ONLINE SUPPLEMENTARY APPENDIX

Supplementary material to the paper:

Pre-hospital One-hoUr Troponin in a low-prevalence population of Acute Coronary Syndrome

The OUT-ACS study

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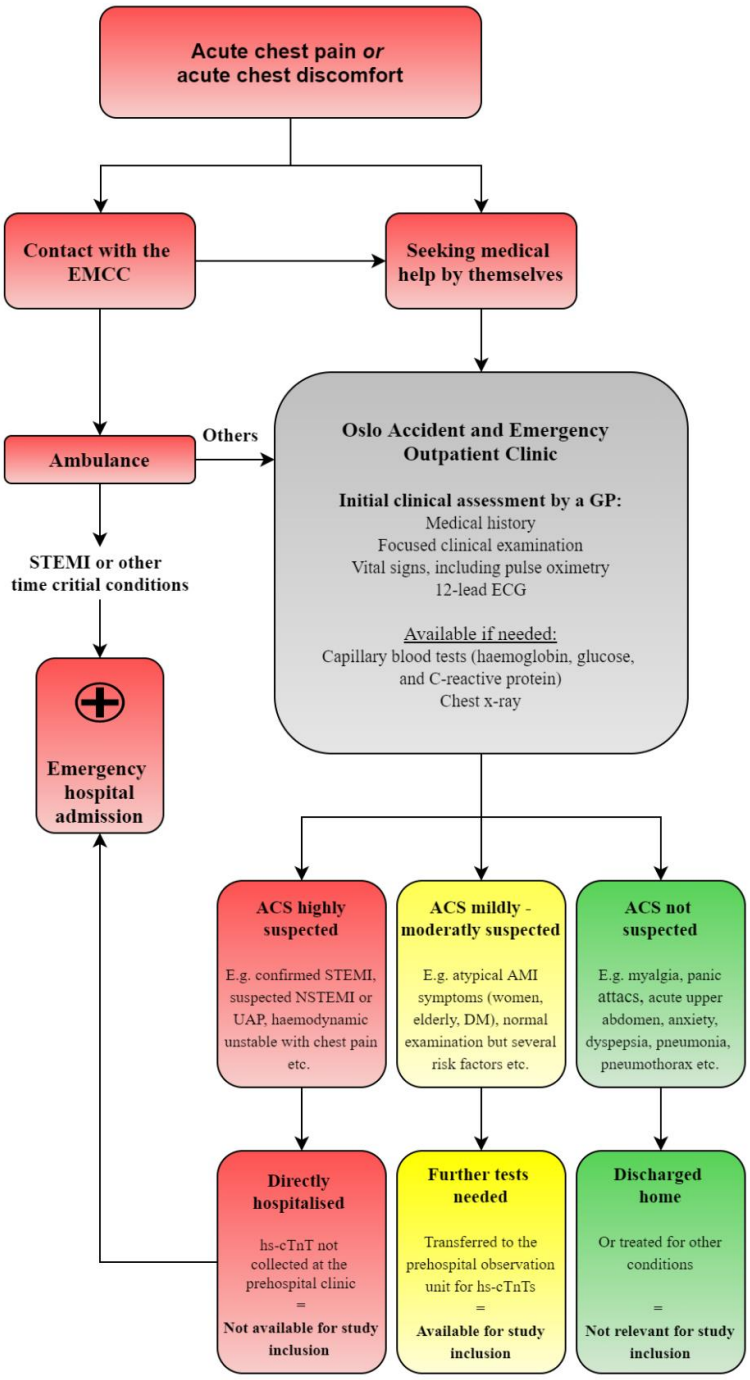
Figure S1 Patient management at Oslo Accident and Emergency Outpatient Clinic prior study enrollment



ACS: acute coronary syndrome; AMI: acute myocardial infarction; DM: diabetes mellitus; ECG: electrocardiogram; EMCC: emergency medical communication centre; GP: general practitioner; hs-cTnT: high-sensitivity cardiac troponin T, NSTEMI; non-ST-segment Elevation Myocardial Infarction; STEMI; ST-Elevation Myocardial Infarction, UAP: unstable angina pectoris

Sample size

We estimated the minimum sample size required based on a presumed AMI prevalence of 5 % in a general practice chest pain population (1-3). A power of 80 %, with a critical level of significance of 5 % resulted in an initial minimum sample size of 1039 patients. However, hs-cTnT was sampled at three different time points (0h, 1h and 4h) for each patient. Due to this clustering effect of the data at the patient level, the initial sample size was inflated using a design effect of 1.6 to give a minimum sample size of 1662 patients.

