SUPPLEMENTAL MATERIAL

Comparison of the efficacy and safety of early rule out pathways for acute myocardial infarction

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Table S1 – Baseline characteristics for the APACE external validation cohort

	APACE Study* (n=2,533)
Age	61 (16.0)
Male (%)	1,722 (68.0)
Primary Symptom	
Chest Pain	2,214 (87.4)
Symptom onset	
Minutes since onset	300 (120-720)
Less than three hours (%)	717 (28.5)
Less than six hours (%)	1,338 (53.2)
Over six hours (%)	1,054 (41.9)
Cardiovascular Risk Factors	
Smoker (%)	635 (25.1)
Diabetes mellitus (%)	451 (17.8)
Hypertension (%)	1,591 (62.8)
Hyperlipidaemia (%)	1,293 (51.0)
Family history (%)	987 (40.9)
Known angina (%)	883 (34.9)
Previous MI (%)	621 (24.5)
Previous PCI (%)	646 (25.5)
Previous CABG (%)	228 (9.0)
Stroke (%)	149 (5.9)
Peripheral vascular disease (%)	146 (5.8)
Troponin concentration at presentation	
<5 ng/L (%)	1,348 (53.2)
≥5 ng/L and ≤ 99th centile (%)	735 (29.0)
>99th centile (%)	450 (17.8)
Adjudicated Diagnosis	
Type 1 myocardial infarction (%)	289 (11.4)
All myocardial infarction (%)	378 (14.9)

**The APACE study is a prospective cohort study of patients with suspected acute coronary syndrome presenting to the Emergency Department of Basel and six other centers in Europe between April 2006 and August 2015. Blood samples were obtained on presentation and at 3, and 6h for high-sensitivity cardiac troponin I testing. All diagnoses were adjudicated by two independent cardiologists; the diagnosis of type 1 myocardial infarction required at least one high-sensitivity cardiac troponin I concentration above the sex-specific 99th centile upper reference limit (16 ng/L women, 34 ng/L men). This study was approved by the local ethics committee.*

Table S2. Patients ruled out by the ESC pathway at 0 and 3 hours meeting the primary outcome

Age	Gender	Time since symptom onset (Minutes)	Troponin concentration, ng/L (hours)	Relative Change (%)	Absolute Change	Presenting Symptom	Index Diagnosis	Risk Factors	Initial ECG	Management
81	Male	444	31 (0) 33 (3) 39 (12)	6.5	2	Chest Pain	Type 1 MI	Hypertension Hyperlipidaemia Ischaemic Heart Disease Previous CABG	Sinus Rhythm ST Depression T wave Inversion	PCI to LCx
57	Male	440	33 (0) 80 (3) 144 (5)	142.4	47	Chest Pain	Type 1 MI	Previous Smoker Family History of CHD	Sinus Rhythm	PCI to OM1
70	Male	375	17 (0) 160 (3) 2583 (6)	841.2	143	Chest Pain	Type 1 MI	Previous Smoker Diabetes Hypertension Hyperlipidaemia Previous MI	Sinus Rhythm RBBB	Medical
84	Male	4900	25 (0) 44 (3)	76.0	19	Chest Pain	Type 1 MI	Hypertension Previous MI Previous PCI Previous CABG Previous Stroke	Atrial Fibrillation	PCI to SVG-D1
82	Female	86	11 (0) 15 (3) 26 (10)	36.4	4	Chest Pain	Type 1 MI	Hypertension	Sinus Rhythm	Medical
62	Male	70	27 (0) 32 (3) 50 (11)	18.5	5	Chest Pain	Type 1 MI	Current Smoker Diabetes Hypertension Hyperlipidaemia Previous MI Previous PCI	Sinus Rhythm	Medical
87	Male	139	5 (0) 16 (3) 691 (10)	220.0	11	Chest Pain	Type 1 MI	Previous Smoker Hypertension Ischaemic Heart Disease Previous CABG	Atrial Fibrillation ST Depression	Medical

