Supplementary material

Analytical details

The Roche Diagnostics hs-cTnT assay has a limit of blank (LoB) of 3 ng/L, a limit of detection (LoD) of 5 ng/L and a CVA of 10% or lower for concentrations >4.5 ng/L. The 99th percentile URL is 9.0 ng/L in women and 16.8 ng/L in men. The hs-TnI assay by Abbott had a LoD of 1.9 ng/L and a 10% coefficient of variation at a concentration >5.2 ng/L. The 99th percentile URL is 15.6 ng/L in women and 34.2 ng/L in men. The cTnT assay (Roche) and the cTnI assay by Abbott target capture and detection epitopes that are midmolecular and adjacent; cTnT capture epitope at aa 125-131 and a single-detection epitope at aa 136-147; cTnI Abbott capture epitope at aa 24 to 40 and a single-detection epitope at aa 41 to 49 (27, 28). The hs-cTnI assay by Siemens has a LoD of 1.6 ng/L and a 10% coefficient of variation >6 ng/L. The 99th percentile URL is 38.6 ng/L in women and 53.5 ng/L in men. The cTnI Siemens assay feature a capture antibody targeting a central epitope at amino acids (aa) 41-50 and two detection antibodies targeting a central epitope at aa 29-34 as well as a distal epitope at aa 171-190.

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| **Table S1.** Number of presumably healthy adults used to determine normal range and the identified percentiles within normal range in women/men, ng/L. Percentiles were estimated using the non-parametric method. | | | | | | |
| Assay | n  women | n  men | 99th percentile | 97.5th percentile | 95th percentile | 90th percentile |
| Roche cobas | 265 | 266 | 9.0/16.8 | 8.4/13.3 | 6.9/11.3 | 6.1/9.2 |
| Abbott Architect | 765 | 766 | 15.6/34.2 | 14.1/27.0 | 8.0/13.0 | 4.8/7.6 |
| Siemens Atellica | 1007 | 994 | 38.6/53.5 | 17.8/26.3 | 10.1/15.9 | 6.3/9.2 |

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| **Table S2a.** Correlation (r) between cTn assays (0-hour samples) grouped by presence or absence of chronic myocardial injury. | | | | | | | |
|  | | CMIa | | No CMI | | All | |
|  |  | n | r | n | r | n | r |
| cTnI Abbott vs. cTnI Siemens | | | |  |  |  |  |
|  | Women | 111 | 0.808  (0.696-0.920) | 350 | 0.716  (0.643-0.790) | 461 | 0.844  (0.795-0.893) |
|  | Men | 107 | 0.793  (0.675-0.911) | 590 | 0.851  (0.808-0.894) | 697 | 0.888  (0.854-0.922) |
|  | All | 218 | 0.821  (0.744-0.898) | 940 | 0.824  (0.787-0.860) | 1158 | 0.876  (0.849-0.904) |
| cTnT Roche vs. cTnI Abbott | | | |  |  |  |  |
|  | Women | 111 | 0.596  (0.444-0.749) | 407 | 0.643  (0.568-0.718) | 518 | 0.741  (0.683-0.799) |
|  | Men | 107 | 0.588  (0.432-0.745) | 658 | 0.744  (0.693-0.795) | 765 | 0.802  (0.759-0.844) |
|  | All | 218 | 0.641  (0.538-0.744) | 1065 | 0.724  (0.683-0.766) | 1283 | 0.785  (0.751-0.819) |
| cTnT Roche vs. cTnI Siemens | | | |  |  |  |  |
|  | Women | 111 | 0.475  (0.308-0.642) | 351 | 0.424  (0.329-0.519) | 462 | 0.671  (0.603-0.738) |
|  | Men | 107 | 0.428  (0.253-0.603) | 593 | 0.658  (0.597-0.719) | 700 | 0.742  (0.692-0.792) |
|  | All | 218 | 0.510  (0.395-0.626) | 944 | 0.617  (0.567-0.667) | 1162 | 0.724  (0.684-0.763) |
| All correlation values are significant with a p-value <0.001. cTn indicates cardiac troponin; CMI, chronic myocardial injury; n, number of patients; r, correlation measured by Pearson´s correlation test.  aStable cTn concentrations with at least one value >99th percentile measured by any of the three cTn assays. | | | | | | | |

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| **Table S2b.** Correlation (r) between cTn assays grouped by adjudicated diagnoses. | | | | | | | | | |
|  | | Coronary artery diseasea | | Other cardiac diseasesb | | Non-cardiac chest painc | | All | |
|  |  | n | r | n | r | n | r | n | r |
| cTnI Abbott vs. cTnI Siemens | | | |  |  |  |  |  |  |
