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Supplementary Methods

Adjudication

All routine clinical assessments were recorded and registered retrospectively. Demographic and clinical characteristics were obtained from electronic medical records. Two independent

cardiologists adjudicated the final diagnosis based on all available clinical, routine laboratory (including cTnT at admission and at 3 and 8–12 hours from admission), electrocardiogram (ECG), ultrasound, and imaging findings, including cardiac computed tomographic angiography and conventional angiography(1). A third adjudicator resolved disagreements. Specific diagnostic criteria were predefined for 22 different medical conditions based on guidelines that were available during planning of the study (see "Diagnostic definitions" below). NSTEMI was defined according to the third universal definition for MI, including a significant rise and fall of cTn with at least one value above the 99th percentile combined with symptoms of ischemia, ECG changes, and image evidence of loss of viable myocardium or intracoronary thrombus.(2) Delta values of 20% (baseline cTnT concentration >14 ng/L) or 50% (baseline cTnT concentration ≤14 ng/L) in serial cTnT measures were regarded as significant, as suggested by the ESC in 2012.(1, 2) Since 2012, several studies have found a significantly lower 99th percentile concentration of cTn for women compared with men,(3-5) but knowledge of sex-specific cutoffs for women regarding diagnosing NSTEMI is partial because of a lack of data on pathophysiology.(6) Consequently, we chose to apply a common cutoff for all patients.

Diagnostic definitions

Myocardial infarction (AMI, MI): defined according to the third universal definition of myocardial infarction (7):

Detection of a rise and/or fall of cardiac biomarker values (preferably cardiac troponin) with at least one value above the 99th percentile upper reference limit (URL) and with at least one of the following:

1. Symptoms of ischemia
2. Development of pathologic Q waves in the electrocardiogram (ECG)
3. New or presumed new significant ST-Segment-T wave (ST-T) changes or new left bundle branch block (LBBB).
4. Identification of an intracoronary thrombus by angiography or autopsy
5. Imaging evidence of new loss of viable myocardium or a new regional wall motion abnormality

Unstable angina pectoris **(**UAP): defined as symptoms suggestive of an ACS without elevation in biomarkers with or without ECG changes indicative of ischemia.(8)

Stable angina was defined as typical angina symptoms lasting >1 month without an increase in magnitude, duration or frequency of the pain and a known history of coronary artery disease.(9)

Pericarditis was diagnosed if at least two of four diagnostic criteria were present, as defined in several studies: typical pleuritic chest pain, detection of a pericardial rub on auscultation, typical ECG changes, new or increased amount of pericardial effusion on echocardiography.(10)

Myocarditis was diagnosed according to the position statement of ESC from 2013.(11)

Takotsubo cardiomyopathy was diagnosed with the modified criteria suggested by The Mayo Clinic in 2008.(12)

Heart failure was defined according to the ESC diagnostic criteria of 2016.(13)

Atrial fibrillation, atrial flutter and other supraventricular arrhythmias were diagnosed by ECG findings and the lack of symptoms and biochemical results supporting another disease.

Aortic stenosis and other valvular diseases were diagnosed in accordance with echocardiographic findings and a history supporting the valve disease as cause of the symptoms.(14)

Myalgia was defined as chest pain provoked by palpation in lack of cardiac disease.

GERD was based on gastroscopic findings, also in the lack of cardiac disease.

Cholecystitis were defined by the Tokyo Guidelines of 2006 while other abdominal diseases were defined according to operative, endoscopic or radiological findings.(15)

Pneumonia was defined by typical symptoms and a chest X-ray supporting the disease, while the diagnosis of both pulmonary embolism and pneumothorax was based on radiologic findings and the lack of concurrent cardiac disease.

COPD was defined in accordance with the criteria by Stephens MB from 2008.(16)

NCCP was defined as chest pain without any specific clinical, radiologic or biochemical findings.