Table S1 STARD checklist for studies on diagnostic accuracy (4)

Section & Topic	No	Item	Reported on page #
TITLE OR ABSTRACT	1	Identification as a study of diagnostic accuracy using at least one measure of accuracy (such as sensitivity, specificity, predictive values, or AUC)	2
ABSTRACT	2	Structured summary of study design, methods, results, and conclusions (for specific guidance, see STARD for Abstracts)	2
INTRODUCTION	3	Scientific and clinical background, including the intended use and clinical role of the index test	4
	4	Study objectives and hypotheses	4
METHODS *Study design*	5	Whether data collection was planned before the index test and reference standard were performed (prospective study) or after (retrospective study)	5
Participants	6	Eligibility criteria	5
	7	On what basis potentially eligible participants were identified (such as symptoms, results from previous tests, inclusion in registry)	5, Figure S1
	8	Where and when potentially eligible participants were identified (setting, location and dates)	5, Figure S1
	9	Whether participants formed a consecutive, random or convenience series	5
Test methods	10a	Index test, in sufficient detail to allow replication	6-7
	10b	Reference standard, in sufficient detail to allow replication	7
	11	Rationale for choosing the reference standard (if alternatives exist)	7
	12a	Definition of and rationale for test positivity cut-offs or result categories of the index test, distinguishing pre-specified from exploratory	7, Figure 2
	12b	Definition of and rationale for test positivity cut-offs or result categories of the reference standard, distinguishing pre-specified from exploratory	8
	13a	Whether clinical information and reference standard results were available to the performers/readers of the index test	8
	13b	Whether clinical information and index test results were available to the assessors of the reference standard	8
Analysis	14	Methods for estimating or comparing measures of diagnostic accuracy	8-9

	15	How indeterminate index test or reference standard results were handled	Table 2, 15
	16	How missing data on the index test and reference standard were handled	9
	17	Any analyses of variability in diagnostic accuracy, distinguishing pre-specified from exploratory	n.a.
	18	Intended sample size and how it was determined	Supplementary appendix
RESULTS			
Participants	19	Flow of participants, using a diagram	10, Figure 1
	20	Baseline demographic and clinical characteristics of participants	11, Table 1
	21a	Distribution of severity of disease in those with the target condition	12, Table S2
	21b	Distribution of alternative diagnoses in those without the target condition	12, Table S3
	22	Time interval and any clinical interventions between index test and reference standard	7
Test results	23	Cross tabulation of the index test results (or their distribution) by the results of the reference standard	13, Figure 2
	24	Estimates of diagnostic accuracy and their precision (such as 95% confidence intervals)	Figure 2-3
	25	Any adverse events from performing the index test or the reference standard	13, Table 2
DISCUSSION	26	Study limitations, including sources of potential bias, statistical uncertainty, and generalisability	16
	27	Implications for practice, including the intended use and clinical role of the index test	16, and 18
OTHER INFORMATION	28	Registration number and name of registry	2, and 10
	29	Where the full study protocol can be accessed	n.a.
	30	Sources of funding and other support; role of funders	19

n.a.: not available

Table S2 Hs-cTnT in patients with acute myocardial infarction

	Total AMI (n=61)	Rule-out (n=1)*	Observation (n=15)	Rule-in (n=45)	
Manifestation at the OAEOC, n					
0h ≥52 ng/L	34	-	-	34	
Δ0-1 hour	11	-	-	11	
Δ0-4 hour	8	1	7	-	
Altered clinical presentation†	8	-	8	-	
Time interval from symptom onset to first hs-cTnT, n				**> 52 ng/L** (n=34)	**Δ0-1 hour** (n=11)
< 2 hours	1	-	-	-	1
2 – 2.99 hours	6	-	3	2	1
3 – 5.99 hours	16	-	5	8	3
6 – 11.99 hours	25	-	5	14	6
12 – 23.99 hours	10	1	1	8	-
> 24 hours	3	-	1	2	-

Hs-cTnT manifestation and symptom duration prior first hs-cTnT sampling among patients with AMI. Further subdivided according to the 0/1-hour algorithm.

ECG: electrocardiogram; hs-cTnT: high-sensitivity cardiac troponin T

* The one false-negative case also underwent endpoint adjudication, as she was not hospitalised for further tests. She was categorised as a potential AMI even though none of her hs-cTnT values exceeded 14 ng/L (Δ0-4 hour > 50 %, hs-cTnT: 5 – 6 – 13 – 8 ng/L at 0 – 1 – 4 – 12 hours, respectively) due to increased focus on sex-specific thresholds for hs-cTn.(5)

† Including relevant change between initial and repeated ECGs

Table S3 Distributions of the prehospital hs-cTnT values

	At least one hs-cTnT > URL (n=293)	All hs-cTnT < URL (n=1418)	Total (n=1711)
According to the 0/1-hour algorithm			
Rule-out	**2**	**1309**	**1311**
Observation	**230**	**104**	**334**
Rule-in	**62**	**4**	**66**
AMI versus non-AMI			
Significant rise/fall	**67**	**3**	**70**
AMI	58	3	61
No-AMI	9	0	9
No rise/fall	**226**	**1415**	**1641**
Disposition after OAEOC			
Primary care	**172**	**1313**	**1485**
No follow-up	34	360	394
Contact regular GP	104	872	976
Admitted municipal STF	15	8	23
Referral to hospital outpatient clinic	18	49	67
Left during observation	1	24	25
Hospital	**132**	**94**	**226**
AMI	58	2	60
No-AMI with significant rise/fall	9	0	9
No-AMI without significant rise/fall	65	92	157
90-day incidence of AMIs or all-cause death	**65**	**5**	**70**

Distribution of hs-cTnT values sampled (0, 1 or 4 hours) during the prehospital observation, classified by hs-cTnT values below or above the URL (14 ng/L). Further subdivided according to the 0/1-hour algorithm, final adjudication, disposition after ended observation at the OAEOC, and 90-day prognosis for AMI or all-cause death.

