Supplemental material to “Incidence and outcomes of unstable angina”

# Supplemental methods

## Follow-up

Patients were contacted via telephone interview performed by trained researchers blinded to the adjudication after 90 days and 1 year. In those patients with an event, review of all available medical records was performed. If patients could not be contacted directly, family physicians and administrative databases of the respective hometowns were contacted.

## Study design and population continued

Both studies were carried out according to the principles of the Declaration of Helsinki and approved by the local ethics committees (Ethic committee Nordwestschweiz, and Scotland A Research Ethics Committee, the Public Benefit and Privacy Panel for Health and Social Care, and by each National Health Service Health Board). Informed consent was obtained.

In APACE, adult patients presenting with any kind of acute chest discomfort including “pain”, “pressure”, “burning”, “stabbing”, and “angina” to the emergency department (ED) with an onset or peak within the last 12 hours were recruited after written informed was obtained. While enrolment was independent of renal function, patients with terminal kidney failure requiring renal replacement therapy were excluded.

High-STEACS prospectively identified a population of patients presenting with suspected acute coronary syndrome (ACS) to EDs in Scotland. All patients underwent an initial clinical assessment that included a clinical history, physical examination, 12-lead-ECG, continuous ECG-rhythm monitoring, pulse oximetry, serial blood testing including (hs)-cTn, and chest radiography. Attending clinicians reviewed all patients at presentation and included those with suspected acute coronary syndrome. They completed a dedicated electronic form that was integrated into the clinical care pathway prior to measurement of plasma cardiac troponin I concentration at presentation. Troponin testing was repeated 6 or 12 hours after the onset of symptoms at their discretion. Additional data, including baseline clinical characteristics, was collected prospectively from the electronic patient record through a dynamic linkage process. Patients were excluded if they had a previous presentation during the study period or were not resident in Scotland.

Treatment of patients was left at the discretion of the attending physician.

### Clinical outcomes High-STEACS

High-STEACS used regional and national registries to ensure that follow-up was complete for the entire study population. TrakCare software application (InterSystems Corporation, Cambridge, MA, USA) is a regional electronic patient record system, which provides data on all hospital admissions to both tertiary or secondary care hospitals in southeast Scotland. When evaluating readmissions with myocardial infarction (MI), all patients were re-adjudicated and classified after review of all clinical notes and investigations, and according to the same criteria used for their index admission. All in-hospital and community deaths are recorded in a comprehensive national database, the General Register of Scotland.

## High-sensitivity cardiac troponin (hs-cTn) measurements

In APACE, hs-cTnT was measured from blood samples collected at presentation to the ED and serially thereafter at one and two hours. Based on studies of the biological variation of cTn[1,2] as well as on data from previous chest pain cohort studies[3,4], a significant absolute change was defined as a rise or fall of at least 4ng/L within two hours, and 2ng/L within one hour[5].

In High-STEACS, hs-cTnI was measured at presentation and repeated 6 or 12 hours after the onset of symptoms at the discretion of the clinician.

### Hs-cTnT assay used in APACE

After centrifugation, samples were frozen at -80°C until assayed in a blinded fashion in a dedicated core laboratory[6]. An additional set of hs-cTnT measurements was performed from fresh blood after centrifugation in patients treated in sites using hs-cTnT as part of routine clinical care. Hs-cTnT was measured on the Elecsys 2010 (Roche). An imprecision corresponding to 10% coefficient of variation was reported at 13 ng/L, limit of detection at 5 ng/L, limit of blank at 3 ng/L, and the 99th percentile of a healthy reference population was reported at 14 ng/L[7].

### Contemporary and hs-cTnI assays used in APACE and High-STEACS

As standard of care, a contemporary sensitive cardiac troponin I assay (ARCHITECT*STAT*troponin I assay, Abbott Laboratories, Abbott Park, IL) was used in High-STEACS for clinical decision-making and reported to the clinicians responsible for the patient’s care. This assay has been validated in our institution[8,9].According to the manufacturer, the limit of detection is 10 ng/L and the upper reference limit (URL; 99th percentile) of a normal reference population is 28 ng/L. The inter-assay coefficient of variation (CV) was <10 % at 50 ng/L under local laboratory conditions and this concentration is used as the diagnostic threshold.