Biochemical analysis

Hs-cTnT was measured using the Roche Diagnostics hs-cTnT assay with limit of blank (LoB) 3 ng/L, limit of detection (LoD) 5 ng/L, 99th percentile 14 ng/L, measurement range 4 – 10 000 ng/L and 10% analytical within-series coefficient of variation (CV_A) at 4.5 ng/L; CV_A was below 5% for concentrations of 10 ng/L or higher(17). Hs-cTnI was measured using the Abbott Diagnostics hs-cTnI assay. The assay has a LoB 0.9 ng/L, LoD 1.7 ng/L, 99th percentile 26 ng/L and measurement range 2-50 000 ng/L, with 10% CV_A at 4.6 ng/L(17).

Glucose, creatinine and lipids were measured using the Cobas 8000 from Roche Diagnostics. The glomerular filtration rate was estimated using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration)(18) formula using an enzymatic isotope dilution mass spectrometry traceable creatinine assay (Roche Diagnostics) with a CV_A less than 3% for concentration > 60 μmol/L.

Supplementary Tables

Supplementary Table S1. Characteristics of responders and non-responders at 3 months. Continuous variables are reported as median values (25th percentile to 75th percentile), proportions are given as absolute numbers (percentages).

Parameter	**Responder N=774 (51.9%)**	**Non-responder N=718 (48.3%)**	**P-value**
Age, median (25th to 75th percentile)	66 (57-73)	58 (47-71)	<0.001
Gender, female, n (%)	305 (39.4)	284 (39.6)	0.953
Risk factors, n (%)			
Hypertension	351 (45.3)	259 (36.1)	<0.001
Hyperlipidemia (known)	342 (44.2)	237 (33.0)	<0.001
Diabetes mellitus	94 (12.1)	82 (11.4)	0.665
Insulin-dependent	25 (3.2)	25 (3.5)	0.787
Family history (MI)	142 (18.3)	127 (17.7)	0.494
Unknown	66 (8.5)	74 (10.3)	0.239
Current smoker	135 (17.4)	147 (20.5)	0.135
Previous smoker	355 (45.9)	297 (41.4)	0.080
Medical history, n (%)			
Prior MI	147 (19.0)	137 (19.1)	0.965
Prior PCI	167 (21.6)	124 (17.3)	0.036
Prior CABG	58 (7.5)	52 (7.2)	0.853
Prior Heart Failure	26 (3.4)	25 (3.5)	0.896
Prior Stroke	25 (3.2)	17 (2.4)	0.350
Peripheral vascular disease	17 (2.2)	12 (1.7)	0.463
Revascularization	146 (18.9)	72 (10.0)	<0.001
Biomarkers			
cTnT, ng/L	8.0 (4.0-18.0)	6.0 (3.0-14.0)	<0.001
cTnI, ng/L	3.8 (1.94-11.31)	2.94 (1.50-7.50)	<0.001

Supplementary Table S2: RAND-12 scores in responders and in the normative population. Data are reported as median values (25th and 75th percentile).

	Responders N= 774	**General population N= 6240**	**P-value**
PCS-12	50 (37-59)	52 (42-55)	0.383
MCS-12	51 (41-58)	58 (54-61)	<0.001

Supplementary Table S3. Univariable linear regression analyses of candidate predictors and quality of life outcome scores.

