SUPPLEMENTAL MATERIALS

High-sensitivity cardiac troponin on presentation to rule out myocardial infarction: a stepped-wedge cluster randomized controlled trial

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Randomisation

Block randomisation was used with sites paired based on the expected number of presentations (***Table I***) and paired sites were randomized to implement the early rule-out pathway during one of three 8-week steps during the randomisation phase. The Royal Alexandra and Inverclyde Hospitals have a single pool of Emergency Medicine staff and therefore were paired and randomized to same block for implementation. 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. Allocation was concealed from sites prior to inclusion in the trial and from individual participants throughout.

Implementation support

To support implementation, we provided educational material and presentations at each site and training for clinical staff in the Emergency Department during the implementation phase. This was reinforced by specialist chest pain nurses who received detailed training prior to implementation and who supported Emergency Department clinicians in the assessment of patients with suspected acute coronary syndrome. The pathway was posted within each department and online in the hospital guidelines portal, and a training tool was made available on-line (www.highsteacs.com). This information was also presented to the wider hospital teams in medical grand round presentations prior to implementation. Finally, the research team and investigators included senior cardiologists, emergency physicians, and cardiology nurses who are clinically active within the hospital clusters; education was therefore reinforced at a local level by these clinical leaders throughout the implementation phase. In a sub-study that will be reported separately, we performed a qualitative assessment of the patient and clinician's experience before and after implementation of the early rule-out pathway.

Trial Outcomes

We used regional and national registries to follow-up the trial population. 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 in-hospital and community deaths, and all hospital admissions are recorded on the national General Register of Scotland and the Scottish Morbidity Record (SMR) respectively. It is a statutory requirement that any deaths occurring in Scotland, or outside Scotland but within the United Kingdom are entered on the Register of Deaths in Scotland within eight days of death. As such, this national registry is complete for all trial participants who remained resident in the United Kingdom (31,428/33,491 [99.8%]).

The primary and secondary safety outcome of myocardial infarction (type 1 or type 4b or type 4c) or cardiac death at 30 days and 1 year was adjudicated by a panel blinded to the study phase. Two physicians independently reviewed all clinical information, and discordant diagnoses were resolved by a third reviewer. All deaths and attendances across any participating site where cardiac troponin was measured and the cardiac troponin concentration was above the sex-specific 99th centile were reviewed and classified according to the Fourth Universal Definition of Myocardial Infarction.[26] Type 1 myocardial infarction was defined as myocardial necrosis (any high-sensitivity cardiac troponin I concentration above the sex-specific 99th centile with a rise and/or fall in troponin 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 4b and type 4c myocardial infarction were defined where myocardial ischemia and myocardial necrosis were associated with stent thrombosis or restenosis documented at angiography, respectively.

The secondary efficacy outcome measure was the proportion of patients discharged from the Emergency Department. Other safety outcome measures included myocardial infarction (type 1, type 4b or type 4c), cardiac death, cardiovascular death, all-cause death, unplanned coronary revascularisation and re-attendance for any reason.

The Scottish national community drug-prescribing database of the Information and Statistics Division (ISD) in NHS Scotland maintains a detailed record of all prescriptions dispensed in the community, which are linked to individual patient identifiers.

Non-adherence was evaluated for three aspects of the early rule-out pathway and was defined as (i) patients with cardiac troponin concentrations <5 ng/L at presentation and symptom onset >2 hours who had repeat testing, (ii) patients with cardiac troponin concentrations <5 ng/L and symptom onset ≤2 hours from presentation who did not have repeat testing, and (iii) patients with cardiac troponin concentrations between 5 ng/L and 99th centile who did not have repeat testing.

Trial Oversight

The HiSTORIC trial was approved by the Scotland A Research Ethics Committee, the Public Benefit and Privacy Panel for Health and Social Care, and Caldicott Guardian as part of the High-STEACS trial programme. On the advice of our ethics committee, the HiSTORIC trial protocol was incorporated into the High-STEACS programme, given the shared data governance, trial steering and data monitoring committees. A separate statistical analysis plan was prepared.