In APACE and High-STEACS, a high-sensitivity assay (ARCHITECT*STAT* high-sensitive troponin I assay, Abbott Laboratories, Abbott Park, IL) was used to measure cardiac troponin I concentrations on plasma excess to clinical requirements. The results were not reported to clinicians responsible for the patients care. This assay has a limit of detection of 1.2 ng/L, an upper reference limit (URL; 99th percentile) of 34 ng/L in men and 16 ng/L in women[10,11]. We previously assessed assay precision in our laboratory reporting a coefficient of variation (CV) of 23% at the limit of detection (1.2 ng/L) and <10% at 6 ng/L[12,13].

## Final adjudication

### APACE (continued)

### For the final adjudication done by two independents cardiologists regarding the final diagnosis of NSTEMI versus UA, hs-cTn concentrations obtained for clinical purposes prior to the index presentation and as well as following the index presentation were available in many patients. E.g. in a patients with a hs-cTnT concentrations of 0h: 22ng, 1h: 23ng/l, 2h; 22ng/L), the availability of a hs-cTnT concentration of 14ng/L several weeks prior or after the index event would argue in favor of NSTEMI in patients with ischemic symptoms, as acute cardiomyocyte injury related to the ischemic event can be documented. In contrast, if in the same patient a hs-cTnT concentration of 22ng/L several weeks prior or after the index event is documented, it would argue in favor of UA, as NO cardiomyocyte injury related to the current ischemic episode can be documented.

### High-STEACS

Adjudication of final diagnoses was performed centrally for all patients in accordance with the criteria detailed in the third universal definition of MI[14]. Myocardial necrosis was identified if cardiac troponin concentrations were >99th percentile URL of the high-sensitivity assay on at least one measurement. Non-ST-segment elevation myocardial infarction (NSTEMI) was defined as myocardial necrosis in the context of an isolated presentation with suspected acute coronary syndrome with chest pain or evidence of myocardial ischaemia on the electrocardiogram. A diagnosis of ST-segment elevation myocardial infarction (STEMI) was made where, in addition to these criteria, there was ST-segment elevation or new left bundle branch block on the resting electrocardiogram. Unstable angina was diagnosed in patients with ischemic symptoms at rest or minor exercise with normal (hs)-cTn levels. In addition, a diagnosis of UA required at least one of the following: evidence of myocardial ischaemia on resting electrocardiogram or stress testing, obstructive coronary artery disease on coronary angiography, or sudden cardiac death or MI occurring during 60-day follow-up. In contrast to the definition used in APACE, the presence of a single troponin concentration above the 99th percentile was deemed sufficient to exclude the diagnosis of UA. As a second difference, objective evidence of ischaemia or obstructive coronary disease was a mandatory criterion in High-STEACS, whereas it was not mandatory in APACE. Accordingly, an elderly patient with known CAD and very typical angina pectoris including response to anti-ischemic therapy in whom no objective ischaemia testing was performed would be adjudicated to have UA in APACE, but not in High-STEACS. Those patients in whom a diagnosis of acute coronary syndrome was excluded were classified as NCoCP. Two independent cardiologists (PA, NLM) reviewed all available medical records, including patient history, physical examination, results of laboratory testing including local contemporary and high-sensitivity troponin concentrations, electrocardiography, echocardiography, exercise stress testing, and coronary angiography from the time of presentation to 60-day follow-up. In situations of initial diagnostic disagreement, cases were reviewed and adjudicated by consensus.

## Angiographic characteristics of UA

In a subgroup of patients with UA or NSTEMI who underwent coronary angiography we did detailed analysis of the angiographic results and characterised the lesions according to the Ambrose criteria[15].