|  | Women | 61 | 0.835  (0.691-0.978) | 19 | 0.987  (0.906-1.068) | 381 | 0.801  (0.741-0.862) | 461 | 0.844  (0.795-0.893) |
|  | Men | 137 | 0.943  (0.887-1.000) | 53 | 0.858  (0.714-1.003) | 507 | 0.859  (0.815-0.904) | 697 | 0.888  (0.854-0.922) |
|  | All | 198 | 0.917  (0.861-0.973) | 72 | 0.896  (0.790-1.002) | 888 | 0.841  (0.806-0.877) | 1158 | 0.876  (0.849-0.904) |
| cTnT Roche vs. cTnI Abbott | | |  |  |  |  |  |  |  |
|  | Women | 66 | 0.625  (0.431-0.820) | 20 | 0.953  (0.803-1.103) | 432 | 0.689  (0.620-0.757) | 518 | 0.741  (0.683-0.799) |
|  | Men | 147 | 0.820  (0.727-0.914) | 60 | 0.861  (0.728-0.995) | 558 | 0.730  (0.673-0.787) | 765 | 0.802  (0.759-0.844) |
|  | All | 213 | 0.770  (0.683-0.856) | 80 | 0.888  (0.784-0.992) | 990 | 0.717  (0.673-0.760) | 1283 | 0.785  (0.751-0.819) |
| cTnT Roche vs. cTnI Siemens | | | |  |  |  |  |  |  |
|  | Women | 61 | 0.635  (0.434-0.836) | 19 | 0.941  (0.767-1.114) | 382 | 0.582  (0.500-0.664) | 462 | 0.671  (0.603-0.738) |
|  | Men | 137 | 0.766  (0.656-0.875) | 53 | 0.825  (0.667-0.984) | 510 | 0.659  (0.594-0.725) | 700 | 0.742  (0.692-0.792) |
|  | All | 198 | 0.741  (0.646-0.835) | 72 | 0.858  (0.735-0.980) | 892 | 0.635  (0.584-0.686) | 1162 | 0.724  (0.684-0.763) |
| All correlation values are significant with a p-value <0.001. cTn indicates cardiac troponin; n, number of patients; r, correlation measured by Pearson´s correlation test.  aUnstable or stable angina pectoris.  bNon-coronary cardiac diseases like pericarditis, myocarditis, Takotsubo cardiomyopathy, heart failure, arrythmias or valve disorders, without dynamic change in cTn values.  cMyalgia, esophageal disease, abdominal diseases, respiratory infections/diseases, pleural effusion, pulmonary embolism, and other non-cardiac conditions, without dynamic change in cTn values. | | | | | | | | | |

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| **Table S3.** Clinical characteristics of patients with CMI diagnosed by any assay, the cTnT assay or a cTnI assay. | | | |
|  | Any assay (n=218) | cTnT Roche assay only (n=152) | cTnI assay only (Abbott and/or Siemens, n=40) |
| Age, median | 76 (68-84) | 76 (71-84) | 70 (63-84) |
| Female gender (%) | 111 (50.9%) | 84 (55.3%) | 11 (27.5%)a |
| **Cardiovascular risk factors** | |  |  |
| Obesityb (%) | 27 (25.7%) | 19 (23.8%) | 6 (40.0%) |
| Active smoker (%) | 32 (14.7%) | 23 (15.1%) | 4 (10.0%) |
| Former smoker (%) | 102 (46.8%) | 75 (49.3%) | 19 (47.5%) |
| Hyperlipidemia (%) | 58 (26.6%) | 45 (29.6%) | 6 (15.0%) |
| Diabetes mellitus (%) | 44 (20.2%) | 29 (19.1%) | 10 (25.0%) |
| Insulin-dependent (%) | 19 (8.7%) | 11 (7.2%) | 5 (12.5%) |
| Hypertension (%) | 122 (56.0%) | 94 (61.8%) | 15 (37.5%)a |
| Family history of CAD (%) | 22 (10.1%) | 14 (9.2%) | 5 (12.5%) |
| **Medical history** |  |  |  |
| Previous AMI (%) | 64 (29.4%) | 44 (28.9%) | 13 (32.5%) |
| Previous PCI (%) | 55 (25.2%) | 37 (24.3%) | 14 (35.0%) |
| Previous CABG (%) | 31 (14.2%) | 21 (13.8%) | 7 (17.5%) |
| Atrial fibrillation (%) | 53 (24.3%) | 38 (25.0%) | 8 (20.0%) |
| Previous stroke (%) | 12 (5.5%) | 12 (7.9%) | 0 (0.0%) |
| Chronic kidney disease (%) | 79 (36.2%) | 54 (35.5%) | 13 (32.5%) |
| Peripheral arterial disease (%) | 10 (4.6%) | 8 (5.3%) | 2 (5.0%) |
| Known heart failure (%) | 21 (9.6%) | 10 (6.6%) | 6 (15.0%) |
| **Clinical and laboratory parameters** | |  |  |
| Systolic blood pressure, mmHg | 147 (144-150) | 148 (144-151) | 143 (134-150) |
| Diastolic blood pressure, mmHg | 82 (79-85) | 82 (79-84) | 82 (77-86) |
| Pulse, bpm | 78 (75-80) | 77 (74-80) | 79 (72-85) |
| Hemoglobin, g/dL | 13.5 (13.3-13.7) | 13.5 (13.3-13.8) | 13.7 (13.1-14.3) |
| Glucose, mmol/L | 6.9 (6.6-7.2) | 6.7 (6.4-7.0) | 7.3 (6.4-8.1) |
| CRP, mg/L, median | 2.0 (0.9-4.5) | 2.0 (0.6-4.0) | 2.0 (0.9-5.0) |
| proBNP, ng/L, median | 88 (32-310) | 82 (33-214) | 199 (39-984)a |