Sample Size

Based on simulation methods, the total sample size of 34,994 patients would provide 99% power at the two-sided 5% level of significance to detect a realistic true difference of at least 60 minutes in mean length of stay. Again, based on simulation methods, a sample size of 34,994 patients ensures that there is at least 74% probability of demonstrating non-inferiority assuming an event rate of 0·7% for the primary safety end-point (myocardial infarction or cardiac death at 30 days following discharge), a one-sided 95% confidence interval is constructed for the difference, and a non-inferiority margin of 0.5% in favour of standard care. No assumption was made about the level of intra-cluster correlation coefficient (ICC).

Our sample size calculation was reviewed following reported observations from the validation phase of the High-STEACS trial,[8] based on the assumption that the rate of the primary safety outcome measure at 30 days would be lower than anticipated at 0.4%. Based on simulation methods, a sample size of 38,994 patients would ensure that there is 90% power to demonstrate non-inferiority assuming an event rate of 0.4% for the primary safety end-point, a one-sided 95% confidence interval is constructed for the difference, and a non-inferiority margin of 0.5% in favour of standard care.

Statistical Analysis

The primary safety outcome was analysed using a linear mixed-effects regression model, adjusting for hospital site (random effect), season, time of presentation since start of study, and an indicator variable for whether the early rule-out pathway had been implemented. The fitted logistic mixed-effects regression model produced adjusted odds ratios. We then calculated average risk differences based on these odds ratios as previously described.[45] Specifically, this

involved calculating subject specific probabilities of the outcome under the intervention and control conditions. We then calculated differences between the probabilities before averaging to produce an estimate of the risk difference. For the upper 90% confidence limit, we used the same method except for the subject specific probabilities under the intervention condition we used the upper limit of the log odds ratio (rather than the point estimate).

Sensitivity analysis

For the primary efficacy endpoint and the primary safety endpoint, the following prespecified sensitivity analyses were also conducted:

(1) ***Calendar matched analysis:*** Although we adjusted for calendar time and season in the primary analysis model, some residual effect may still remain. Therefore, we compared outcomes during the calendar matched period in the validation and implementation phases using the same regression model as for the primary analysis, but without adjustment for time or season. The advantage of this before-and-after analysis is that it compares the intervention when it is fully embedded into clinical practice.

(2) ***As randomized analysis:*** Whilst, the early rule-out pathway was implemented across three steps in the randomisation phase, we had to accept some flexibility in the date of implementation. The primary analysis model was based on the actual dates the intervention was introduced, but using the same regression model we conducted an "as randomized" analysis based on the intended dates that the intervention would have been introduced.

(3) ***Randomisation phase:*** A sensitivity analysis was performed only using data collected within the randomisation phase when sites utilized both the standard care and early rule-out

pathway. This was proposed to reduce the risk of confounding bias due to secular changes over time, at the expense of a reduced sample size.

We observed that the results of our primary and sensitivity analyses were highly sensitive to the model specification, and results varied across these analyses (***Table S3***). Although non-inferiority was not concluded for the primary analysis of the safety outcome at 30 days, in our pre-specified sensitivity analysis restricted to calendar matched periods in the validation and implementation phases, the early rule-out pathway was superior to standard care. These divergent results may be due to the low event rate leading to overfitting models or they may be due to a true exposure-time effect whereby safety outcomes improved as the intervention became more firmly embedded into practice. If the latter was true, then our concern was that adjustment for differences in the rate of the primary safety outcome measure over time would confound a potential benefit of the intervention, hence the importance of the sensitivity analyses. The before and after comparison of the calendar matched periods, has the advantage of reducing the risk of bias due to seasonality, and by excluding patients presenting during the randomisation phase it allows a comparison of the efficacy and safety of the pathway when it is fully embedded into practice, at the expense of not being able to adjust for any natural secular changes over time.

We had to accept some flexibility in the date of implementation, which limited our ability to interpret the planned sensitivity analysis within the randomisation phase. As a consequence of pressures on the Emergency Department a number of sites implemented the rule-out pathway earlier than planned, and therefore very few patients were evaluated using the standard care pathway during this phase.