	SAQ7-AF				**SAQ7-QL**		
Variable	B	95% Cl	P-value	Variable	B	95% Cl	P-value
Age	-0.02	-0.10, 0.06	0.676	Age	0.008	-0.12, 0.14	0.898
Gender	-0.14	-2.87, 2.56	0.920	Gender	-2.66	-7.10, 1.79	0.241
cTnT	0.009	-0.002, 0.02	0.116	cTnT	0.02	0.001, 0.4	0.037
cTnI	0.001	0.000, 0.001	0.115	cTnI	0.001	0.000, 0.002	0.049
Prior MI	-6.44	-9.79, -3.09	<0.001	Prior MI	-5.41	-10.82, -0.002	0.050
Prior PCI	-7.43	-10.63, -4.23	<0.001	Prior PCI	-7.40	-12.57, -2.24	0.005
Prior CABG	-4.93	-9.86, 0.012	0.051	Prior CABG	-11.02	-19.28, 2.75	0.009
Prior Stroke	-1.95	-9.37, 5.48	0.607	Prior Stroke	-1.41	-7.08, 4.25	0.624
Prior Heart failure	-0.52	-9.37, 5.48	0.607	Prior Heart failure	-11.49	-23.20, 0.22	0.054
Hypertension	-4.06	-6.716, -1.404	0.003	Hypertension	-6.11	-10.42, -1.79	0.006
Current smoker	-0.05	-3.54, 3.45	0.980	Current smoker	-8.04	-13.76, 2.32	0.006
Reduced renal function	-4.65	-9.61, 0.31	0.066	Reduced renal function	-6.71	-14.80, 1.36	0.103
Diabetes	-4.97	-9.02, -0.93	0.016	Diabetes	-5.81	-12.37, 0.74	0.082
BMI	-0.24	-0.63, 0.15	0.231	BMI	-0.19	-0.85, 0.47	0.577
eGFR	0.05	-0.04, 0.15	0.280	eGFR	0.03	-0.12, 0.19	0.667
Revascularization	2.51	-0.88, 5.89	0.146	Revascularization	5.64	0.175, 11.11	0.043
NSTEMI	3.30	-0.49, 7.09	0.088	NSTEMI	4.79	-1.31, 10.90	0.124
UAP	-9.16	-12.66, -5.65	<0.001	UAP	-9.14	-14.78, -3.50	0.002
Non-coronary cardiac disease	-2.34	-7.63, 2.95	0.386	Non-coronary cardiac disease	-8.76	-17.71, 0.19	0.055
Non-cardiac disease	2.03	-3.36, 7.42	0.460	Non-cardiac disease	2.52	-6.36, 11.40	0.578
NCCP	3.81	1.15, 6.47	0.005	NCCP	4.83	0.50, 9.16	0.029

	SAQ7-PL				**SAQ7**		
Variable	B	95% Cl	P-value	Variable	B	95% Cl	P-value
Age	-0.31	-0.43, -0.20	<0.001	Age	-0.11	-0.20, -0.02	0.018
Gender	-1.46	-5.37, 2.42	0.461	Gender	-1.58	-4.59, 1.43	0.304
cTnT	0.006	-0.009, 0.02	0.435	cTnT	0.01	-0.001, 0.023	0.068
cTnI	0.0008	-0.001, 0.001	0.426	cTnI	0.001	0.000, 0.001	0.076
Prior MI	-11.40	-16.19, -6.61	<0.001	Prior MI	-7.94	-11.66, -4.23	<0.001
Prior PCI	-9.74	-14.38, -5.14	<0.001	Prior PCI	-8.20	-11.74, -4.66	<0.001

Prior CABG	-16.81	-23.99, -9.63	<0.001	Prior CABG	-9.13	-14.66, -3.60	0.001
Prior Stroke	-5.38	-10.43, -0.33	0.037	Prior Stroke	-3.13	-7.33, 0.70	0.106
Prior Heart failure	-17.15	-27.56, -6.74	0.001	Prior Heart failure	-10.14	-18.16, -2.12	0.013
Hypertension	-6.62	-10.39, -2.85	0.001	Hypertension	-5.01	-7.95, -2.07	0.001
Current smoker	-5.49	-10.50. -0.49	0.032	Current smoker	-3.54	-7.41, 0.34	0.073
Reduced renal function	-16.64	-24.02, -9.27	<0.001	Reduced renal function	-8.64	-14.11, -3.16	0.002
Diabetes	-5.27	-11.05, 0.52	0.074	Diabetes	-4.93	-9.41, -0.44	0.031
BMI	-0.08	-0.67, 0.52	0.806	BMI	-0.15	-0.59, 0.30	0.526
eGFR	0.33	0.19, 0.47	<0.001	eGFR	0.13	0.02, 0.24	0.017
Revascularization	3.48	-1.37, 8.33	0.159	Revascularization	4.10	0.29, 7.82	0.035
NSTEMI	3.34	-2.08, 8.77	0.226	NSTEMI	4.10	-0.12, 8.32	0.057
UAP	-6.86	-11.92, -1.81	0.008	UAP	-8.70	-12.59, -4.81	<0.001
Non-coronary cardiac disease	-8.02	-15.2, -0.43	0.039	Non-coronary cardiac disease	-5.86	-11.80, 0.08	0.053
Non-cardiac disease	-2.17	-9.86, 5.53	0.581	Non-cardiac disease	1.44	-4.63, 7.50	0.643
NCCP	4.93	1.14, 8.72	0.011	NCCP	4.33	1.38, 7.28	0.004