| eGFR, ml/min/1.37m2 | 65.9 (62.7-69.0) | 66.2 (63.0-69.5) | 71.7 (62.5-81.0) |
| **Ejection fraction** |  |  |  |
| >50% (%) | 66 (71.0%) | 43 (71.7%) | 15 (71.4%) |
| 30-49% (%) | 14 (15.1%) | 9 (15.0%) | 4 (19.0%) |
| <30% (%) | 13 (14.0%) | 8 (13.3%) | 2 (9.5%) |
| **Symptom triggers** |  |  |  |
| Dependent on position (%) | 14 (6.4%) | 9 (5.9%) | 5 (12.5%) |
| Dependent on respiration (%) | 21 (9.6%) | 13 (8.6%) | 4 (10.0%) |
| Dependent on palpation (%) | 22 (10.1%) | 18 (11.8%) | 1 (2.5%) |
| CMI indicates chronic myocardial injury; AMI, acute myocardial infarction; PCI, percutaneous coronary intervention, CABG, coronary artery bypass grafting.  aSignificantly different compared to patients with CMI diagnosed by the cTnT assay only; p-value <0.05.  bBMI>30, measured in 48.2% of patients (105 patients in total; 80 identified with cTnT only and 15 identified with a cTnI assay only)  ceGFR <60 ml/min/1.37m2  dMeasured in 42.7% of patients (93 patients in total; 60 identified with cTnT only and 21 identified with a cTnI assay only) | | | |

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| **Table S4.** Difference in area under the receiver operating characteristics (AUC-ROC) curve for the three endpoints with cTn as continuous variables. | | | |
|  | cTnI (Abbott) vs.  cTnI (Siemens) | cTnT (Roche) vs.  cTnI (Abbott) | cTnT (Roche) vs.  cTnI (Siemens) |
| **Primary endpointa** |  |  |  |
| AUC women | 0.774 (0.733-0.812)  vs.  0.702 (0.657-0.743)  p=0.041 | 0.685 (0.640-0.727)  vs.  0.774 (0.733-0.812) p=0.021 | 0.685 (0.640-0.727)  vs.  0.702 (0.657-0.743)  p=0.757 |
| AUC men | 0.682 (0.645-0.716)  vs.  0.628 (0.591-0.664) p<0.001 | 0.689 (0.653-0.724)  vs.  0.682 (0.645-0.716)  p=0.758 | 0.689 (0.653-0.724)  vs.  0.628 (0.591-0.664) p=0.010 |
| AUC all | 0.718 (0.691-0.744)  vs.  0.662 (0.634-0.689) p<0.001 | 0.697 (0.670-0.724)  vs.  0.718 (0.691-0.744)  p=0.316 | 0.697 (0.670-0.724)  vs.  0.662 (0.634-0.689) p=0.123 |
| **Secondary endpointb** |  |  |  |
| AUC women | 0.824 (0.786-0.858)  vs.  0.769 (0.727-0.807)  p=0.016 | 0.800 (0.761-0.836)  vs.  0.824 (0.786-0.858)  p=0.394 | 0.800 (0.761-0.836)  vs.  0.769 (0.727-0.807)  p=0.357 |
| AUC men | 0.720 (0.685-0.753)  vs.  0.674 (0.638-0.709)  p<0.001 | 0.745 (0.711-0.777)  vs.  0.720 (0.685-0.753)  p=0.230 | 0.745 (0.711-0.777)  vs.  0.674 (0.638-0.709)  p<0.001 |
| AUC all | 0.762 (0.736-0.786)  vs.  0.714 (0.687-0.740)  p<0.001 | 0.770 (0.745-0.794)  vs.  0.762 (0.736-0.786)  p=0.600 | 0.770 (0.745-0.794)  vs.  0.714 (0.687-0.740)  p=0.001 |
| **Tertiary endpointc** |  |  |  |
| AUC women | 0.836 (0.798-0.868)  vs.  0.768 (0.726-0.806)  P=0.058 | 0.880 (0.846-0.908)  vs.  0.836 (0.798-0.868)  p=0.072 | 0.880 (0.846-0.908)  vs.  0.768 (0.726-0.806)  p=0.002 |
| AUC men | 0.766 (0.733-0.798)  vs.  0.732 (0.697-0.764)  p=0.034 | 0.808 (0.776-0.836)  vs.  0.766 (0.733-0.798)  p=0.061 | 0.808 (0.776-0.836)  vs.  0.732 (0.697-0.764)  p=0.005 |
| AUC all | 0.796 (0.771-0.819)  vs.  0.750 (0.724-0.775)  p=0.005 | 0.836 (0.813-0.857)  vs.  0.796 (0.771-0.819)  p=0.018 | 0.836 (0.813-0.857)  vs.  0.750 (0.724-0.775)  p<0.001 |
| All differences with p-value <0.05 are highlighted. AUC indicates area under the curve; cTnT, cardiac troponin T; cTnI, cardiac troponin T, w, women; m, men, p, p-value for difference.  aCardiovascular mortality, acute myocardial infarction or revascularization.  bAll-cause mortality, AMI, revascularization or hospitalization due to heart failure or stroke.  cAll-cause mortality. | | | |

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| **Table S5.** Prognostic precision of high-sensitivity cardiac troponins at different percentile cutoff values and limit of detection provided by manufacturers for the primary endpoint of CV death, AMI or revascularization. | | | | | | | | | | | | |
