Supplementary File

Exclusion criteria applied to all study cohorts

ST-segment elevation myocardial infarction or new left bundle branch block, significant arrhythmias (sustained supraventricular tachycardia, second-degree or complete heart block, or sustained or recurrent ventricular arrhythmias), age <18 years, a clear cause other than ACS for the symptoms, pregnancy, inappropriate recruitment (e.g. terminal illness), unwillingness to consent, and if follow-up was considered impossible.

Supplementary Table 1. Outcome adjudication processes by study site

Site	Methods of adjudication of 30 day Major Adverse Cardiac Events
Brisbane, Australia	Single cardiology review of all cases. Second cardiologist reviewed 10% of non-cardiovascular and all cardiovascular endpoints (including unstable angina, and arrhythmias). Disagreements settled by discussion.
Christchurch, New Zealand	Double adjudication in parallel by two cardiologists. Third cardiology adjudicator for any disagreements.
Poole, UK	Double adjudication in parallel by one emergency medicine physician and one cardiologist. Disagreements settled by discussion.

Supplementary Table 2. Troponin assays used for adjudicated outcomes by study site

Site	Assay and Manufacturer	99th Percentile	Limit of Detection	10% Coefficient of Variation	Serial testing time-point
Brisbane, Australia (ADAPT Observational)	Access AccuTnI assay, Beckman Coulter, Chaska, MN	40ng/L	10ng/L	60ng/L	Presentation and at least 6 hours after presentation
Brisbane, Australia (IMPACT Interventional)	Access AccuTnI assay, Beckman Coulter, Chaska, MN	40ng/L	10ng/L	60ng/L	Presentation and at least 2 hours after presentation for low risk patients
Christchurch, New Zealand (ADAPT Observational)	Architect Troponin I, Abbott Diagnostics, Chicago, Illinois	30ng/L	10ng/L	32ng/L	Presentation and at least 6 hours after presentation
Christchurch, New Zealand (ADAPT-ADP Randomized Controlled Trial)	Architect Troponin I, Abbott Diagnostics, Chicago, Illinois	30ng/L	10ng/L	32ng/L	Presentation and at least 2 hours after presentation for low risk patients
Christchurch, New Zealand (EDACS-ADP Randomized Controlled Trial)	ARCHITECT high-sensitivity Troponin I,Abbott Diagnostics, Chicago, Illinois	16ng/L for women and 34ng/L for men (sex-specific cut-offs used)	2ng/L	4.7ng/L	Presentation and at least 2 hours after presentation for low risk patients
Poole, UK (TRUST Observational)	Elecsys high-sensitivity Troponin T, Roche, Basel, Switzerland	14ng/L	5ng/L	13ng/L	Presentation and at least 6 hours after presentation

Supplementary Table 3. Characteristics of patients classified by hs-cTn assay separated by study site/country.