Table I. Number of patients with suspected acute coronary syndrome attending the Emergency Department in participating sites in the year prior to enrolment in the trial

Participating sites	**Total**
Royal Infirmary of Edinburgh	4,667
Western General Hospital	1,357
St John's Hospital	1,889
Royal Alexandra Hospital *	3,167
Inverclyde Royal Hospital *	1,570
Glasgow Royal Infirmary	5,242
Queen Elizabeth University Hospital †	2,951

* The Royal Alexandra and Inverclyde Hospitals have a single pool of Emergency Medicine staff and therefore were paired and randomized to same block for implementation.
† Number of presentations for Queen Elizabeth University Hospital were estimated based on the number of presentations to the Southern General Hospital prior to this site closing and patients from the Southern General Hospital, Victoria Infirmary and Western Infirmary being redirected to the Queen Elizabeth University Hospital.

Table II. Characteristics of trial participants stratified by phase

	Validation	Randomisation	Implementation
No. of participants	10,724	9,336	11,432
Age (years)	59±17	59±17	58±17
Women	4,789 (45)	4,261 (46)	5,202 (46)
Presenting complaint			
Chest pain	9,123 (85)	7,796 (84)	9,671 (85)
Dyspnoea	319 (3)	296 (3)	342 (3)
Palpitation	310 (3)	279 (3)	339 (3)
Syncope	536 (5)	606 (6)	559 (5)
Other	436 (4)	359 (4)	521 (5)
Past medical history			
Myocardial infarction	1,075 (10)	769 (8)	729 (6)
Ischaemic heart disease	2,960 (28)	2,174 (23)	2,212 (19)
Cerebrovascular disease	644 (6)	511 (5)	529 (5)
Diabetes mellitus	751 (7)	572 (6)	589 (5)
Previous revascularisation			
PCI	1,161 (11)	811 (9)	859 (8)
CABG	190 (2)	108 (1)	154 (1)
Medications at presentation			
Aspirin	3,119 (29)	2,351 (25)	2,553 (22)
Dual anti-platelet therapy*	571 (5)	337 (4)	361 (3)
Statin	4,478 (42)	3,608 (39)	4,079 (36)
ACE inhibitor or ARB	3,515 (33)	2,951 (32)	3,303 (29)
Beta-blocker	3,186 (30)	2,556 (27)	2,806 (25)
Oral anti-coagulant †	772 (7)	641 (7)	754 (7)
***Electrocardiogram*‡**			
Normal	4,317 (73)	3,148 (74)	4,570 (76)
Myocardial ischaemia	1,281 (22)	863 (20)	1,144 (19)
ST-segment elevation	75 (1)	49 (1)	69 (1)
ST-segment depression	98 (2)	66 (2)	88 (1)
T-wave inversion	451 (8)	335 (8)	439 (7)
Other	692 (12)	452 (11)	567 (9)
Haematology and clinical chemistry			
Haemoglobin, g/L	137±20	136±23	137±22
eGFR, mL/min	81±23	81±22	82±21
Presentation hs-cTnI, ng/L	3 [1-6]	3 [1-6]	3 [1-6]
Peak hs-cTnI, ng/L	3 [1-7]	3 [1-7]	3 [1-7]
Serial (≥2) tests §	4,957 (46)	3,424 (37)	3,523 (31)
Time intervals			
Symptom onset to presentation ≤2 hrs	2,122 (20)	1,774 (19)	1,768 (15)
Presentation to first test, mins	66 [46-98]	67 [46-98]	65 [43-96]
First test to second test, mins	465 [275-606]	357 [209-548]	193 [142-368]

Presented as No. (%), mean±SD or median [inter-quartile range]. Abbreviations: ACE = angiotensin converting enzyme; ARB = angiotensin receptor blockers; eGFR = estimated glomerular filtration rate; CABG = coronary artery bypass grafting; PCI = percutaneous coronary intervention. * Two medications from aspirin, clopidogrel, prasugrel or ticagrelor. † Includes warfarin or novel oral anti-coagulants. ‡ Proportions reported for the 16,217 (51%) participants with electrocardiographic data available. § Serial testing was defined as two or more tests within 24 hours of presentation.