|  |  | True pos | False pos | True neg | False neg | Odds ratio | NPV  (95% CI) | Sens  (95% CI) | PPV  (95% CI) | Spes  (95% CI) | >Perc.a | AUC |
| Troponin T (Roche) | | | | | | | | | | | | |
|  | 99th percentile  9.0/16.8 ng/L (w/m) | 31 | 176 | 878 | 62 | 2.5  (1.6-4.0) | 93.4  (92.5-94.3) | 33.3  (23.9-43.9) | 15.0  (11.4-19.5) | 83.3  (80.9-85.5) | 18.0 | 0.583  (0.554-0.612) |
|  | 97.5th percentile  8.4/13.3 ng/L (w/m) | 45 | 221 | 833 | 48 | 3.5  (2.3-5.4) | 94.6  (93.4-95.5) | 48.4  (37.9-59.0) | 16.9  (13.8.20.5) | 79.0  (76.5-81.5) | 23.2 | 0.637  (0.609-0.665) |
|  | 95th percentile  6.9/11.3 (w/m) | 51 | 291 | 763 | 42 | 3.2  (2.1-4.9) | 94.8  (93.5-95.8) | 54.8  (44.2-65.2) | 14.9  (12.4-17.7) | 72.4  (69.6-75.1) | 29.8 | 0.636  (0.608-0.664) |
|  | 90th percentile  6.1/9.2 ng/L (w/m) | 58 | 334 | 720 | 35 | 3.6  (2.3-5.5) | 95.4  (94.0-96.4) | 62.4  (51.7-72.2) | 14.8  (12.6-17.2) | 68.3  (65.4-71.1) | 34.2 | 0.653  (0.625-0.681) |
|  | Limit of detection  5 ng/L (all) | 80 | 664 | 390 | 13 | 3.6  (2.0-6.6) | 96.8  (94.7-98.0) | 86.0  (77.3-92.3) | 10.7  (9.9-11.7) | 37.0  (34.1-40.0) | 64.9 | 0.615  (0.586-0.643) |
| Troponin I (Abbott) | | | | | | | | | | | | |
|  | 99th percentile  15.6/34.2 ng/L (w/m) | 9 | 37 | 1017 | 84 | 2.9  (1.4-6.3) | 92.4 (91.9-92.8) | 9.7  (4.5-17.6) | 19.6  (10.8-32.8) | 96.5  (95.2-97.5) | 4.0 | 0.531  (0.501-0.560) |
|  | 97.5th percentile  14.1/27.0 ng/L (w/m) | 11 | 49 | 1005 | 82 | 2.8  (1.4-5.5) | 92.5  (91.9-93.0) | 11.8  (6.1-20.2) | 18.3  (10.8-29.4) | 95.4  (93.9-96.5) | 5.2 | 0.536  (0.507-0.565) |
|  | 95th percentile  8.0/13.0 ng/L (w/m) | 19 | 113 | 941 | 74 | 2.1  (1.2-3.7) | 92.7  (92.0-93.4) | 20.4  (12.8-30.1) | 14.4  (9.8-20.7) | 89.3  (87.3-91.1) | 11.5 | 0.549  (0.519-0.578) |
|  | 90th percentile  4.8/7.6 ng/L (w/m) | 38 | 199 | 855 | 55 | 3.0  (1.9-4.6) | 94.0  (92.9-94.9) | 40.9  (30.8-51.5) | 16.0  (12.7-20.1) | 81.1  (78.6-83.4) | 20.7 | 0.610  (0.581-0.638) |
|  | Limit of detection  1.9 ng/L (all) | 84 | 673 | 381 | 9 | 5.3  (2.6-10.6) | 97.7  (95.8-98.8) | 90.3  (82.4-95.5) | 11.1  (10.3-11.9) | 36.2  (33.2-39.1) | 66.0 | 0.632  (0.604-0.660) |
| Troponin I (Siemens) | | | | | | | | | | | | |
|  | 99th percentile  38.6/53.5 ng/L (w/m) | 8 | 45 | 1009 | 85 | 2.1  (0.97-4.6) | 92.2  (91.8-92.7) | 8.6  (3.8-16.3) | 15.1  (8.0-26.8) | 95.7  (94.3-96.9) | 4.6 | 0.522  (0.492-0.551) |
|  | 97.5th percentile  17.8/26.3 ng/L (w/m) | 13 | 98 | 956 | 80 | 1.6  (0.85-3.0) | 92.3  (91.7-92.9) | 14.0  (7.7-22.7) | 11.7  (7.2-18.5) | 90.7  (88.8-92.4) | 9.7 | 0.524  (0.494-0.553) |
|  | 95th percentile  10.1/15.9 ng/L (w/m) | 25 | 165 | 889 | 68 | 2.0  (1.2-3.2) | 92.9  (92.0-93.7) | 26.9  (18.2-37.1) | 13.2  (9.5-17.9) | 84.4  (82.0-86.5) | 16.6 | 0.556  (0.527-0.585) |
|  | 90th percentile  6.3/9.2 ng/L (w/m) | 39 | 279 | 775 | 54 | 2.0  (1.3-3.1) | 93.5  (92.4-94.5) | 41.9  (31.8-52.6) | 12.3  (9.7-15.3) | 73.6  (70.8-76.2) | 27.7 | 0.577  (0.548-0.606) |
|  | Limit of detection  1.6 ng/L (all) | 90 | 950 | 104 | 3 | 3.3  (1.0-10.6) | 97.2  (91.8-99.1) | 96.8  (90.9-99.3) | 8.6  (8.3-9.0) | 9.9  (8.1-11.8) | 90.7 | 0.533  (0.504-0.562) |
| W indicates women; m, men; NPV, negative predictive value; PPV, positive predictive value; AUC, area under the receiver operator characteristics curve.  aPercent of patients with high-sensitivity cardiac troponin concentration at presentation above given percentile. | | | | | | | | | | | | |

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| **Table S6.** Prognostic precision of high-sensitivity cardiac troponins at different percentile cutoff values and limit of detection provided by manufacturers for the secondary endpoint of all-cause mortality, AMI, revascularization, or hospitalization due to heart failure or stroke. | | | | | | | | | | | | |
