d]	335 (29)	823 (27)	1169 (29)	636 (33)	2963 (29)
Noncardiovascular death	290 (25)	425 (14)	354 (9)	86 (5)	1155 (11)

ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; CABG, coronary artery bypass grafting; DAPT, dual antiplatelet therapy; eGFR, estimated glomerular filtration rate; hs-cTn, high-sensitivity cardiac troponin; MI, myocardial infarction; PCI, percutaneous coronary intervention.
[a]Subsequent type 1 or type 4b myocardial infarction.
[b]Defined as urgent or emergency percutaneous coronary intervention or coronary artery bypass grafting from discharge to 1 year later.
[c]Bleeding Academic Research Consortium type 3 or type 5.
[d]Excludes type 1 or type 4b myocardial infarction.
Values are median [interquartile range] or n (%) unless otherwise indicated.

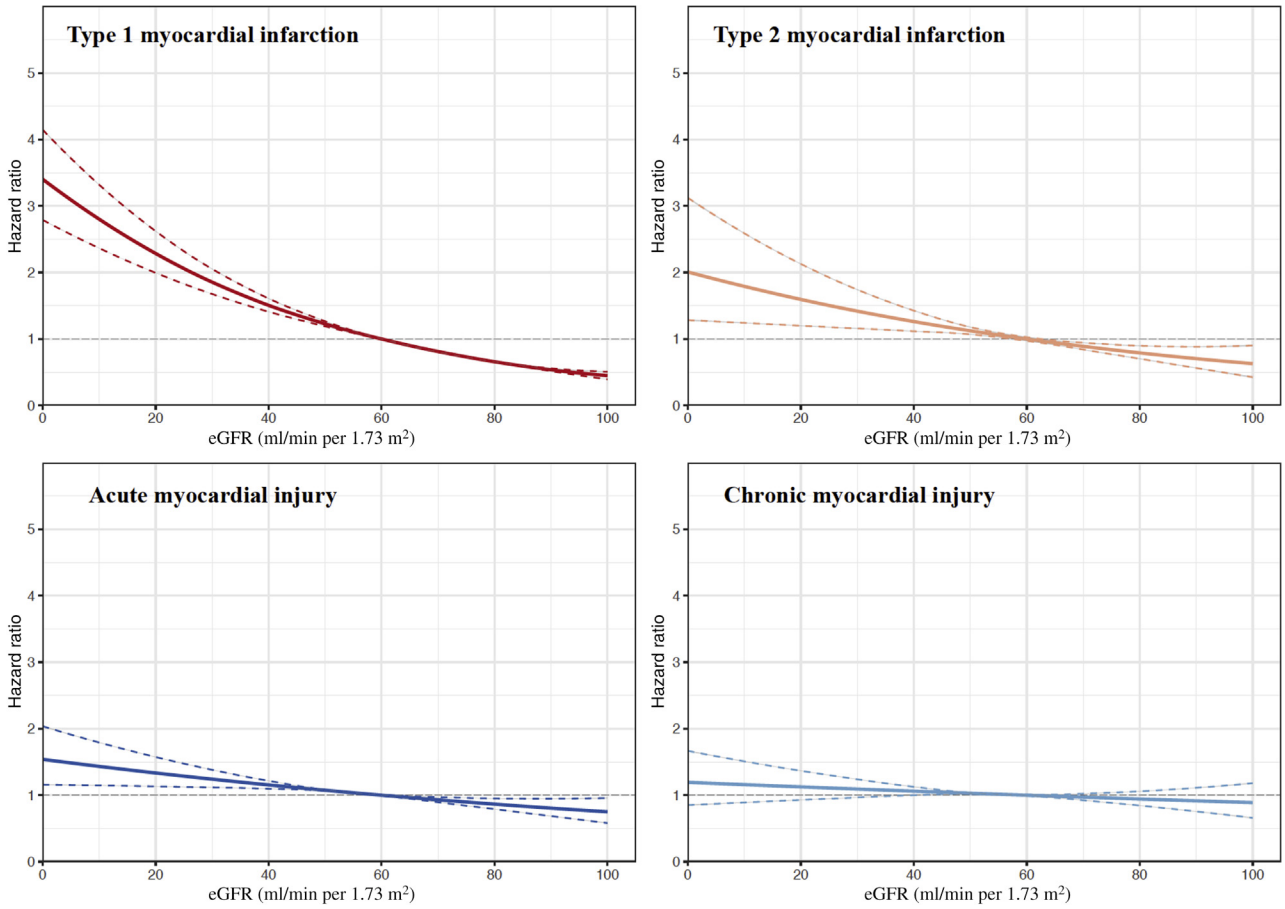

Figure 2 | Hazard ratios of subsequent myocardial infarction or cardiovascular death at 1 year according to estimated glomerular filtration rate (eGFR; the primary explanatory variable), stratified by the adjudicated diagnosis during the index presentation. Hazard ratios were standardized against the value obtained for an estimated glomerular filtration rate of 60 ml/min per 1.73 m^2 within each diagnostic subgroup. Models were adjusted for age, sex, social deprivation status, peak troponin concentration, and comorbidities (diabetes mellitus, ischemic heart disease, and cerebrovascular disease). Type 1 myocardial infarction (red); type 2 myocardial infarction (gold); acute myocardial injury (dark blue); and chronic myocardial injury (light blue). Colored dashed lines represent 95% confidence intervals. Horizontal gray dashed line represents hazard ratio of 1.0.

example, all-cause death at 1 year occurred in 7% with an eGFR ≥90 versus 50% with an eGFR <30 ml/min per 1.73 m^2.

Treatment effectiveness in patients with type 1 myocardial infarction