Table III. Primary and sensitivity analyses for the safety outcome of myocardial infarction or cardiac death following discharge to 30 days

	All	Standard care	Early rule-out	Adjusted odds ratio	95% CI	90% CI	Adjusted risk differences	90% CI	P-value*
Primary analysis									
No. of participants	n=31,492	n=14,700	n=16,792						
No. of events, %	113 (0.4%)	57 (0.4%)	56 (0.3%)	1.97	0.95 to 4.08	1.07 to 3.63	0.26%	0.02% to 0.70%	P=0.068
Sensitivity analysis (1) calendar matched									
No. of participants	n=18,241	n=8,673	n=9,568						
No. of events, %	66 (0.4%)	43 (0.5%)	23 (0.2%)	0.48	0.29 to 0.80	0.32 to 0.74	-0.26%	-0.34% to -0.13%	P=0.005
Sensitivity analysis (2) as randomized									
No. of participants	n=31,492	n=13,650	n=17,842						
No. of events, %	113 (0.4%)	62 (0.5%)	51 (0.3%)	0.53	0.23 to 1.22	0.26 to 1.07	-0.17%	-0.27% to 0.02%	P=0.135
Sensitivity analysis (3) randomisation phase only									
No. of participants	n=9,336	n=3,976	n=5,360						
No. of events, %	37 (0.4%)	8 (0.2%)	29 (0.5%)	2.74	1.16 to 6.43	1.33 to 5.61	0.34%	0.07% to 0.91%	P=0.021

Abbreviations: CI = confidence interval

* P-values refer to tests of the adjusted odds ratios.

Table IV. Post-hoc analysis of the event rates for the primary and secondary safety outcome with and without the inclusion of type 2 myocardial infarction

	All n=31,492	**Standard care n=14,700**	**Early rule-out n=16,792**
Safety outcome at 30 days			
Type 1/4b/4c MI or Cardiac Death	113 (0.4)	57 (0.4)	56 (0.3)
Type 1/2/4b/4c MI or Cardiac Death	139 (0.4)	71 (0.5)	68 (0.4)
Myocardial infarction at 30 days			
Type 1/4b/4c	82 (0.3)	44 (0.3)	38 (0.2)
Type 1/2/4b/4c	108 (0.3)	58 (0.4)	50 (0.3)
Myocardial infarction at 1 year			
Type 1/4b/4c	422 (1.3)	238 (1.6)	184 (1.1)
Type 1/2/4b/4c	631 (2.0)	366 (2.5)	265 (1.6)

Values represent number (%) of outcome events

Figure I. Cumulative incidence of a *post-hoc* safety outcome of myocardial infarction or cardiac death at 30 days including type 2 myocardial infarction events

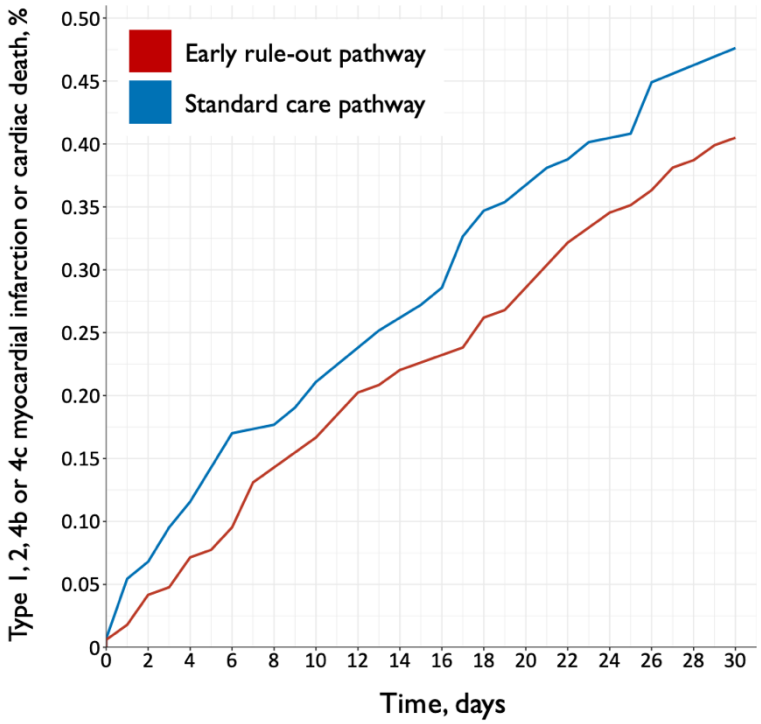

Figure II. Event rate for the primary safety outcome of myocardial infarction or cardiac death at 30 days by month of presentation from the start of the trial