|  |  | True pos | False pos | True neg | False neg | Odds ratio | NPV  (95% CI) | Sens  (95% CI) | PPV  (95% CI) | Spes  (95% CI) | >Perc.a | AUC |
| Troponin T (Roche) | | | | | | | | | | | | |
|  | 99th percentile  9.0/16.8 ng/L (w/m) | 74 | 133 | 852 | 88 | 5.4  (3.8-7.7) | 90.6  (89.4-91.8) | 45.7  (37.8-53.7) | 35.8  (30.6-41.2) | 86.5  (84.2-88.6) | 18.0 | 0.661  (0.633-0.688) |
|  | 97.5th percentile  8.4/13.3 ng/L (w/m) | 90 | 176 | 809 | 72 | 5.7  (4.0-8.1) | 91.8  (90.4-93.1) | 55.6  (47.6-63.4) | 33.8  (29.7.38.3) | 82.1  (79.6-84.5) | 23.2 | 0.688  (0.661-0.715) |
|  | 95th percentile  6.9/11.3 (w/m) | 102 | 240 | 745 | 60 | 5.3  (3.7-7.5) | 92.6  (91.0-93.8) | 63.0  (55.0-70.4) | 29.8  (26.6-33.3) | 75.6  (72.8-78.3) | 29.8 | 0.693  (0.665-0.720) |
|  | 90th percentile  6.1/9.2 ng/L (w/m) | 115 | 277 | 708 | 47 | 6.2  (4.3-9.0) | 93.8  (92.2-95.1) | 71.0  (63.4-77.8) | 29.3  (26.5-32.3) | 71.9  (69.0-74.7) | 34.2 | 0.714  (0.687-0.740) |
|  | Limit of detection  5 ng/L (all) | 145 | 599 | 386 | 17 | 5.5  (3.3-9.2) | 95.8  (93.5-97.3) | 89.5  (83.7-93.8) | 19.4  (18.3-20.6) | 39.2  (36.1-42.3) | 64.9 | 0.643  (0.615-0.671) |
| Troponin I (Abbott) | | | | | | | | | | | | |
|  | 99th percentile  15.6/34.2 ng/L (w/m) | 15 | 31 | 954 | 147 | 3.2  (1.7-6.0) | 86.7  (86.1-87.3) | 9.3  (5.3-14.8) | 32.6  (21.1-46.7) | 96.9  (95.6-97.9) | 4.0 | 0.531  (0.501-0.560) |
|  | 97.5th percentile  14.1/27.0 ng/L (w/m) | 19 | 41 | 944 | 143 | 3.1  (1.7-5.4) | 86.9  (86.2-87.5) | 11.7  (7.2-17.7) | 31.7  (21.6-43.8) | 95.9  (94.4-97.0) | 5.2 | 0.538  (0.509-0.567) |
|  | 95th percentile  8.0/13.0 ng/L (w/m) | 44 | 88 | 897 | 118 | 3.8  (2.5-5.7) | 88.4  (87.4-89.4) | 27.2  (20.5-34.7) | 33.3  (26.6-40.8) | 91.1  (89.1-92.8) | 11.5 | 0.591  (0.562-0.620) |
|  | 90th percentile  4.8/7.6 ng/L (w/m) | 73 | 164 | 821 | 89 | 4.1  (2.9-5.9) | 90.3  (88.9-91.4) | 45.1  (37.3-53.1) | 30.8  (26.3-35.7) | 83.4  (80.9-85.7) | 20.7 | 0.642  (0.614-0.670) |
|  | Limit of detection  1.9 ng/L (all) | 150 | 607 | 378 | 12 | 7.8  (4.2-14.2) | 96.9  (94.8-98.2) | 92.6  (87.4-96.1) | 19.8  (18.7-20.8) | 38.4  (35.3-41.5) | 66.0 | 0.655  (0.627-0.682) |
| Troponin I (Siemens) | | | | | | | | | | | | |
|  | 99th percentile  38.6/53.5 ng/L (w/m) | 17 | 36 | 949 | 145 | 3.1  (1.7-5.7) | 86.8  (86.2-87.4) | 10.5  (6.2-16.3) | 32.1  (21.4-45.1) | 96.4  (95.0-97.4) | 4.6 | 0.534  (0.505-0.563) |
|  | 97.5th percentile  17.8/26.3 ng/L (w/m) | 30 | 81 | 904 | 132 | 2.5  (1.6-4.0) | 87.3  (86.4-88.1) | 18.5  (12.9-25.4) | 27.0  (20.1-35.2) | 91.8  (89.9-93.4) | 9.7 | 0.551  (0.522-0.581) |
|  | 95th percentile  10.1/15.9 ng/L (w/m) | 55 | 135 | 850 | 107 | 3.2  (2.2-4.7) | 88.9  (87.7-89.9) | 34.0  (26.7-41.8) | 29.0  (23.8-34.7) | 86.3  (84.0-88.4) | 16.6 | 0.601  (0.572-0.630) |
|  | 90th percentile  6.3/9.2 ng/L (w/m) | 83 | 235 | 750 | 79 | 3.4  (2.4-4.7) | 90.5  (89.0-91.8) | 51.2  (43.3-59.2) | 26.1  (22.7-29.9) | 76.1  (73.4-78.8) | 27.7 | 0.637  (0.608-0.665) |
|  | Limit of detection  1.6 ng/L (all) | 157 | 883 | 102 | 5 | 3.6  (1.5-9.0) | 95.3  (89.5-98.0) | 96.9  (92.9-99.0) | 15.1  (14.6-15.5) | 10.4  (8.6-12.5) | 90.7 | 0.536  (0.507-0.566) |
| W indicates women; m, men; NPV, negative predictive value; PPV, positive predictive value; AUC, area under the receiver operator characteristics curve.  aPercent of patients with high-sensitivity cardiac troponin concentration at presentation above given percentile. | | | | | | | | | | | | |

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| **Table S7.** Prognostic precision of high-sensitivity cardiac troponins at different percentile cutoff values and limit of detection provided by manufacturers for the tertiary endpoint of all-cause mortality. | | | | | | | | | | | | |