	PCS-12				**MCS-12**		
Variable	B	95% Cl	P-value	Variable	B	95% Cl	P-value
Age	-0.03	-0.09, 0.03	0.326	Age	0.002	-0.06, 0.06	0.988
Gender	-1.60	-4.02, 0.83	0.196	Gender	-1.79	-4.24, 0.66	0.151
cTnT	0.01	-0.002	0.103	cTnT	0.02	0.001, 0.03	0.052
cTnI	0.002	0.001, 0.005	0.070	cTnI	0.002	0.001, 0.005	0.064
Prior MI	-4.18	-7.35, -1.01	0.010	Prior MI	-2.77	-5.98, 0.45	0.092
Prior PCI	-3.57	-6.62	0.021	Prior PCI	-2.40	-5.49, 0.68	0.127
Prior CABG	-4.36	-9.51, 0.79	0.097	Prior CABG	-1.49	-6.71, 3.72	0.574
Prior Stroke	-1.586	-3.99, 0.82	0.196	Prior Stroke	-2.34	-4.76, 0.09	0.059
Prior Heart failure	-6.22	-17.77, 5.33	0.290	Prior Heart failure	-4.89	-16.56, 6.78	0.411
Hypertension	-3.86	-6.20, -1.52	0.001	Hypertension	-2.12	-4.50, 0.27	0.082
Current smoker	-2.68	-5.76, 0.49	0.098	Current smoker	-3.77	-6.91, -0.63	0.019
Reduced renal function	-3.97	-10.89, 2.96	0.259	Reduced renal function	2.15	-5.16, 9.46	0.562
Diabetes	-4.70	-8.43, -0.96	0.014	Diabetes	-2.44	-6.23, 1.36	0.207
BMI	-0.47	-0.85, -0.09	0.015	BMI	-0.30	-0.69, 0.09	0.127
eGFR	-0.002	-0.12, 0.12	0.974	eGFR	-0.10	-0.22, 0.03	0.118
Revascularization	2.71	-0.39, 5.82	0.086	Revascularization	2.77	-0.37, 5.91	0.084
NSTEMI	3.04	-0.71, 6.80	0.112	NSTEMI	3.18	-0.61, 6.97	0.100

UAP	-3.63	-6.57, -0.69	0.016	UAP	-0.97	-3.97, 2.00	0.525
Non-coronary cardiac disease	-0.004	-5.17, 5.16	0.999	Non-coronary cardiac disease	-0.86	-6.07, 4.36	0.747
Non-cardiac disease	-1.96	-7.02, 3.09	0.445	Non-cardiac disease	-0.520	-5.63, 5.59	0.841
NCCP	1.62	-0.76, 4.00	0.182	NCCP	-0.42	-2.83, 1.96	0.734

Supplementary Table S4: Mediator analysis investigating which variables that could mediate the predictive value of an UAP diagnosis for the different outcomes (dependent variables). Variables that changed the unstandardized B more than 10% are marked* below.

SAQ7-AF	B (unstandardized)	SE	β(standardized)	t	P-value
UAP ± 10% B (-10.076 to -8.244)	-9.160	1.786	-0.184	-5.129	<0.001
Revascularization*	5.077	1.742	0.107	2.914	0.004
UAP	-10.426	1.835	-0.209	-5.681	<0.001
Age	-0.006	0.041	-0.005	-0.143	0.887
UAP	-9.061	1.789	-0.182	-5.066	<0.001
Gender	-1.015	1.377	-0.027	-0.737	0.461
UAP	-9.239	1.799	-0.186	-5.136	<0.001
cTnT	0.007	0.005	0.048	1.336	0.182
UAP	-9.098	1.793	-0.182	-5.075	<0.001
Prior MI	-5.437	1.697	-0.115	-3.204	0.001
UAP	-8.353	1.788	-0.168	-4.672	<0.001
Prior CABG	-2.339	2.538	-0.034	-0.921	0.357
UAP	-8.715	1.827	-0.175	-4.770	<0.001
Hypertension	-3.450	1.339	-0.092	-2.576	0.010
UAP	-8.642	1.786	-0.174	-4.839	<0.001
Reduced renal function	-4.176	2.494	-0.075	-1.675	0.095
UAP	-8.824	2.386	-0.166	-3.698	<0.001
Diabetes	-3.933	2.042	-0.069	-1.926	0.054
UAP	-8.714	1.791	-0.175	-4.865	-1.926