73	Male	180	26 (0) 29 (3) 41 (9)	11.5	3	Chest Pain	Type 1 MI	Previous Smoker Hypertension Hyperlipidaemia Family history of CHD Previous MI Previous CABG	Sinus Rhythm LBBB	Medical
58	Male	122	26 (0) 33 (3) 46 (11)	26.9	7	Dyspnoea	Type 1 MI	Previous Smoker Diabetes Family history of CHD Ischaemic Heart Disease Previous MI Previous CABG Previous Stroke	Sinus Rhythm T wave inversion	Medical
63	Female	151	10 (0) 16 (3) 167 (10)	60.0	6	Chest Pain	Type 1 MI	Current Smoker Family history of CHD	Sinus Rhythm ST Depression	PCI to LAD
66	Male	89	12 (0) 31 (3) 202 (10)	158.3	19	Chest Pain	Type 1 MI	Hypertension Previous MI Previous PCI	Sinus Rhythm	Medical
60	Male	81	2 (0) 6 (3) 2932 (11)	200.0	4	Chest Pain	Type 1 MI	Current Smoker Family History of CHD Ischaemic Heart Disease Previous PCI	Sinus Rhythm T wave inversion (old)	PCI to RCA/D1
56	Male	262	8 (0) 14 (3) 307 (10)	75.0	6	Chest Pain	Type 1 MI	Previous Smoker Hypertension Hyperlipidaemia Family history of CHD Ischaemic Heart Disease Previous MI Previous PCI	Sinus Rhythm	Medical
77	Male	272	21 (0) 26 (3) 56 (10)	23.8	5	Chest Pain	Type 1 MI	Previous Smoker Diabetes Hypertension Hyperlipidaemia Family history of CHD Previous MI Previous PCI	Atrial Fibrillation Inferior Q waves	Medical
66	Male	305	22 (0) 36 (3)	63.6	14	Chest Pain	Type 1 MI	Ischaemic Heart Disease Hypertension	Sinus Rhythm Bradycardia	PCI to LCx Instent Restenosis

			50 (8)					Hyperlipidaemia Previous MI Previous PCI		
60	Male	295	14 (0) 14 (3) 170 (8)	0	0	Chest Pain	Type 1 MI	Current Smoker Hypertension Hyperlipidaemia Family history of CHD Ischaemic heart disease Previous MI	Sinus Rhythm Bradycardia	Angiography 70% stenosis OM1 Medical
88	Female	222	15 (0) 19 (3)	26.7	4	Chest Pain	Type 1 MI	Ischaemic heart disease Previous MI Previous PCI Family history of CHD	Sinus Rhythm	Medical
89	Female	165	16 (0) 18 (3) 24 (10)	12.5	2	Chest Pain	Type 1 MI	Hypertension Family history of CHD Ischaemic Heart Disease	Sinus Rhythm	Medical
82	Male	126	19 (0) 20 (3) 22 (11) Re-attendance 52 (0) 44 (3) 24 (10)	5.3	1	Chest Pain	Musculoskeletal Chest Pain	Previous Smoker Diabetes Hyperlipidaemia Family history of CHD Ischaemic Heart Disease Previous MI Previous CABG	Sinus Rhythm First Degree HB Left Axis Deviation RBBB	Re-presented with ongoing chest pain two days post index presentation Missed Type 1 MI
73	Female	425	9 (0) 11 (3)	22.2	2	Chest Pain	Paroxysmal AF	Previous Smoker Hypertension Hyperlipidaemia Ischaemic Heart Disease Previous MI Previous PCI	Atrial Fibrillation RBBB T wave inversion	Re-presented with inferior STEMI 14 days post index presentation PCI to RCA Type 1 MI

Demarcations for missed index events with ≥6 hours symptoms (n=4), <6 hours symptoms (n=14) and 30 day events (n=2)
AF = atrial fibrillation, CABG = coronary artery bypass graft, CHD = coronary heart disease, LBBB = left bundle branch block, RBBB = right bundle branch block, MI = myocardial infarction, PCI = percutaneous coronary intervention, STEMI = ST-segment elevation myocardial infarction.