|  |  | True pos | False pos | True neg | False neg | Odds ratio | NPV  (95% CI) | Sens  (95% CI) | PPV  (95% CI) | Spes  (95% CI) | >Perc.a | AUC |
| Troponin T (Roche) | | | | | | | | | | | | |
|  | 99th percentile  9.0/16.8 ng/L (w/m) | 52 | 155 | 901 | 39 | 7.8  (4.9-12.1) | 95.9  (94.4-97.0) | 57.1  (46.3-67.5) | 25.1  (19.4-31.6) | 85.3  (83.0-87.4) | 18.0 | 0.712  (0.685-0.738) |
|  | 97.5th percentile  8.4/13.3 ng/L (w/m) | 61 | 204 | 852 | 29 | 8.9  (5.6-14.2) | 96.7  (95.3-97.8) | 68.1  (57.5-77.5) | 23.3  (18.4.28.9) | 80.7  (78.2-83.0) | 23.2 | 0.744  (0.718-0.769) |
|  | 95th percentile  6.9/11.3 (w/m) | 69 | 273 | 783 | 22 | 9.0  (5.5-14.8) | 97.3  (95.9-98.3) | 75.8  (65.7-84.2) | 20.2  (16.1-24.8) | 74.2  (71.4-76.8) | 29.8 | 0.750  (0.724-0.775) |
|  | 90th percentile  6.1/9.2 ng/L (w/m) | 76 | 316 | 740 | 15 | 11.9  (6.7-21.0) | 98.0  (96.7-98.9) | 83.5  (74.3-90.5) | 19.4  (15.6-23.7) | 70.1  (67.2-72.8) | 34.2 | 0.768  (0.742-0.792) |
|  | Limit of detection  5 ng/L (all) | 86 | 658 | 398 | 5 | 10.5  (4.2-25.9) | 98.8  (97.1-99.6) | 94.5  (87.6-98.2) | 11.6  (9.4-14.1) | 37.7  (34.8-40.7) | 64.9 | 0.661  (0.633-0.688) |
| Troponin I (Abbott) | | | | | | | | | | | | |
|  | 99th percentile  15.6/34.2 ng/L (w/m) | 13 | 33 | 1023 | 78 | 5.2  (2.6-10.2) | 92.9  (91.2-94.4) | 14.3  (7.8-23.2) | 28.3  (16.0-43.5) | 96.9  (95.6-97.8) | 4.0 | 0.556  (0.527-0.585) |
|  | 97.5th percentile  14.1/27.0 ng/L (w/m) | 16 | 44 | 1012 | 75 | 4.9  (2.6-9.1) | 93.1  (91.4-94.5) | 17.6  (10.4-27.0) | 26.7  (16.1-39.7) | 95.8  (94.5-97.0) | 5.2 | 0.567  (0.538-0.596) |
|  | 95th percentile  8.0/13.0 ng/L (w/m) | 32 | 100 | 956 | 59 | 5.2  (3.2-8.4) | 94.2  (92.6-95.6) | 35.2  (25.4-45.9) | 24.2  (17.2-32.5) | 90.5  (88.6-92.2) | 11.5 | 0.628  (0.600-0.657) |
|  | 90th percentile  4.8/7.6 ng/L (w/m) | 47 | 190 | 866 | 44 | 4.9  (3.1-7.6) | 95.2  (93.6-96.5) | 51.7  (40.9-62.3) | 19.8  (15.0-25.5) | 82.0  (79.6-84.3) | 20.7 | 0.668  (0.640-0.696) |
|  | Limit of detection  1.9 ng/L (all) | 88 | 669 | 387 | 3 | 17.0  (5.3-54.0) | 99.2  (97.8-99.8) | 96.7  (90.7-99.3) | 11.6  (9.4-14.1) | 36.7  (33.7-39.6) | 66.0 | 0.667  (0.639-0.694) |
| Troponin I (Siemens) | | | | | | | | | | | | |
|  | 99th percentile  38.6/53.5 ng/L (w/m) | 14 | 39 | 1017 | 77 | 4.7  (2.5-9.1) | 93.0  (91.3-94.4) | 15.4  (8.7-24.5) | 26.4  (15.3-40.3) | 96.3  (95.0-97.4) | 4.6 | 0.558  (0.529-0.587) |
|  | 97.5th percentile  17.8/26.3 ng/L (w/m) | 25 | 86 | 970 | 66 | 4.3  (2.6-7.1) | 93.6  (92.0-95.0) | 27.5  (18.6-37.8) | 22.5  (15.1-31.4) | 91.9  (90.0-93.4) | 9.7 | 0.597  (0.568-0.625) |
|  | 95th percentile  10.1/15.9 ng/L (w/m) | 36 | 154 | 902 | 55 | 3.8  (2.4-6.0) | 94.3  (92.6-95.6) | 39.6  (29.5-50.4) | 19.0  (13.6-25.3) | 85.4  (83.1-87.5) | 16.6 | 0.625  (0.596-0.653) |
|  | 90th percentile  6.3/9.2 ng/L (w/m) | 56 | 262 | 794 | 35 | 4.8  (3.1-7.6) | 95.8  (94.2-97.0) | 61.5  (50.8-71.6) | 17.6  (13.6-22.3) | 75.2  (72.5-77.8) | 27.7 | 0.684  (0.656-0.710) |
|  | Limit of detection  1.6 ng/L (all) | 87 | 953 | 103 | 4 | 2.4  (0.8-6.5) | 96.3  (90.7-99.0) | 95.6  (89.1-98.8) | 8.4  (6.8-10.2) | 9.8  (8.0-11.7) | 90.7 | 0.527  (0.497-0.556) |
| W indicates women; m, men; NPV, negative predictive value; PPV, positive predictive value; AUC, area under the receiver operator characteristics curve.  aPercent of patients with high-sensitivity cardiac troponin concentration at presentation above given percentile. | | | | | | | | | | | | |

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| **Table S8.** Prognostic precision for high-sensitivity cardiac troponin I using biologic equivalent cutoff values compared to high-sensitivity cardiac troponin T for the primary endpoint of CV death, AMI, or revascularization. | | | | | | | | | | | | |
