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**Appendix 1.** TIMI score strategy

|  |  |
| --- | --- |
| **TIMI score** | |
| Age ≥65 years  ≥3 risk factors for coronary artery disease\*  Use of Aspirin in the last 7 days†  Previous coronary stenosis ≥50%  ≥2 anginal events in last 24 h or persistent discomfort | 1  1  1  1  1 |
| **RULE-OUT REQUIRES:** | |
| **TIMI Score ≤1 points**  *AND*  **No sign of acute ischemia on the ECG**  *AND*  **Hs-cTnT ≤14 ng/L ≥6h after symptom onset** | |

Abbreviations as in table 1.

\* Risk factors defined as family history of coronary artery disease, hypertension, hypercholesterolemia, diabetes, or being a current smoker

† Defined as the patient reporting taking Aspirin

**Appendix 2.** EDACS strategy

|  |  |
| --- | --- |
| **EDACS** | |
| **Age** |  |
| 18-45 | +2 |
| 46-50 | +4 |
| 51-55 | +6 |
| 56-60 | +8 |
| 61-65 | +10 |
| 66-70 | +12 |
| 71-75 | +14 |
| 76-80 | +16 |
| 81-85 | +18 |
| 86+ | +20 |
|  |  |
| **Male sex** | +6 |
| **Aged 18-50 years and either** |  |
| known coronary artery disease\* or | +4 |
| ≥3 risk factors† |  |
| **Symptoms and signs** |  |
| Diaphoresis | +3 |
| Radiates to arm or shoulder | +5 |
| Pain worsened with inspiration | -4 |
| Pain is reproduced by palpation | -6 |
| **RULE-OUT REQUIRES:** | |
| **EDACS < 16 points**  *AND*  **No sign of acute ischemia on the ECG**  *AND*  **Hs-cTnT ≤14 ng/L ≥6h after symptom onset** | |

Abbreviations as in table 1.

\*Coronary artery disease defined as previous myocardial infarction, coronary artery bypass graft or percutaneous coronary intervention; †Risk factors defined as family history of coronary artery disease, hypertension, hypercholesterolemia, diabetes, or being a current smoker

**Appendix 3.** HEART score strategy

|  |  |  |
| --- | --- | --- |
| **HEART Score** | | |
| **History\*** | Highly suspicious | 2 |
|  | Moderately suspicious | 1 |
|  | Slightly or nonsuspicious | 0 |
|  |  |  |
| **ECG** | Acute ischemia | 2 |
|  | LBBB, RBBB, LVH, PM | 1 |
|  | None of the above | 0 |
|  |  |  |
| **Age** | ≥65 years | 2 |
|  | 45 – 65 years | 1 |
|  | <45 years | 0 |
|  |  |  |
| **Risk factors†** | ≥3 risk factors, or history of atherosclerotic disease ‡ | 2 |
|  | 1 or 2 risk factors | 1 |
|  | No risk factors | 0 |
|  |  |  |
| **Troponin** | > 42 ng/L | 2 |
|  | 15-42 ng/L | 1 |
|  | ≤ 14 ng/L | 0 |
| **RULE-OUT REQUIRES:** | | |
| **HEART Score ≤3 points**  *AND*  **Hs-cTnT ≤14 ng/L ≥6h after symptom onset** | | |

LBBB = left bundle branch block; RBBB = right bundle branch block; LVH = left ventricle hypertrophy; PM = paced rhythm. Other abbreviations as in table 1.

\* A score of 0 was given if the history was deemed as low/very low risk for ACS, a score of 1 if assessed as intermediate risk, and a score of 2 if assessed as high risk; † Risk factors were defined as diabetes, current smoker, hypertension, hypercholesterolemia, BMI≥30, and family history of coronary artery disease;‡ History of atherosclerotic disease defined as peripheral arterial disease, myocardial infarction, past coronary revascularization procedure, or stroke.