In patients with type 1 myocardial infarction who underwent coronary revascularization or received dual antiplatelet therapy, the likelihood of experiencing the primary outcome at 1 year was similar in those with and without kidney impairment (Figure 3). Compared with patients who did not undergo revascularization, the risk of the primary outcome was lower in those undergoing revascularization, overall (adjusted odds ratio: 0.62; 95% CI: 0.51–0.75) and at all strata of kidney function: 0.75 (95% CI: 0.38–1.44) in those with an eGFR <30, 0.68 (95% CI: 0.48–0.94) in those with an eGFR 30 to 59, and 0.58 (95% CI: 0.37–0.92) in those with an eGFR ≥90 ml/min per 1.73 m^2 (Figure 3). Similarly, the likelihood of experiencing the primary outcome was lower in patients who received new dual antiplatelet therapy compared with patients who did not, overall (adjusted odds ratio: 0.44; 95% CI: 0.37–0.53) and at all strata of kidney function: 0.46 (95% CI: 0.26–0.79) in those with an eGFR <30, 0.44 (95% CI: 0.33–0.59) in those with an eGFR 30 to 59, and 0.39 (95% CI: 0.25–0.61) in those with an eGFR ≥90 ml/min per 1.73 m^2.

In contrast, comparing patients with type 1 myocardial infarction who did and did not receive a new prescription of a calcium channel antagonist during the index admission, there was no overall improvement in the primary outcome at 1 year (adjusted odds ratio: 1.13: 95% CI: 0.38–3.34).

DISCUSSION

We systematically evaluated the diagnosis, management, and outcomes of patients with and without kidney impairment who were found to have myocardial injury or infarction before and after implementation of high-sensitivity cardiac troponin testing. We found that elevated cardiac troponin concentrations were 3 times more common in patients with kidney impairment than in those with normal kidney function. In patients