|  |  | True pos | False pos | True neg | False neg | Odds ratio | NPV  (95% CI) | Sens  (95% CI) | PPV  (95% CI) | Spes  (95% CI) | >Perc.a | AUC |
| Troponin I (Abbott) | | | | | | | | | | | | |
|  | 99th percentile  4.1/8.7 ng/L (w/m) | 36 | 204 | 850 | 57 | 2.6  (1.7-4.1) | 93.7  (92.7-94.6) | 38.7  (28.8-49.4) | 15.0  (11.7-19.0) | 80.7  (78.1-83.0) | 20.9 | 0.597c  (0.568-0.625) |
|  | 97.5th percentile  3.8/6.8 ng/L (w/m) | 41 | 244 | 810 | 52 | 2.6  (1.7-4.0) | 94.0  (92.9-95.0) | 44.1  (33.8-54.8) | 14.4  (11.5-17.8) | 76.9  (74.2-79.4) | 24.8 | 0.605c  (0.576-0.633) |
|  | 95th percentile  3.1/5.7 ng/L (w/m) | 49 | 290 | 764 | 44 | 2.9  (1.9-4.5) | 94.6  (93.3-95.6) | 52.7  (42.1-63.1) | 14.5  (12.0-17.3) | 72.5  (69.7-75.2) | 29.6 | 0.626c  (0.597-0.654) |
|  | 90th percentile  2.8/4.6 ng/L (w/m) | 58 | 354 | 700 | 35 | 3.3  (2.1-5.1) | 95.2  (93.9-96.3) | 62.4  (51.7-72.2) | 14.1  (12.1-16.4) | 66.4  (63.5-69.3) | 35.9 | 0.644  (0.615-0.672) |
| Troponin I (Siemens) | | | | | | | | | | | | |
|  | 99th percentile  6.9/16.5 ng/L (w/m) | 27 | 198 | 856 | 66 | 1.8  (1.1-2.9) | 92.8  (91.9-93.7) | 29.0  (20.1-39.4) | 12.0  (8.8-16.1) | 81.2  (78.7-83.5) | 19.6 | 0.551  (0.522-0.580) |
|  | 97.5th percentile  6.3/12.5 ng/L (w/m) | 33 | 232 | 822 | 60 | 1.9  (1.2-3.1) | 93.2  (92.2-94.1) | 35.5  (25.8-46.1) | 12.5  (9.6-16.1) | 78.0  (75.4-80.5) | 23.1 | 0.567b  (0.538-0.596) |
|  | 95th percentile  5.0/10.3 ng/L (w/m) | 40 | 298 | 756 | 53 | 1.9  (1.2-2.9) | 93.5  (92.3-94.5) | 43.0  (32.8-53.7) | 11.8  (9.4-14.7) | 71.7  (68.9-74.4) | 29.5 | 0.574  (0.544-0.603) |
|  | 90th percentile  4.3/8.1 ng/L (w/m) | 48 | 364 | 690 | 45 | 2.0  (1.3-3.1) | 93.9  (92.5-95.0) | 51.6  (41.0-62.1) | 11.7  (9.6-14.0) | 65.6  (62.5-68.3) | 35.9 | 0.585  (0.556-0.614) |
| W indicates women; m, men; NPV, negative predictive value; PPV, positive predictive value; AUC, area under the receiver operator characteristics curve.  aPercent of patients with high-sensitivity cardiac troponin concentration at presentation above given percentile.  bSignificantly different compared to percentile provided by manufacturer, p<0.05  cSignificantly different compared to percentile provided by manufacturer, p<0.01 | | | | | | | | | | | | |

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| **Table S9.** Prognostic precision of high-sensitivity cardiac troponin I using biologic equivalent cutoff values compared to high-sensitivity cardiac troponin T for the secondary endpoint of all-cause mortality, AMI, revascularization, or hospitalization due to heart failure or stroke. | | | | | | | | | | | | |
|  |  | True pos | False pos | True neg | False neg | Odds ratio  (95% CI) | NPV  (95% CI) | Sens  (95% CI) | PPV  (95% CI) | Spes  (95% CI) | >Perc.a | AUC |
| Troponin I (Abbott) | | | | | | | | | | | | |
|  | 99th percentile  4.1/8.7 ng/L (w/m) | 71 | 169 | 816 | 91 | 3.8  (2.7-5.4) | 90.0  (88.6-91.2) | 43.8  (36.1-51.8) | 29.6  (25.2-34.4) | 82.8  (80.3-85.2) | 20.9 | 0.633c  (0.605-0.661) |
|  | 97.5th percentile  3.8/6.8 ng/L (w/m) | 81 | 204 | 781 | 81 | 3.8  (2.7-5.4) | 90.6  (89.2-91.9) | 50.0  (42.1-58.0) | 28.4  (24.6-32.6) | 79.3  (76.6-81.8) | 24.8 | 0.646c  (0.618-0.674) |
|  | 95th percentile  3.1/5.7 ng/L (w/m) | 95 | 244 | 741 | 67 | 4.3  (3.1-6.1) | 91.7  (90.2-93.0) | 58.6  (50.7-66.3) | 28.0  (24.7-31.6) | 75.2  (72.4-77.9) | 29.6 | 0.669c  (0.641-0.697) |
|  | 90th percentile  2.8/4.6 ng/L (w/m) | 110 | 302 | 683 | 52 | 4.8  (3.3-6.8) | 92.9  (91.3-94.3) | 67.9  (60.1-75.0) | 26.7  (24.0-29.6) | 69.3  (66.4-72.2) | 35.9 | 0.686b  (0.658-0.713) |
| Troponin I (Siemens) | | | | | | | | | | | | |
|  | 99th percentile  6.9/16.5 ng/L (w/m) | 60 | 165 | 820 | 102 | 2.9  (2.0-4.2) | 88.9  (87.7-90.1) | 37.0  (29.6-45.0) | 26.7  (22.2-31.7) | 83.3  (80.8-85.5) | 19.6 | 0.601c  (0.572-0.630) |