**Appendix 4.** Definition of unstable angina (UA)

|  |
| --- |
| The diagnosis of UA required normal or slightly elevated hs-cTnT levels without a significant rise or fall  *and*  A history consistent with UA defined as rest angina, new-onset angina of Canadian Cardiovascular Society class ≥3, or increasing angina  *and*  At least one of the following:   * stenosis ≥70% in a vessel on coronary angiography * positive stress test if no angiography was performed * new ischemic ECG changes in patients managed without stress test or angiography   An UA diagnosis could also be adjudicated in patients who were discharged after MI was ruled out and were subsequently diagnosed with MI or suffered death of cardiac or unknown cause within 30 days from the index visit. |

**Appendix 5. Comparison between included and excluded patients**

|  |  |  |  |
| --- | --- | --- | --- |
| **Baseline characteristics** | **Patients included**  **N = 966** | **Patients excluded**  **N = 201** | **P-value** |
| Age, y | 60.8 (17.3) | 59.2 (18.9) | 0.24 |
| Female gender | 438 (45.3) | 91 (45.3) | 0.99 |
| Medical history, n. (%) |  |  |  |
| Diabetes | 138 (14.3) | 24 (11.9) | 0.38 |
| Hypertension | 422 (43.7) | 84 (41.8) | 0.62 |
| COPD | 71 (7.3) | 17 (8.5) | 0.59 |
| MI | 196 (20.3) | 38(18.9) | 0.66 |
| CABG or PCI | 201 (20.8) | 38 (18.9) | 0.54 |
| Stroke/TIA | 86 (8.9) | 19 (9.5) | 0.80 |
| Other risk factors, n. (%) |  |  |  |
| Family history of CAD\* | 230 (23.8) | 35(17.4) | 0.16 |
| Current or previous  smoker | 549 (56.8) | 108 (53.7) | 0.60 |
| BMI ≥30 kg/m2 | 208 (21.5) | 36 (17.9) | 0.83 |
| Medication, n. (%) |  |  |  |
| Aspirin | 279 (28.9) | 56 (27.9) | 0.77 |
| Warfarin or NOAC | 101 (10.5) | 15 (7.5) | 0.20 |
| Nitrates | 230 (23.8) | 39 (19.4) | 0.18 |
| Statin | 294 (30.4) | 55 (27.4) | 0.39 |

Values are mean (SD) or n (%). Abbreviations as in Table 1.

**Appendix 6: 2x2 tables of the different rule-out strategies for an outcome of MI**

|  |  |  |  |
| --- | --- | --- | --- |
| **Rule-out strategy** | **MI**  **(n=30)** | **No MI**  **(n=468)** | **Total**  **(n=498)** |
| Troponin**\*** |  |  |  |
| Positive | 29 | 97 | 126 |
| Negative | 1 | 371 | 372 |
| Troponin\*  + ECG† |  |  |  |
| Positive | 29 | 105 | 134 |
| Negative | 1 | 363 | 364 |
| Troponin\* + ECG†  + Patient history‡ |  |  |  |
| Positive | 30 | 123 | 153 |
| Negative | 0 | 345 | 345 |
| Troponin\* + ECG†  + TIMI score§ |  |  |  |
| Positive | 30 | 238 | 268 |
| Negative | 0 | 230 | 230 |
| Troponin\* + ECG†  + EDACS score ‖ |  |  |  |
| Positive | 29 | 188 | 217 |
| Negative | 1 | 280 | 281 |
| Troponin\* + HEART score¶ |  |  |  |
| Positive | 30 | 188 | 218 |
| Negative | 0 | 280 | 280 |
| Troponin\*  + GRACE score#  + pain free |  |  |  |
| Positive | 30 | 367 | 397 |
| Negative | 0 | 101 | 101 |
| The numbers represent the following |  |  |  |
| Strategy Positive | True Positive | False Positive | Test positive |
| Strategy Negative | False Negative | True Negative | Test negative |

\*Defined as high sensitive cardiac troponin T ≤14 ng/L ≥6h after symptom onset; † Defined as ECG showing no signs of acute ischemia; ‡ Defined as patient history not assessed as high risk; § Defined as TIMI score ≤1; ‖

Defined as EDACS <16; ¶ Defined as HEART score ≤3; # Defined as GRACE score <140.