## Supplemental statistical analyses

To adjust for potential influencing variables, we performed multivariable Cox proportional hazards regression, using forced entry. For occurrence of future non-fatal MI we included age, gender, cardiovascular risk factors (hypertension, hypercholesterolemia, diabetes, active smoker), known CAD, previous myocardial infarction, and previous revascularisation. For all-cause death we included additional factors associated with mortality (renal insufficiency, obstructive lung disease, malignancy). For the analysis of future non-fatal MI, we performed a subdistribution competing risk analysis to account for all-cause mortality as sensitivity analysis[16].

## Sensitivity analysis using hs-cTnI for adjudication of final diagnosis in APACE

For the APACE study, we performed a second adjudication using the same stringent methodology including radiologic testing, ECG, echocardiography, cardiac exercise test, lesion severity and morphology in coronary angiography, cardiac magnetic resonance imaging pertaining to the patient from the time of ED presentation to 90-day follow up, and serial hs-cTnI (rather than hs-cTnT) blood concentrations from study samples[17]*.*

Kaplan Meier plot and log-rank test were repeated for mortality and future non-fatal MI using the newly adjudicated final diagnosis using hs-cTnI.

# Supplemental Results

## Revascularisation procedures and resource use

In APACE, 1054 (26%) patients underwent coronary angiography within 30 days. The respective rates of angiography within the diagnostic groups were: UA 65% (238/366), NSTEMI 76% (474/622), NCCP 5% (105/2154, eTable 2). 57% (207/366) and 66% (410/622) of patients with UA and NSTEMI underwent revascularisation within 30 days, respectively (p=0.004). Rates of revascularisation were similar in both groups at 1 year (65% versus 66%, p=0.677).

In High-STEACS, 559 (11%) patients underwent coronary angiography within 30 days (eTable 3). The respective rates of angiography within the diagnostic groups were: UA 21% (29/137), NSTEMI 55% (359/651), and NCoCP 2% (65/3951). 18% and 43% of patients with UA and NSTEMI underwent revascularisation, respectively (p<0.001).

We chose a subgroup of 212 patients from APACE and High-STEACS including 84 patients with UA and 128 patients with NSTEMI for comparison of angiographic data. We found a difference in maximal stenosis in percent (95% vs 90%, respectively), but lesion morphology, filling defects, ulcerations, or TIMI flow <3 did not differ significantly (eTable 4).

## Sensitivity analysis using hs-cTnI for adjudication of final diagnosis in APACE

Results were similar for the adjudication of hs-cTnI as for hs-cTnT in the APACE cohort, with mortality in patients with UA (3.3%, 95% CI 1.4-5.1) being significantly lower than in patients with NSTEMI (10.0%, 7.5-12.3, p<0.001), while future non-fatal myocardialinfarction did not statistically differ in UA (10.3%, 7.1-13.4) vs NSTEMI (8.8%, 6.5-11.1, p=0.411, eFigure 2).

.

# Supplemental Tables

**eTable 1** Baseline characteristics of patients with unstable angina according to the presence or absence of troponin elevations above the 99th percentile

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **APACE** | | **High-STEACS** | |
| **Unstable angina  <99th percentile n = 215** | **Unstable angina  ≥99th percentile n = 151** | **Unstable angina  (all <99th percentile) n = 137** | **Unstable angina  ≥99th percentile n = 50** |
| Age - years | 64 [57, 73] | 74 [66, 80] | 72 [63, 79] | 74.00 (14.71) |
| Sex - male | 175 (81.4) | 123 (81.5) | 89 (65.0) | 14 (28.0) |
| **Risk factors** |  |  |  |  |
| Hypertension | 190 (88.4) | 142 (94) | 61 (47.7) | 22 (45.8) |
| Hypercholesterolemia | 181 (84.2) | 119 (78.8) | 65 (50.8) | 15 (31.2) |
| BMI - kg/m2 | 27 [24, 30] | 27 [24, 30] |  |  |
| Diabetes mellitus | 57 (26.6) | 37 (24.5) | 37 (28.9) | 11 (22.9) |
| Active smoker | 50 (23.3) | 18 (11.9) | 29 (37.2) | 8 (30.8) |
| Positive family history | 104 (50.5) | 59 (40.1) |  |  |
| **Past medical history** |  |  |  |  |
| Coronary artery disease | 153 (71.2) | 115 (76.2) | 97 (75.8) | 23 (47.9) |
| Prior myocardial infarction | 106 (49.3) | 87 (57.6) | 53 (41.4) | 12 (25.0) |
| Prior coronary revascularisation | 135 (62.8) | 103 (68.2) | 48 (37.5) | 9 (18.8) |
| **Vital parameters at admission** |  |  |  |  |
| Systolic blood pressure - mmHg | 142 [131, 160] | 145 [127, 159] | 137 [120, 158] | 76.14 (19.10) |
| Heart rate - beats/min | 69 [62, 80] | 69 [61, 81] | 69.00 [64, 77] | 148.40 (35.08) |
| Breathing rate - breaths/min | 16 [14, 20] | 17 [14, 19] | n.a. |  |
| **Electrocardiography** |  |  |  |  |
| ST-segment depression | 16 (7.5) | 18 (12.1) | 7 (5.2) | 1 (2.2) |
| T-wave inversion | 28 (13) | 43 (28.5) | 19 (13.9) | 9 (18.0) |