SAQ7-QL	B (unstandardized)	SE	β(standardized)	t	P-value
UAP ± 10% B (-10.067 to -8.228)	-9.143	2.872	-0.119	-3.183	0.002
Revascularization*	8.526	2.850	0.115	2.992	0.003
UAP	-11.188	2.953	-0.145	-3.789	<0.001
Age	0.021	0.066	0.012	0.313	0.754
UAP	-9.014	2.880	-0.117	-3.130	0.002
Gender	-3.441	2.260	-0.057	-1.523	0.128
UAP	-9.428	2.887	-0.122	-3.266	0.001
cTnT	0.017	0.009	0.072	1.930	0.054
UAP	-8.962	2.880	-0.116	-3.112	0.002
Prior PCI*	-5.876	2.685	-0.084	-2.189	0.029
UAP	-7.532	2.939	-0.098	-2.563	0.011
Prior CABG*	-8.779	4.275	-0.078	-2.054	0.040
UAP	-7.780	2.924	-0.101	-2.661	0.008
Prior Heart failure	-12.017	5.928	-0.075	-2.027	0.043
UAP	-9.123	2.868	-0.118	-3.181	0.002
Hypertension	-5.548	2.196	-0.094	-2.527	0.012
UAP	-8.322	2.874	-0.108	-2.896	0.004

Current smoking UAP	-8.155 -9.061	2.897 2.860	-0.105 -1.118	-2.815 -3.169	0.005 0.002
Diabetes UAP	-4.763 -8.520	3.338 2.888	-0.053 -0.111	-1.427 -2.950	0.154 0.003

SAQ7-PL	B (unstandardized)	SE	β(standardized)	t	P-value
UAP ± 10% B (-7.550 to -6.177)	-6.864	2.574	-0.098	-2.667	0.008
Revascularization* UAP	5.485 -8.217	2.531 2.647	0.082 0.002	2.167 -3.104	0.031 0.002
Age* UAP	-0.302 -5.861	-0.057 2.532	-0.190 -0.083	-5.271 -2.315	<0.001 0.021
Gender UAP	-2.074 -7.102	1.980 -7.102	-0.039 -0.101	-1.047 -2.745	0.295 0.006
cTnT UAP	0.005 -7.052	0.008 2.573	0.024 -0.101	0.650 -2.741	0.516 0.006
Prior MI* UAP	-10.772 -5.446	2.453 2.559	-0.160 -0.077	-4.391 -2.128	<0.001 0.034
Prior CABG* UAP	-15.401 -4.413	3.747 2.609	-0.153 -0.063	-4.110 -1.691	<0.001 0.091
Prior Stroke UAP	-5.219 -6.669	2.563 2.566	-0.074 -0.095	-2.036 -2.599	0.042 0.010
Prior Heart failure UAP	-17.492 -6.995	5.282 2.555	-0.120 -0.100	-3.312 -2.738	0.001 0.006
Hypertension* UAP	-6.159 -5.949	1.926 2.569	-0.117 -0.085	-3.197 -2.316	0.001 0.021
Current smoking UAP	-5.775 -7.031	2.542 2.566	-0.083 -0.100	-2.272 -2.740	0.023 0.006
Reduced renal function UAP	-16.257 -6.192	3.751 3.491	-0.196 -0.080	-4.334 -1.774	<0.001 0.077
Diabetes UAP	-4.466 -6.364	2.954 2.585	-0.056 -0.091	-1.512 -2.462	0.131 0.014