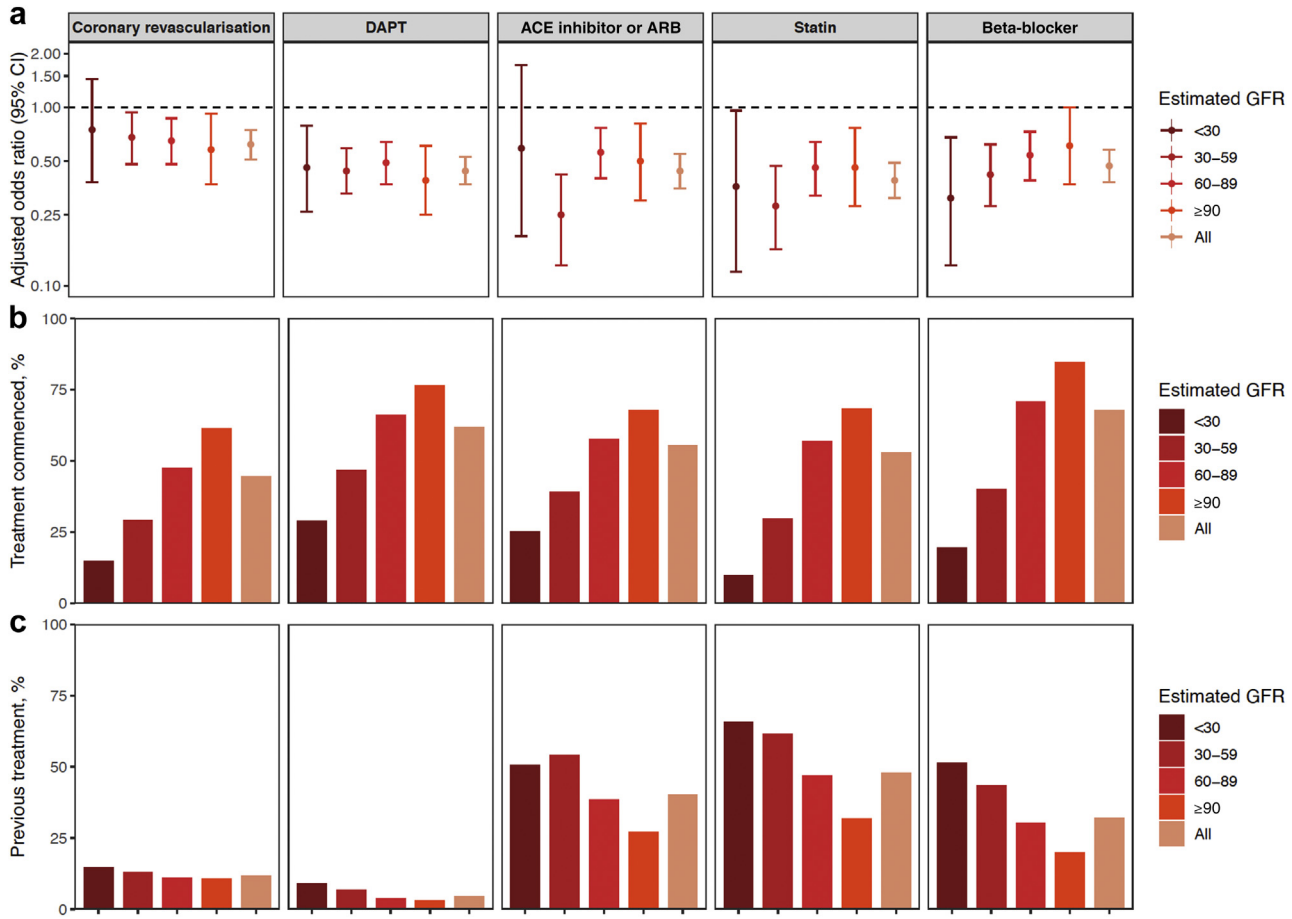

Figure 3 | Management of patients with type 1 myocardial infarction and adjusted odds ratio of subsequent myocardial infarction or cardiovascular death at 1 year, stratified by treatment received during index hospitalization and estimated glomerular filtration rate (GFR) category. (**a**) Output of multivariable logistic regression model evaluating the odds of type 1 or 4b myocardial infarction and cardiovascular death at 1 year in patients who received each intervention or treatment compared with those who did not, shown for all patients and stratified by estimated glomerular filtration rate category. Models were 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 comorbidities (cerebrovascular disease, diabetes, ischemic heart disease, and myocardial infarction). (**b**) Treatment commenced during index hospitalization, shown for all patients and stratified by estimated glomerular filtration rate category. Patients already receiving each treatment prior to index presentation were excluded, except in the case of the coronary revascularization. (**c**) Treatment predating index hospitalization, shown for all patients and stratified by estimated glomerular filtration rate category. ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CI, confidence interval; DAPT, dual antiplatelet therapy.