Baseline characteristics of patients with UA split for whether they had any hs-cTn measurement ≥99th percentile with no evidence of acute myocardial necrosis. Values shown as absolute numbers with (percentages) or median with [interquartile range]

**eTable 2**Revascularisation procedures and resource use in the APACE cohort. Frequency of use and results from coronary angiography and revascularisation procedures, shown as absolute numbers and (percentages) for unstable angina (UA), non-ST-segment elevation myocardial infarction (NSTEMI).and non-cardiac chest pain (NCCP); \*percentage of total coronary angiographies performed within 30 days; CAD = coronary artery disease; PCI = percutaneous coronary intervention

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Unstable Angina n = 366** | **NSTEMI n = 622** | p-value UA vs NSTEMI | **NCCP n = 2154** | p-value UA vs NCCP |
| Coronary angiography 30days, n (%) | 238 (65) | 474 (76.2) | <0.001 | 105 (4.9) | <0.001 |
| no significant CAD | 1 (0.4) | 24 (5.1) | 0.001 | 66 (63.5) | <0.001 |
| 1-vessel CAD, n (%) | 67 (28.2) | 102 (21.5) | 8 (7.7) |
| 2-vessel CAD, n (%) | 49 (20.6) | 118 (24.9) | 15 (14.4) |
| 3-vessel CAD, n (%) | 121 (50.8) | 230 (48.5) | 15 (14.4) |
| Coronary angiography during initial stay (%\*) | 204 (85.7) | 461 (97.3) | <0.001 | 88 (83.8) | <0.001 |
| Coronary revascularisation in 30days, n (%) | 207 (56.6) | 410 (65.9) | 0.003 | 7 (0.3) | <0.001 |
| PCI, n (%) | 196 (53.6) | 387 (62.2) | 0.009 | 7 (0.3) | <0.001 |
| Coronary bypass surgery, n (%) | 11 (3) | 23 (3.7) | 0.718 | 0 (0) | <0.001 |
| Coronary stenosis <75%, n (%) | 25 (12.2) | 17 (4.2) | <0.001 | 4 (-) | - |
| Coronary stenosis ≥75-99%, n (%) | 151 (73.7) | 272 (67.2) | 3 (-) |
| Coronary occlusion, n (%) | 29 (14.1) | 116 (28.6) | 0 (-) |
| Coronary intervention in one year, n (%) | 238 (65) | 413 (66.4) | 0.677 | 26 (1.2) | <0.001 |
| Stress testing performed in 30 days | 143 (39.1) | 161 (25.9) | <0.001 | 480 (22.4) | <0.001 |
| Ergometry, n (%) | 75 (20.5) | 116 (18.6) | 0.505 | 318 (14.8) | 0.006 |
| Myocardial perfusion imaging, n (%) | 94 (25.7) | 60 (9.6) | <0.001 | 195 (9.1) | <0.001 |
| Admitted for ≥1 day | 285 (77.9) | 583 (93.7) | <0.001 | 619 (28.7) | <0.001 |