|  | 97.5th percentile  6.3/12.5 ng/L (w/m) | 73 | 192 | 793 | 89 | 3.3  (2.4-4.8) | 89.9  (88.5-91.1) | 45.1  (37.3-53.1) | 27.6  (23.5-32.0) | 80.5  (77.9-82.9) | 23.1 | 0.628c  (0.599-0.656) |
|  | 95th percentile  5.0/10.3 ng/L (w/m) | 83 | 255 | 730 | 79 | 3.0  (2.1-4.2) | 90.2  (88.7-91.6) | 51.2  (43.3-59.2) | 24.6  (21.3-28.1) | 74.1  (71.3-76.8) | 29.5 | 0.627  (0.598-0.655) |
|  | 90th percentile  4.3/8.1 ng/L (w/m) | 96 | 316 | 669 | 66 | 3.1  (2.2-4.3) | 91.0  (89.3-92.5) | 59.3  (51.3-66.9) | 23.3  (20.6-26.2) | 67.9  (64.9-70.8) | 35.9 | 0.636  (0.607-0.664) |
| Tn cutoff values are for women and men respectively. NPV indicates negative predictive value; PPV, positive predictive value; AUC, area under the receiver operator characteristics curve.  aPercent of patients with high-sensitivity cardiac troponin concentration at presentation above given percentile.  bSignificantly different compared to percentile provided by manufacturer, p<0.05  cSignificantly different compared to percentile provided by manufacturer, p<0.001 | | | | | | | | | | | | |

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| **Table S10.** Prognostic precision of high-sensitivity cardiac troponin I using biologic equivalent cutoff values compared to high-sensitivity cardiac troponin T for the tertiary endpoint of all-cause mortality. | | | | | | | | | | | | |
|  |  | True pos | False pos | True neg | False neg | Odds ratio  (95% CI) | NPV  (95% CI) | Sens  (95% CI) | PPV  (95% CI) | Spes  (95% CI) | >Perc.a | AUC |
| Troponin I (Abbott) | | | | | | | | | | | | |
|  | 99th percentile  4.1/8.7 ng/L (w/m) | 46 | 194 | 862 | 45 | 4.5  (2.9-7.0) | 95.0  (93.4-96.4) | 50.6  (39.9-61.2) | 19.2  (14.4-24.7) | 81.6  (79.2-83.9) | 20.9 | 0.661d  (0.633-0.688) |
|  | 97.5th percentile  3.8/6.8 ng/L (w/m) | 54 | 231 | 825 | 37 | 5.2  (3.3-8.1) | 95.7  (94.1-97.0) | 59.3  (48.5-69.5) | 19.0  (14.6-24.0) | 78.1  (75.5-80.6) | 24.8 | 0.687d  (0.660-0.714) |
|  | 95th percentile  3.1/5.7 ng/L (w/m) | 62 | 277 | 779 | 29 | 6.0  (3.8-9.5) | 96.4  (94.9-97.6) | 68.1  (57.5-77.5) | 18.3  (14.3-22.8) | 73.8  (71.0-76.4) | 29.6 | 0.710c  (0.682-0.736) |
|  | 90th percentile  2.8/4.6 ng/L (w/m) | 69 | 343 | 713 | 22 | 6.5  (4.0-10.7) | 97.0  (95.5-98.1) | 75.8  (65.7-84.2) | 16.8  (13.3-20.7) | 67.5  (64.6-70.3) | 35.9 | 0.717b  (0.690-0.743) |
| Troponin I (Siemens) | | | | | | | | | | | | |
|  | 99th percentile  6.9/16.5 ng/L (w/m) | 39 | 186 | 870 | 52 | 3.5  (2.3-5.5) | 94.4  (92.7-95.8) | 42.9  (32.5-53.7) | 17.3  (12.6-22.9) | 82.4  (80.0-84.6) | 19.6 | 0.626c  (0.597-0.654) |
|  | 97.5th percentile  6.3/12.5 ng/L (w/m) | 51 | 214 | 842 | 40 | 5.0  (3.2-7.8) | 95.5  (93.9-96.7) | 56.0  (45.3-66.4) | 19.3  (14.7-24.5) | 79.7  (77.2-82.1) | 23.1 | 0.679d  (0.651-0.706) |
|  | 95th percentile  5.0/10.3 ng/L (w/m) | 56 | 282 | 774 | 35 | 4.4  (2.8-6.8) | 95.7  (94.0-97.0) | 61.5  (50.8-71.6) | 16.6  (12.8-21.0) | 73.3  (70.5-75.9) | 29.5 | 0.674b  (0.646-0.701) |
|  | 90th percentile  4.3/8.1 ng/L (w/m) | 61 | 351 | 705 | 30 | 4.1  (2.6-6.4) | 95.9  (94.2-97.2) | 67.0  (56.4-76.5) | 14.8  (11.5-18.6) | 66.8  (63.8-69.6) | 35.9 | 0.669  (0.641-0.696) |
| Tn cutoff values are for women and men respectively. NPV indicates negative predictive value; PPV, positive predictive value; AUC, area under the receiver operator characteristics curve.  aPercent of patients with high-sensitivity cardiac troponin concentration at presentation above given percentile.  bSignificantly different compared to percentile provided by manufacturer, p<0.05  cSignificantly different compared to percentile provided by manufacturer, p<0.01  dSignificantly different compared to percentile provided by manufacturer, p<0.001 | | | | | | | | | | | | |