with kidney impairment compared to those without, type 1 myocardial infarction was twice as common, while type 2 myocardial infarction and nonischemic myocardial injury were 4 to 5 times more common. Following implementation of high-sensitivity cardiac troponin testing, rates of coronary angiography, revascularization, and the prescription of evidence-based treatments increased in patients with normal kidney function, but this was not the case in patients with kidney impairment. Patients with type 1 myocardial infarction and kidney impairment remained less likely to undergo revascularization or to receive evidence-based therapies than those with normal kidney function, and perhaps as a consequence, they were more likely to have a subsequent myocardial infarction or cardiovascular death at 1 year.

The present study has a number of notable features. First, it was free from case selection bias because patients with suspected acute coronary syndrome were enrolled consecutively across multiple sites, irrespective of age, sex, social deprivation status, or kidney function. Second, the diagnosis of myocardial infarction was adjudicated according to the Fourth Universal Definition of Myocardial Infarction. Third, patient follow-up was performed using routine electronic regional and national health care datasets, thus minimizing reporting bias and loss to follow-up. Fourth, the size of our patient population, particularly those with an eGFR <30 ml/min per 1.73 m^2, is large and compares favorably with other published work.[16–18] Therefore, we believe our patient population is representative and our findings to be generalizable.

Previously, we showed that outcomes of patients with kidney impairment and suspected acute coronary syndrome did not improve following implementation of high-sensitivity cardiac troponin testing, despite the identification of more

patients who are at risk.[13] Perhaps contrary to widely held clinical perceptions, our current analysis found that implementation increased the identification of all types of myocardial infarction and injury in patients with and without kidney impairment, particularly type 1 myocardial infarction. However, implementation failed to address the disparities in management between those with and without kidney impairment. The reasons for this are complex but likely are related to the observation that half of all patients with elevated cardiac troponin concentrations and kidney impairment had a diagnosis of nonischemic myocardial injury or myocardial infarction secondary to other conditions. While several studies have identified kidney impairment as a risk factor for type 2 myocardial infarction and acute and chronic myocardial injury,[19–22] this figure is higher than those in previous reports[20,21] and is important given the poor prognosis associated with these diagnoses[5] and the lack of evidence available to guide the management of such patients.[22]

Despite major advances in the diagnosis and management of type 1 myocardial infarction,[23] our findings confirm that patients with kidney impairment continue to experience a disproportionately higher risk of subsequent events and cardiovascular death in the era of high-sensitivity cardiac troponin testing.[24,25] In our fully adjusted analysis, compared to those with normal kidney function, patients with elevated cardiac troponin concentrations and kidney impairment had a 50% increased risk of the primary outcome. While decreasing eGFR was associated with worse outcomes for all diagnostic classifications, it conferred the poorest prognosis in type 1 myocardial infarction, where we have the most evidence-based therapies to improve outcomes.

These findings are at least partly related to the disparity in the use of established therapies in patients with kidney impairment. This "therapeutic nihilism" is well described[26] and was also apparent in our study. For example, in patients with type 1 myocardial infarction, half of those with normal kidney function underwent coronary revascularization, compared to one quarter of those with kidney impairment. However, in keeping with other studies,[27–30] both coronary revascularization and preventative therapies were associated with a lower risk of the primary outcome in patients with type 1 myocardial infarction—irrespective of the presence of kidney impairment. Nevertheless, it is likely that the treatment gap we observed will persist in the absence of definitive randomized trial data in patients with type 1 myocardial infarction and kidney impairment.[31] Furthermore, high-quality evidence supporting the use of such treatments in patients with kidney failure—those who have the highest cardiovascular risk[32]—is lacking and should therefore be considered a priority for future research.