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **eTable 3** Revascularisation procedures and resource use in the High-STEACS cohort. Frequency of use and results from coronary angiography and revascularisation procedures shown as absolute numbers and (percentages) for unstable angina (UA), non-ST-segment elevation myocardial infarction (NSTEMI).and non-coronary chest pain (NCoCP); PCI = percutaneous coronary intervention | **Unstable Angina n = 137** | **NSTEMI n = 651** | p-value UA vs NSTEMI | **NCoCP n = 3951** | p-value UA vs NCoCP |
| Coronary angiography 30days, n (%) | 29 (21.2) | 359 (55.1) | <0.001 | 65 ( 1.6) | <0.001 |
| no significant CAD | 2 ( 6.9) | 39 (10.9) | 0.343 | 39 (60.0) | <0.001 |
| 1-vessel CAD, n (%) | 9 (31.0) | 138 (38.4) | 7 (10.8) |
| 2-vessel CAD, n (%) | 7 (24.1) | 99 (27.6) | 11 (16.9) |
| 3-vessel CAD, n (%) | 11 (37.9) | 83 (23.1) | 8 (12.3) |
| Coronary revascularisation in 30days, n (%) | 24 (17.5) | 277 (42.5) | <0.001 | 13 ( 0.3) | <0.001 |
| PCI, n (%) | 21 (15.3) | 249 (38.2) | <0.001 | 7 ( 0.2) | <0.001 |
| Coronary bypass surgery, n (%) | 3 ( 2.2) | 28 ( 4.3) | 0.361 | 6 ( 0.2) | <0.001 |

**eTable 4** Results from coronary angiography performed in a subgroup (n=212) of patients with unstable angina compared to patients with non-ST-elevation myocardial infarction, with lesion morphology characterised using the Ambrose criteria. Data shown as median with interquartile range (IQR) or counts with percentage. Seven cases were not adjudicable

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  |  | Unstable angina n = 84 | NSTEMI n = 128 | p-value |
| Stenosis %, median (IQR) | | 95 (82,5-99) | 90 (75-95) | 0.01 |
| Lesion morphology | |  |  | 0.49 |
|  | Concentric | 22 (27%) | 22 (18%) |
|  | Eccentric Typ I | 12 (14%) | 13 (11%) |
|  | Eccentic Typ II | 25 (30%) | 47 (39%) |
|  | Multiple Irregularities | 13 (16%) | 21 (17%) |
|  | Totally occluded | 11 (13%) | 19 (16%) |
| Filling defect | | 10 (13%) | 24 (19%) | 0.34 |
| Plaque ulceration | | 13 (17%) | 30 (24%) | 0.29 |
| Plaque irregularity | | 39 (51%) | 68 (54%) | 0.66 |
| TIMI flow < 3 | | 19 (24%) | 33 (26%) | 0.87 |

**eTable 5** Sensitivity analysis showing the incidence of prognostic endpoints all-cause death and future non-fatal acute myocardial infarction (AMI) in unstable angina, stratified according to those without vs with any hs-cTn measurement >99th percentile, calculated using Kaplan Meier estimates for 1-year