AMI: acute myocardial infarction; GP: general practitioners; hs-cTnT: high-sensitivity cardiac troponin T; OAEOC: Oslo Accident and Emergency Outpatient Clinic; STF; short-term facility; URL: upper reference limit

Table S4 Characteristics of misclassified patients according to the 0/1-hour algorithm

	Sex	Age	Symptom onset to hs-cTnT (hours)	Hs-cTnT at OAEOC			According to the 0/1h algorithm	Disposition after OAEOC	Final diagnosis (ICD-10)
				0h	1h	4h			
False negative (n=1)	F	70	18.0	5	6	13	Rule-out	Primary care	Pain upper abdomen, gastralgia (R10.1)
False positives (n=21)	M	81	15.8	47	42	49	Rule-in	Primary care	Chest pain, unspecified (R07.4)
	M	59	5.3	11	4	6	Rule-in	Primary care	Chest pain, unspecified (R07.4)
	F	64	5.4	10	4	4	Rule-in	Primary care	Chest pain, unspecified (R07.4)
	F	53	3.5	11	17	10	Rule-in	Primary care	Chest pain, unspecified (R07.4)
	F	42	3.5	8	13	8	Rule-in	Primary care	Precordial pain (R07.2)
	M	92	7.3	61	65	61	Rule-in	Primary care	Tendency to fall (R29.6)
	M	56	15.6	71	73	75	Rule-in	Primary care	Syncope (R55.0)
	M	84	8.6	52	50	45	Rule-in	Primary care	Acute upper respiratory infection, unspecified (J06.9)
	F	83	16.0	63	62	64	Rule-in	Primary care	COPD, exacerbation (J44.1), heart failure (I50.9)
	M	85	22.0	26	31	33	Rule-in	Primary care	Urethrotrigonitis (N30.0)
	M	42	22.8	18	5	8	Rule-in	Hospital	Chest pain, unspecified (R07.4)
	M	88	14.6	62	60	53	Rule-in	Hospital	Chest pain, unspecified (R07.4)
	M	92	86.1	71	66	58	Rule-in	Hospital	Chest pain, unspecified (R07.4), paroxysmal AF (I48.0)
	M	41	3.2	39	47	X	Rule-in	Hospital	Tachycardia (R00.0)
	M	50	4.7	6	11	X	Rule-in	Hospital	Tachycardia (R00.0)
	M	73	2.9	90	90	X	Rule-in	Hospital	Ventricular tachycardia (I47.2)
	M	69	4.5	170	177	X	Rule-in	Hospital	Atherosclerotic heart disease (I25.1)
	M	93	2.9	60	60	X	Rule-in	Hospital	Atherosclerotic heart disease (I25.1), angina pectoris (I20.9)
	M	64	2.7	14	21	41	Rule-in	Hospital	Acute myocarditis, unspecified (I40.9)
	F	86	5.9	38	33	X	Rule-in	Hospital	Heart failure (I50.9), chest pain, unspecified (R07.4), essential hypertension (I10)
	F	87	103.9	161	165	161	Rule-in	Hospital	PE (I26.9), heart failure (I50.9), chronic AF (I48.2)

AF: atrial fibrillation; COPD: chronic obstructive pulmonary disease; hs-cTnT: high-sensitivity cardiac troponin T; ICD-10: international classification of diseases 10th revision; OAEOC: Oslo Accident and Emergency Outpatient Clinic; PE: pulmonary embolism; X: not sampled due to early hospitalisation

References

1. Bruyninckx R, Aertgeerts B, Bruyninckx P, Buntinx F. Signs and symptoms in diagnosing acute myocardial infarction and acute coronary syndrome: a diagnostic meta-analysis. Br J Gen Pract. 2008;58(547):105-11.
2. Verdon F, Herzig L, Burnand B, Bischoff T, Pecoud A, Junod M, et al. Chest pain in daily practice: occurrence, causes and management. Swiss Med Wkly. 2008;138(23-24):340-7.
3. Bösner S, Becker A, Haasenritter J, Abu Hani M, Keller H, Sonnichsen AC, et al. Chest pain in primary care: epidemiology and pre-work-up probabilities. Eur J Gen Pract. 2009;15(3):141-6.
4. Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig L, et al. STARD 2015: an updated list of essential items for reporting diagnostic accuracy studies. BMJ. 2015;351:h5527.
5. Mueller T, Egger M, Peer E, Jani E, Dieplinger B. Evaluation of sex-specific cut-off values of high-sensitivity cardiac troponin I and T assays in an emergency department setting - Results from the Linz Troponin (LITROP) study. Clin Chim Acta. 2018;487:66-74.