SAQ7 summary	B (unstandardized)	SE	β(standardized)	t	P-value
UAP ± 10% B (-9.570 to -7.830)	-8.700	1.981	-0.156	-4.391	<0.001
Revascularization* UAP	6.630 -10.309	1.949 2.033	0.124 -0.184	3.402 -5.070	0.001 <0.001
Age UAP	-0.097 -8.331	0.045 1.981	-0.076 -0.149	-2.147 -4.205	0.032 <0.001
Gender UAP	-2.382 -8.945	1.527 1.994	-0.056 -0.160	-1.560 -4.486	0.119 <0.001
cTnT UAP	0.010 -8.675	0.006 1.987	0.058 -0.155	1.623 -4.365	0.105 <0.001

Prior MI* UAP	-7.100 -7.728	1.886 1.979	-0.133 -0.138	-3.764 -3.906	<0.001 <0.001
Prior CABG* UAP	-6.903 -7.562	2.856 2.020	-0.087 -0.135	-2.417 -3.743	0.016 <0.001
Prior Heart failure UAP	-10.654 -8.731	4.039 1.975	-0.093 -0.156	-2.638 -4.420	0.009 <0.001
Hypertension UAP	-4.448 -8.026	1.489 1.981	-0.106 -0.144	-2.987 -4.052	0.003 <0.001
Current smoking UAP	-3.761 -8.680	1.950 1.979	-0.068 -0.155	-1.928 -4.385	0.054 <0.001
Reduced renal function UAP	-8.176 -7.894	2.770 2.655	-0.130 -0.131	-2.952 -2.973	0.003 0.003
Diabetes UAP	-3.940 -8.218	2.275 1.991	-0.062 -0.147	-1.732 -4.128	0.084 <0.001

PCS-12	B (unstandardized)	SE	β(standardized)	t	P-value
UAP ± 10% B (-3.994 to -3.268)	-3.631	1.497	-0.124	-2.426	0.016
Revascularization* UAP	3.990 -4.596	1.619 1.541	0.130 -0.157	2.464 -2.982	0.014 0.003
Age UAP	-0.028 -3.554	0.031 1.499	-0.046 -0.121	-0.899 -2.371	0.369 0.018
Gender UAP	-1.937 -3.859	1.231 1.503	-0.081 -0.132	-1.574 -2.567	0.116 0.011
cTnT UAP	0.011 -3.558	0.007 1.493	0.078 0.007	1.521 -2.383	0.129 0.018
Prior MI* UAP	-3.822 -3.241	1.612 1.496	-0.121 -0.111	-2.371 -2.166	0.018 0.031
Hypertension* UAP	-3.579 -3.095	1.193 1.492	-0.153 -0.106	-3.001 -2.075	0.003 0.039
Current smoking UAP	-2.628 -3.599	1.579 1.494	-0.085 -0.123	-1.664 -2.409	0.097 0.016
Diabetes UAP	-4.286 -3.271	1.900 1.497	-0.115 -0.112	-2.256 -2.185	0.025 0.029
BMI UAP	-0.469 -3.298	0.191 1.956	-0.170 -0.116	-2.457 -1.686	0.015 0.093

MCS-12	B (unstandardized)	SE	β(standardized)	t	P-value
UAP ± 10% B (-1.067 to -0.873)	-0.970	1.524	-0.033	-0.636	0.525
Revascularization* UAP	3.234 -1.797	1.651 1.572	0.104 -0.061	1.959 -1.143	0.051 0.254
Age UAP	0.001 -0.996	0.032 1.526	0.002 -0.034	0.039 -0.653	0.969 0.514

Gender* UAP	-1.898 -1.243	1.252 1.529	-0.078 -0.042	-1.516 -0.813	0.130 0.417
Prior Stroke UAP	-2.337 -0.992	1.234 1.518	-0.097 -0.034	-1.893 -0.654	0.059 0.514
Current smoking UAP	-3.767 -0.985	1.600 1.514	-0.120 -0.033	-2.354 -0.651	0.019 0.516

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