Table S3. Patients ruled out by the High-STEACS pathway at 0 and 3 hours meeting the primary outcome

Age	Gender	Time since symptom onset (Minutes)	Troponin concentration, ng/L (hours)	Relative Change (%)	Absolute Change	Presenting Symptom	Index Diagnosis	Risk Factors	Initial ECG	Management
81	Male	444	31 (0) 33 (3) 39 (12)	6.45	2	Chest Pain	Type 1 MI	Hypertension Hyperlipidaemia Ischaemic Heart Disease Previous CABG	Sinus Rhythm ST Depression T wave Inversion	PCI to LCx
60	Male	295	14 (0) 14 (3) 170 (8)	0	0	Chest Pain	Type 1 MI	Current Smoker Hypertension Hyperlipidaemia Family history of CHD Ischaemic heart disease Previous MI	Sinus Rhythm Bradycardia	Angiography 70% stenosis OM1 Medical
82	Male	126	19 (0) 20 (3) 22 (11) Re-attendance 52 (0) 44 (3) 24 (10)	5.3	1	Chest Pain	Musculoskeletal Chest Pain	Previous Smoker Diabetes Hyperlipidaemia Family history of CHD Ischaemic Heart Disease Previous MI Previous CABG	Sinus Rhythm First Degree HB Left Axis Deviation RBBB	Re-presented with ongoing chest pain two days post index presentation Missed Type 1 MI
73	Female	425	9 (0) 11 (3)	22.2	2	Chest Pain	Paroxysmal AF	Previous Smoker Hypertension Hyperlipidaemia Ischaemic Heart Disease Previous MI Previous PCI	Atrial Fibrillation RBBB T wave inversion	Re-presented with inferior STEMI 14 days post index presentation PCI to RCA Type 1 MI

Demarcation for missed index events (n=2) and 30 day events (n=2)

AF = atrial fibrillation, CABG = coronary artery bypass graft, CHD = coronary heart disease, LBBB = left bundle branch block, RBBB = right bundle branch block, MI = myocardial infarction, PCI = percutaneous coronary intervention. STEMI = ST-segment elevation myocardial infarctioz

Table S4 – 2x2 table for internal validation of delta criteria at three hours

	Type 1 MI	No Type 1 MI
Change ≥3 ng/L at 3 hours	40	52
Change <3 ng/L at 3 hours	2	216

Patients with cardiac troponin concentrations ≥5 ng/L and <99th centile on presentation are re-tested at three hours. Those with a change in cardiac troponin of <3 ng/L are ruled out if they remain <99th centile.

Table S5 – 2x2 table for external validation of delta criteria at three hours

	Type 1 MI	No Type 1 MI
Change ≥3 ng/L at 3 hours	51	170
Change <3 ng/L at 3 hours	0	514

Patients with cardiac troponin concentrations ≥5 ng/L and <99th centile on presentation are re-tested at three hours. Those with a change in cardiac troponin of <3 ng/L are ruled out if they remain <99th centile.

Table S6 – 2x2 table with diagnostic performance of the High-STEACS pathway at 6 hours

	Type 1 MI	No Type 1 MI
Pathway rules in	187	88
Pathway rules out	4	939

Patients with cardiac troponin concentrations <5 ng/L who present over two hours from time of symptom onset are ruled out on presentation. Those ≥5 ng/L and <99th centile on presentation, and those who present within two hours of symptom onset are re-tested at three hours. Those with a change in cardiac troponin of <3 ng/L are ruled out if they remain <99th centile, with all other patients admitted for peak testing at six hours.