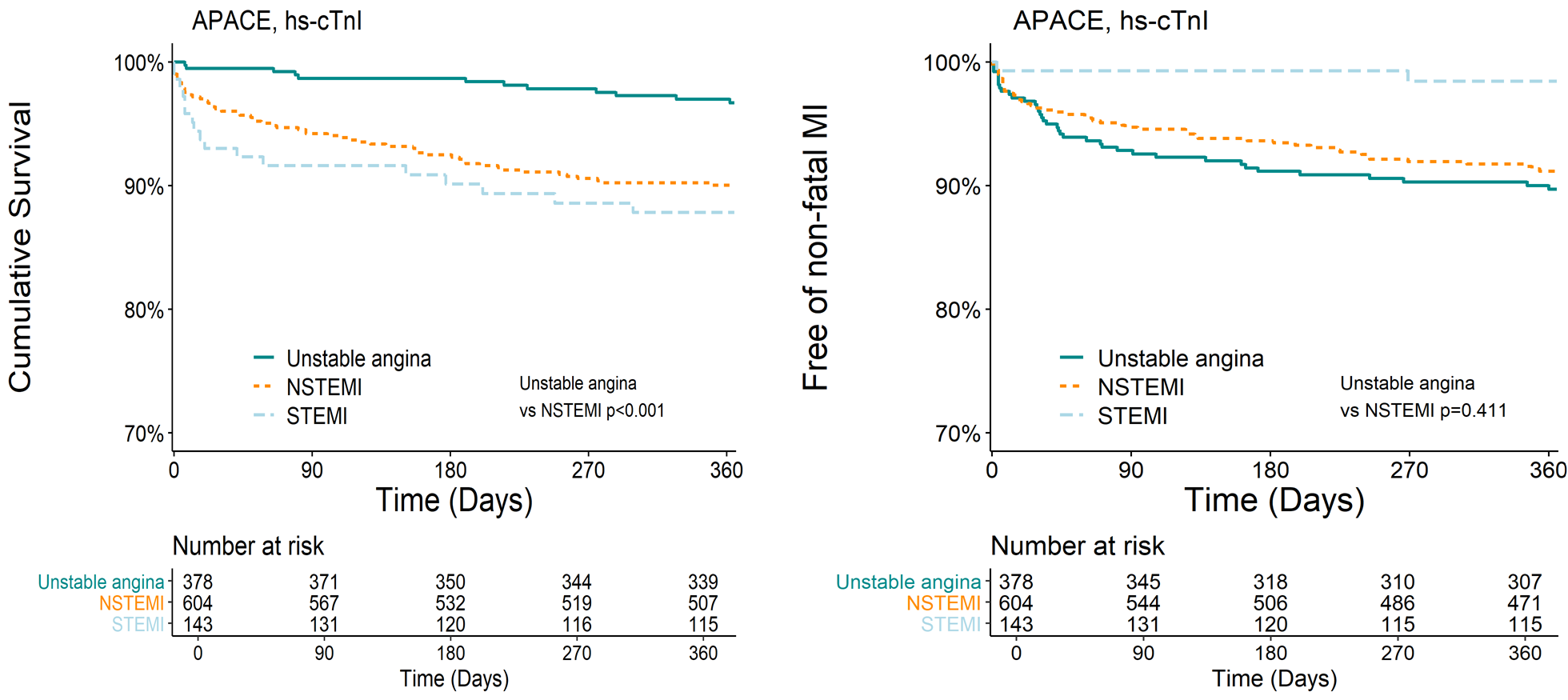
|  |  |  |
| --- | --- | --- |
|  | **Unstable angina <99th percentile** | **Unstable angina ≥99th percentile** |
| All-cause death in 30 days | 1 (0.3%, 0.0-3.8) | 3 (1.5%, 0-3.2) |
| All-cause death in 1 year | 9 (2.6%, 0.9-4.3) | 18 (9.5%, 5.2-13.5) |
| Future AMI in 30 days | 8 (2.3%, 0.7-3.8) | 13 (6.5%, 3.0-9.1) |
| Future AMI in 1 year | 20 (5.7%, 3.3-8.1) | 26 (14.6%, 9.5-19.5) |

# Supplemental Figures and Figure legends

**eFigure 1**Patient flow chart for High-STEACS. All patients enrolled into APACE were included in this analysis.

******

**eFigure 2 Sensitivity analysis** showing 1-year survival (Panel left) and 1-yearsurvival free from future non-fatal myocardial infarction (Panel right) ofpatients stratified according to final adjudicated diagnoses adjudicated with hs-cTnI in APACE. P-values were calculated using the Log-rank test; NSTEMI = non-ST-segment elevation myocardial infarction; STEMI = ST-segment elevation myocardial infarction

******

# Supplemental references

1 Vasile VC, Saenger AK, Kroning JM, *et al.* Biological and analytical variability of a novel high-sensitivity cardiac troponin T assay. *Clin Chem* 2010;**56**:1086–90. doi:10.1373/clinchem.2009.140616