Abbreviations as in Table 1.

**Appendix 7.** Diagnostic accuracy of rule-out strategies for an outcome of 30-day MACE including urgent/emergency PCI/CABG

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Rule-out strategy** | **Sensitivity**  **% (95% CI)** | **Specificity**  **% (95% CI)** | **NPV**  **% (95% CI)** | **LR-**  **(95% CI)** | **MACE missed n** |
| Hs-cTnT**\*** | 77.6 (63.4-88.2) | 80.4 (76.4-84.0) | 97.0 (94.8-98.5) | 0.28 (0.17-0.47) | 11 |
| Hs-cTnT**\***  + ECG† | 79.6 (65.7-89.8) | 78.8 (74.8-82.5) | 97.3 (95.0-98.7) | 0.26 (0.15-0.45) | 10 |
| Hs-cTnT**\*** + ECG†  + Patient history‡ | 93.9 (83.1-98.7) | 76.2 (72.0-80.0) | 99.1 (97.5-99.8) | 0.08 (0.03-0.24) | 3 |
| Hs-cTnT**\*** + ECG†  + TIMI§ | 98.0 (89.2-100) | 51.0 (46.3-55.7) | 99.6 (97.6-100) | 0.04 (0.01-0.28) | 1 |
| Hs-cTnT**\*** + ECG†  + EDACS‖ | 93.9 (83.1-98.7) | 61.9 (57.3-66.4) | 98.9 (96.9-99.8) | 0.10 (0.03-0.30) | 3 |
| Hs-cTnT**\*** + HEART¶ | 100 (92.8-100) | 62.4 (57.7-66.9) | 100 (98.7-100) | 0.00 | 0 |
| Hs-cTnT**\***  + GRACE#  + pain-free | 91.8 (80.4-97-7) | 21.6 (17.9-25.7) | 96.0 (90.2-98.9) | 0.38 (0.15-1.0) | 4 |

MACE = major adverse cardiac event; UA = unstable angina; Other abbreviations as in table 1 and 2.

\*Defined as high sensitivity cardiac troponin T ≤14 ng/L ≥6h after symptom onset; † Defined as ECG showing no signs of acute ischemia; ‡ Defined as patient history not assessed as high risk; § Defined as TIMI score ≤1; ‖ Defined as EDACS <16; ¶ Defined as HEART score ≤3; # Defined as GRACE score <140.

**Appendix 8.** Diagnostic accuracy of a hs-cTnT ≤14 ng/l based on time of symptom onset to 0h hs-cTnT measurement for an outcome of index visit MI.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Symptom onset to 0h hs-cTnT, h** | **n (%)** | **NPV % (95% CI)** | **Proportion ruled out, n (%)** | | |
| **≥1** | 904 (93.6) | 98.5 (97.2-99.3) | 662 (68.5) |  |
| **≥2** | 825 (85.4) | 98.7 (97.4-99.4) | 602 (62.3) |  |
| **≥3** | 724 (74.9) | 98.9 (97.6-99.6) | 529 (54.8) |  |
| **≥4** | 622 (64.4) | 99.6 (98.4-100) | 461 (47.7) |  |
| **≥5** | 544 (56.3) | 99.8 (98.6-100) | 407 (42.1) |  |
| **≥6** | 498 (51.6) | 99.7 (98.5-100) | 372 (38.5) |  |
| **≥7** | 461(47.7) | 99.7 (98.4-100) | 344 (35.6) |  |
| **≥8** | 430 (44.5) | 99.7 (98.3 -100) | 323 (33.4) | |  | | --- | |  | |
| **≥9** | 404 (41.8) | 99.7 (98.2 -100) | 305 (31.6) |  |
| **≥10** | 382 (39.5) | 99.7 (98.1-100) | 294 (30.4) |  |
| **≥11** | 361 (37.4) | 99.6 (98.0-100) | 279 (28.9) |  |
| **≥12** | 351 (36.3) | 99.6 (98.0-100) | 271 (28.1) |  |

Abbreviations as in table 1 and 2.