Figure S1. Study population, adjudicated diagnosis and 30 day outcomes

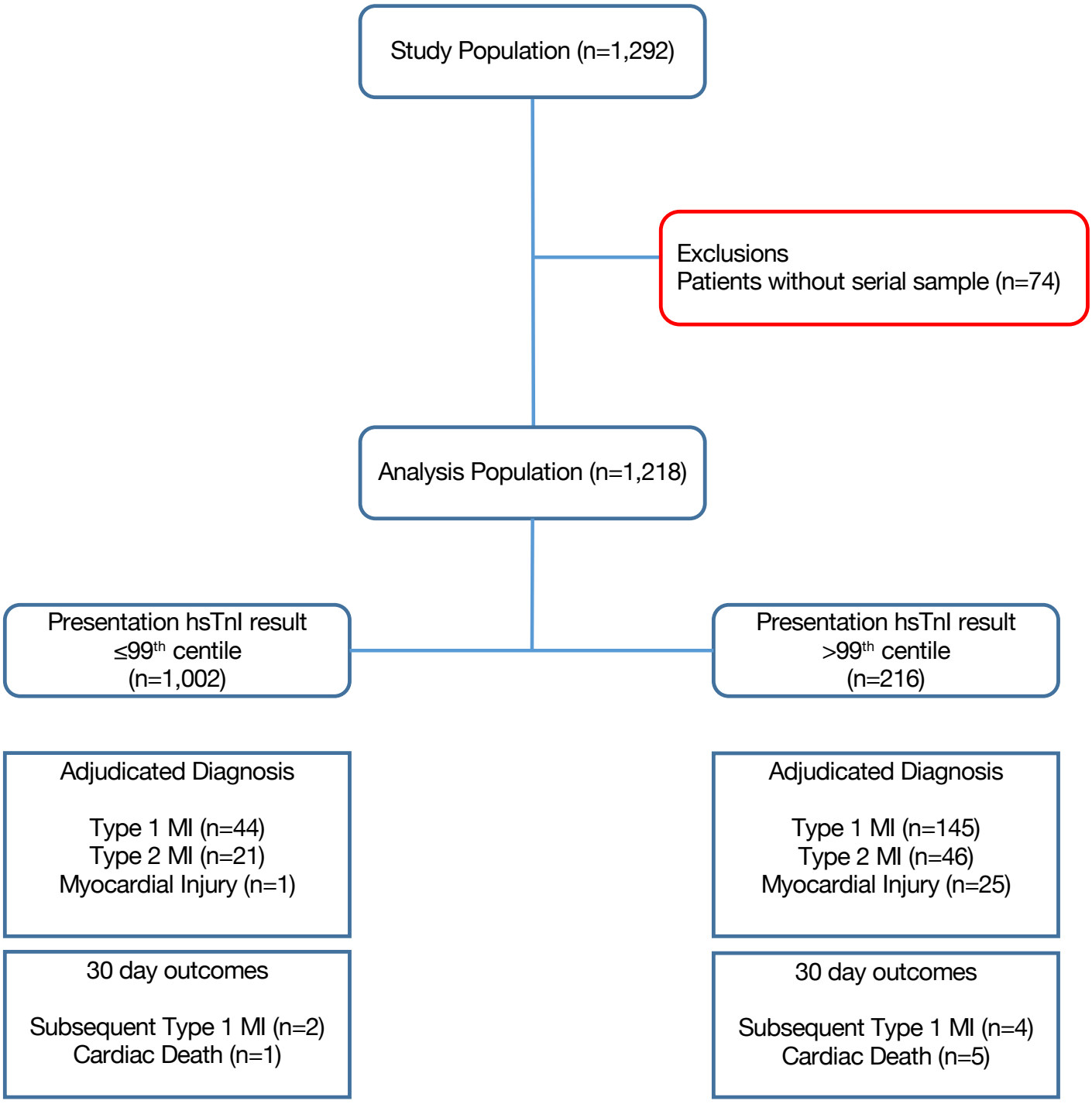
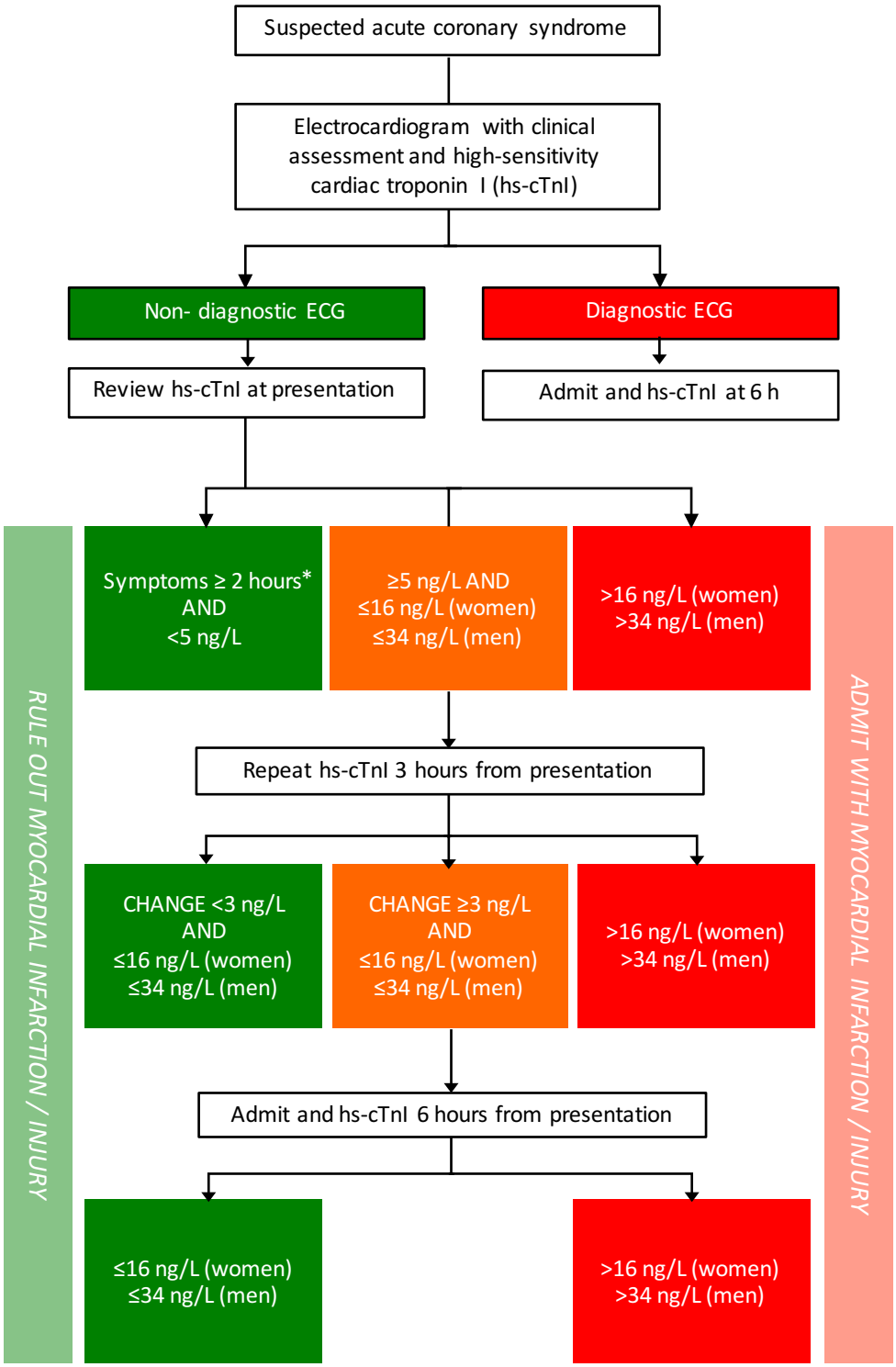


Figure S2. Diagnostic algorithm of the High-STEACS pathway



*Diagnostic algorithm of the High-STEACS pathway, currently being evaluated as part of a multi-centre stepped-wedge cluster randomised trial in unselected consecutive patients across Scotland. *In the High-STEACS pathway, patients with cardiac troponin concentrations <5 ng/L who present within two hours of symptom onset are retested at three hours.*