2 Wu AHBB, Lu QA, Todd J, *et al.* Short- and long-term biological variation in cardiac troponin I measured with a high-sensitivity assay: implications for clinical practice. *Clin Chem* 2009;**55**:52–8. doi:10.1373/clinchem.2008.107391

3 Apple FS, Pearce LA, Smith SW, *et al.* Role of monitoring changes in sensitive cardiac troponin I assay results for early diagnosis of myocardial infarction and prediction of risk of adverse events. *Clin Chem* 2009;**55**:930–7. doi:10.1373/clinchem.2008.114728

4 Hammarsten O, Fu MLXX, Sigurjonsdottir R, *et al.* Troponin T percentiles from a random population sample, emergency room patients and patients with myocardial infarction. *Clin Chem* 2012;**58**:628–37. doi:10.1373/clinchem.2011.171496

5 Reichlin T, Twerenbold R, Maushart C, *et al.* Risk stratification in patients with unstable angina using absolute serial changes of 3 high-sensitive troponin assays. *Am Heart J* 2013;**165**:371–8.e3. doi:10.1016/j.ahj.2012.11.010

6 Agarwal SK. Sources of variability in measurements of cardiac troponin T in a community-based sample: the atherosclerosis risk in communities study. *Clin Chem* 2011;**57**:891–7. doi:dx.doi.org/10.1373/clinchem.2010.159350

7 Giannitsis E, Kurz K, Hallermayer K, *et al.* Analytical Validation of a High-Sensitivity Cardiac Troponin T Assay. *Clin Chem* 2010;**56**:254–61. doi:10.1373/clinchem.2009.132654

8 Mills NL, Churchhouse AMD, Lee KK, *et al.* Implementation of a sensitive troponin I assay and risk of recurrent myocardial infarction and death in patients with suspected acute coronary syndrome. *JAMA* 2011;**305**:1210–6. doi:10.1001/jama.2011.338

9 Mills NL, Lee KK, McAllister DA, *et al.* Implications of lowering threshold of plasma troponin concentration in diagnosis of myocardial infarction: cohort study. *BMJ* 2012;**344**:e1533. doi:10.1136/bmj.e1533

10 Shah AS V, Newby DE, Mills NL. High sensitivity cardiac troponin in patients with chest pain. 2013;**347**:f4222.

11 Shah AS V, Griffiths M, Lee KK, *et al.* High sensitivity cardiac troponin and the under-diagnosis of myocardial infarction in women: prospective cohort study. *BMJ* 2015;**350**:g7873. doi:10.1136/bmj.g7873

12 Chin CWL, Shah AS V, McAllister DA, *et al.* High-sensitivity troponin I concentrations are a marker of an advanced hypertrophic response and adverse outcomes in patients with aortic stenosis. *Eur Heart J* 2014;**35**:2312–21. doi:10.1093/eurheartj/ehu189

13 Shah AS V, Chin CWL, Vassiliou V, *et al.* Left ventricular hypertrophy with strain and aortic stenosis. *Circulation* 2014;**130**:1607–16. doi:10.1161/CIRCULATIONAHA.114.011085

14 Thygesen K, Alpert JS, Jaffe AS, *et al.* Third universal definition of myocardial infarction. *Eur Heart J* 2012;**33**:2551–67. doi:10.1093/eurheartj/ehs184

15 Ambrose JA, Almeida OD, Sharma SK, *et al.* Angiographic evolution of intracoronary thrombus and dissection following percutaneous transluminal coronary angioplasty (the Thrombolysis and Angioplasty in Unstable Angina [TAUSA] trial). *Am J Cardiol* 1997;**79**:559–63.

16 Austin PC, Lee DS, Fine JP. Introduction to the Analysis of Survival Data in the Presence of Competing Risks. *Circulation* 2016;**133**:601–9. doi:10.1161/CIRCULATIONAHA.115.017719

17 Boeddinghaus J, Twerenbold R, Nestelberger T, *et al.* Clinical Validation of a Novel High-Sensitivity Cardiac Troponin I Assay for Early Diagnosis of Acute Myocardial Infarction. *Clin Chem* 2018;**64**:1347–60. doi:10.1373/clinchem.2018.286906