	Brisbane, Australia		Christchurch, New Zealand		Poole, United Kingdom	
	hs-cTnT cohort (n=704)	**hs-cTnI cohort (n=1761)**	**hs-cTnT cohort (n=1534)**	**hs-cTnI cohort (n=1904)**	**hs-cTnT cohort (n=921)**	**hs-cTnI cohort (n=867)**
Age, years; mean (SD)	53.6 (14.4)	51.7 (13.1)	62.6 (12.8)	61.9 (12.8)	58.0 (13.3)	57.9 (13.0)
Sex (% male)	418 (59.4)	1046 (59.4)	903 (58.9)	1133 (59.5)	545 (59.2)	515 (59.4)
Ethnicity (% Caucasian)	609 (88.6)[b]	1555 (89.3)[c]	1257 (82.2)[a]	1535 (80.8)[a]	875 (95.0)	827 (95.4)
Risk factors n (%)						
Hypertension	329 (46.7)	726 (41.2)	834 (54.4)	1030 (54.1)	504 (51.7)	477 (55.0)
Diabetes	84 (11.9)	212 (12.0)	236 (15.4)	286 (15)	156 (16.9)	145 (16.7)
Dyslipidemia	327 (46.4)	712 (40.4)	842 (54.9)	1024 (53.8)	604 (65.6)	583 (67.2)
Smoking Current	196 (27.8)	494 (28.1)	241 (15.7)	296 (15.5)	220 (23.9)	210 (24.2)
Family History of CAD	332 (47.2)	727 (41.3)	904 (58.9)	1033 (54.3)	334 (36.3)	327 (37.7)
Medical History n (%)						
Angina	144 (20.4)	245 (13.9)	576 (37.5)	661 (34.7)	240 (26.1)	223 (25.7)
Myocardial Infarction	107 (15.2)	212 (12.0)	430 (28.0)	514 (27.0)	197 (21.4)	190 (21.9)
Percutaneous Coronary Intervention	73 (10.4)	142 (8.1)	293 (25.3)	391 (25.6)	178 (19.3)	168 (19.4)
Congestive Cardiac Failure	21 (3.0)	30 (1.7)	111 (7.2)	121 (6.4)	30 (3.3)	24 (2.8)
Stroke/TIA	51 (7.2)	96 (5.5)	92 (7.1)	108 (7.1)	60 (6.5)	57 (6.6)
CABG	43 (6.1)	76 (4.3)	131 (8.5)	150 (7.9)	49 (5.3)	41 (4.7)
TIMI Risk Score						
Age ≥65	142 (20.2)	263 (14.9)	648 (42.2)	756 (39.7)	327 (35.5)	303 (34.9)
≥3 Risk Factors for Coronary Artery Disease	201 (28.6)	418 (23.7)	538 (35.1)	628 (33.0)	307 (33.3)	298 (34.4)
Significant Coronary Stenosis	137 (19.5)	265 (15.1)	509 (33.2)	594 (31.2)	261 (28.3)	250 (28.8)
Severe Angina	304 (43.2)	761 (43.2)	576 (37.5)	661 (34.7)	71 (7.7)	61 (7.0)
Aspirin Use in Past 7 Days	165 (23.4)	346 (19.6)	764 (49.8)	910 (47.8)	349 (37.9)	329 (37.9)
Time from chest pain onset to ED presentation Median hours [Interquartile Range]	4.4 [1.6 - 19.5]	3.4 [1.5 - 14.7]	4.8 [2.8 - 10.1]	4.5 [2.5 - 9.4]	2.3 [1.4 - 5.3]	2.3 [1.3 - 5.0]
MACE within 30 Days n (%)	43 (6.1)	85 (4.8)	238 (15.6)	277 (14.6)	95 (10.3)	83 (9.6)

Data missing for ethnicity in [a]4 cases, [b]17 cases and [c]19 cases.

Supplementary Table 4. Summary statistics of the suggested NICE algorithm according to high-sensitivity troponin assay and TIMI score threshold in patients presenting less than 3 hours from symptom onset.

	Hs-cTnT		**Hs-cTnI**	
TIMI Score 0 2x2	**MACE**	**No MACE**	**MACE**	**No MACE**
Test Positive: hs-cTn>LoD or TIMI>0	267	1404	300	1911
Test Negative (Rule-out): hs-cTn≤LoD and TIMI=0	2	315	2	445
Sensitivity (95% CI)	99.3% (97.3% to 99.9%)		99.3% (97.6% to 99.9%)	
Negative Predictive Value (95% CI)	99.4% (97.7% to 99.9%)		99.6% (98.4% to 99.9%)	
Specificity (95% CI)	18.3% (16.5% to 20.2%)		18.9% (17.3% to 20.5%)	
Positive Predictive Value (95% CI)	16.0% (14.3% to 17.8%)		13.6% (12.2% to 15.1%)	
TIMI Score ≤1 2x2	**MACE**	**No MACE**	**MACE**	**No MACE**
Test Positive: hs-cTn>LoD or TIMI>1	265	1190	299	1508
Test Negative (Rule-out): hs-cTn≤LoD and TIMI≤1	4	529	3	848
Sensitivity (95% CI)	98.5% (96.2% to 99.6%)		99.0% (97.1% to 99.8%)	
Negative Predictive Value (95% CI)	99.2% (98.1% to 99.8%)		99.6% (99.0% to 99.9)	
Specificity (95% CI)	30.8% (28.6% to 33.0%)		36.0% (34.1% to 38.0%)	
Positive Predictive Value (95% CI)	18.2% (16.3% to 20.3%)		16.5% (14.9% to 18.3%)	

TIMI Score ≤2 2x2	**MACE**	**No MACE**	**MACE**	**No MACE**
Test Positive: hs-cTn>LoD or TIMI>2	262	1100	296	1351
Test Negative (Rule-out): hs-cTn≤LoD and TIMI≤2	7	619	6	1005
Sensitivity (95% CI)	97.4% (94.7% to 98.9%)		98.0% (95.7% to 99.3%)	
Negative Predictive Value (95% CI)	98.9% (97.7% to 99.5%)		99.4% (98.7% to 99.8%	
Specificity (95% CI)	36.0% (33.7% to 38.3%)		42.7% (40.6% to 44.7%)	
Positive Predictive Value (95% CI)	19.2% (17.2% to 21.4%)		18.0% (16.1% to 19.9%)	