Several limitations merit consideration. First, it was not possible to discriminate between acute and chronic kidney injury because only a single measure of creatinine was available for each episode. While both are independently associated with increased cardiovascular risk, these conditions are distinct and may result in cardiovascular disease through different mechanisms.[33,34] Second, serum creatinine data were missing in ~3% of all enrolled patients. Third, fewer patients with kidney impairment underwent established investigations following their index presentation with suspected acute coronary syndrome, and therefore diagnostic misclassification may have been more common in this group. Fourth, as with all subgroup analyses, the trial was not powered for the primary outcome. However, the main purpose of this prespecified secondary analysis was to understand why the trial was neutral and to provide important insights into the diagnosis and management of patients with kidney impairment and suspected acute coronary syndrome.

CONCLUSIONS

Elevated cardiac troponin concentrations were 3-fold more common in patients with kidney impairment than in those with normal kidney function. Implementation of high-sensitivity cardiac troponin testing increased the diagnosis of type 1 myocardial infarction in both patients with and without kidney impairment. Despite this, patients with kidney impairment were no more likely to undergo angiography or revascularization, or to receive preventative therapies, and continued to experience poorer outcomes than those with normal kidney function.

APPENDIX

List of *High*-STEACS Investigators

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Adjudication panel: Dr. Anoop S.V. Shah, Dr. Atul Anand, Dr. Andrew R. Chapman, Dr. Kuan Ken Lee, Dr. Jack P.M. Andrews, Dr. Philip D. Adamson, Dr. Alastair Moss, Dr. Mohamed S. Anwar, Dr. John Hung, and Prof. Nicholas L. Mills.

Biochemistry subgroup committee: Dr. Simon Walker, Dr. Jonathan Malo, Mr. Alan Reid, Dr. Anne Cruikshank, and Prof. Paul O. Collinson.

Data monitoring committee: Prof. Colin M. Fischbacher, Dr. Bernard L. Croal, Prof. Stephen J. Leslie.

Edinburgh Clinical Trials Unit: Mrs. Catriona Keerie, Mr. Richard A. Parker, Mr. Allan Walker, Mr. Ronnie Harkess, Mr. Christopher Tuck, Mr. Tony Wackett, and Prof. Christopher Weir.

National Health Service Greater Glasgow and Clyde Safe Haven: Dr. Roma Armstrong, Ms. Laura Stirling, Ms. Claire MacDonald, Mr. Imran Sadat, and Mr. Frank Finlay.

National Health Service Lothian Research Governance, eHealth, and Safe Haven: Dr. Heather Charles, Ms. Pamela Linksted, Mr. Stephen Young, Mr. Bill Alexander, and Mr. Chris Duncan.

DISCLOSURE

ASVS and ARC have received honoraria from Abbott Diagnostics. NLM has received honoraria from Abbott Diagnostics, Siemens Healthineers, Roche

Diagnostics, and LumiraDx; and the University of Edinburgh has received research grants from Abbott Diagnostics and Siemens Healthineers. FSA has received honoraria (advisory board) from Siemens Healthineers and LumiraDx; nonsalaried research through research foundation from Abbott Diagnostics, Abbott PC, Beckman Coulter, Siemens Healthineers, Quidel, Ortho-Clinical Diagnostics, Roche Diagnostics; and has served on the board of directors of HyTest. CB is named on institutional research and/or consultancy agreements between the University of Glasgow and Abbot Vascular, AstraZeneca, Coroventis, GSK, HeartFlow, Menarini, Novartis, and Siemens Healthcare. All the other authors declared no competing interests.

DATA STATEMENT

Access to trial data was restricted to approved members of the research team who had completed information governance training. Source analysis code can be made available on request to the corresponding author.

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The High-Sensitivity Troponin in the Evaluation of Patients With Acute Coronary Syndrome (High-STEACS) trial is registered as NCT01852123 with ClinicalTrials.gov.

AUTHOR CONTRIBUTIONS

The *High*-STEACS Investigators contributed to the conception or design of the work or the acquisition, analysis, or interpretation of data for the work. They were involved in drafting and revising the manuscript and have given final approval of the version to be published. The *High*-STEACS investigators are accountable for the work.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary Methods.

Figure S1. Flow diagram of patients included in secondary analysis, according to estimated glomerular filtration rate ([eGFR], <60 or ≥ 60 ml/min per 1.73 m^2) category, study phase, and adjudicated diagnosis.

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

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

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

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

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

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