Characterization of the Observe Zone of the ESC 2015 high-sensitivity cardiac troponin 0h/1h-algorithm for the Early Diagnosis of Acute Myocardial Infarction

Thomas Nestelberger, MD^{1,2*}; Karin Wildi, MD^{1,2*}; Jasper Boeddinghaus, MD^{1,2}; Raphael Twerenbold, MD^{1,2}; Tobias Reichlin, MD^{1,2}; Maria Rubini Giménez, MD^{1,2}; Christian Puelacher, MD^{1,2}; Cedric Jaeger, MD^{1,2}; Karin Grimm, MD^{1,2}; Zaid Sabti, MD¹; Petra Hillinger, MD¹; Nikola Kozuharov, MD¹; Jeanne du Fay de Lavallaz MS^{1,2}; Florentina Pinck, MS¹; Beatriz Lopez, MD^{2,3}; Emilio Salgado, MD^{2,3}; Òscar Miró, MD^{2,3}; Roland Bingisser, MD⁴; Jens Lohrmann, MD^{1,4}; Stefan Osswald, MD¹,
Christian Mueller, MD^{1,2}.

¹*Department of Cardiology and Cardiovascular Research Institute Basel (CRIB), University Hospital Basel, Switzerland;* ²*GREAT network;* ³*Emergency department, Hospital Clinic, Barcelona, Catalonia, Spain;* ⁴*Department of Emergency Medicine, University Hospital Basel, Switzerland*

*both authors have contributed equally and should be considered first author

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Correspondence to:

Prof. Dr. Christian Müller, Department of Cardiology and *Cardiovascular Research Institute Basel (CRIB)*, University Hospital Basel; Petersgraben 4, CH-4031 Basel, Switzerland

Phone Number: +41 61 328 65 49; Fax number: +41 61 265 53 53

E-mail: christian.mueller@usb.ch

ABSTRACT

Objective: The novel high-sensitivity cardiac troponin (hs-cTn) 0h/1h-algorithm substantially improves the early triage of patient's assigned "rule-out" or "rule-in" of acute myocardial infarction (AMI), while diagnostic uncertainty remains in that 25-30% of patients assigned to "observe". We aimed to better characterize these patients.

Methods: In a prospective multicenter diagnostic study, we applied the hs-cTnT 0h/1h-algorithm in 2213 unselected patients presenting with symptoms suggestive of AMI to the emergency department. The final diagnosis was adjudicated by two independent cardiologists using all available information. Survival at 720-days was the prognostic endpoint. Findings were validated using a hs-cTnI 0h/1h-algorithm.

Results: Twenty-four percent (n=523) of patients were assigned to "observe" by the hs-cTnT 0h/1h-algorithm. These patients differed significantly in multiple characteristics from "rule-out" and "rule-in" patients: they were older, in 75% male, and very often (57%) had pre-existing coronary artery disease (CAD). Diagnostic uncertainty for the presence of an AMI/UA was high. Only 39% of patients were suitable for coronary computed tomography angiography (CCTA). The most common final adjudicated diagnoses were non-cardiac disease (38%), non-coronary cardiac disease (24%), unstable angina (UA, 21%), and AMI (15%). Absolute hs-cTnT-changes within 3h had the highest diagnostic accuracy for AMI (AUC 0.86). Cumulative 720-day survival rate was 86%, which was significantly lower as compared to "rule-out" ($p<0.001$) and comparable to "rule-in" ($p=ns$). Findings were similar for the hs-cTnI "observe" zone.

Conclusion: “Observe” patients are typically elderly men with pre-existing CAD and high long-term mortality. Absolute hs-cTn-changes within 3h, functional stress imaging and coronary angiography are the key diagnostic modalities.

INTRODUCTION

Patients with symptoms suggestive of acute myocardial infarction (AMI) account for approximately 10% of all emergency department (ED) consultations.[1] Rapid identification of AMI as life-threatening disorder is important for the early initiation of appropriate, evidence-based therapy. The diagnosis of AMI is based on clinical assessment, the 12-lead ECG and biomarkers of myocardial necrosis (cardiac troponin (cTn)).[2][3][4] The recently developed high-sensitivity cardiac troponin (hs-cTn) assays, which allow measurement of even low cTn concentrations with high precision, have been shown to largely overcome the sensitivity deficit of conventional cTn within the first hours and provide higher overall diagnostic accuracy in the diagnosis of AMI.[5][6][7] Clinical use of hs-cTn allows the application of recently developed rapid “rule-out” and “rule-in” protocols.[8][9][10][11][12][13][14][15][16][17] Among these, the hs-cTn 0h/1h-algorithm has particular appeal and is recommended for clinical use in the recent ESC 2015 guidelines,[13] as it is well validated, and allows accurate “rule-in” and/or safe “rule-out” in 70-75% of patients. This algorithm interprets hs-cTn levels and their early changes as quantitative variables and assigns patients with suspected AMI and no significant ST-segment elevation in the initial ECG into three groups: patients with low initial hs-cTn levels AND no hs-cTn change within 1h to “rule-out”, patients with at least moderately elevated hs-cTn concentrations OR a relevant change within 1h to “rule-in” and the remaining patients to the “observe” zone. While patient’s management is largely defined and simplified in patients assigned “rule-out” and “rule-in”, it remains challenging in many patients assigned to the “observe” zone. It is currently unknown, which further risk stratification and work-up would be best suited for these patients.

Detailed characterization of patients in the “observe” zone (e.g. presence of pre-existing coronary artery disease (CAD)) to develop targeted diagnostic strategies and to evaluate the suitability of existing imaging tools including coronary computed tomography angiography (CCTA) for advancing the rapid identification of the serious underlying causes of chest pain in the “observe” zone.[18] This was the aim of this study.

METHODS

Patient Population

The Advantageous Predictors of Acute Coronary Syndrome Evaluation (APACE) Study is an ongoing prospective international multicenter diagnostic study. From April 2006 to June 2013, consecutive patients older than 18 years presenting to the ED with symptoms suggestive of AMI with an onset or peak within the last 12 hours were recruited in nine hospitals in three countries (Switzerland, Spain, Italy), after written informed consent was obtained. While recruitment was independent from renal function at presentation, patients with end-stage renal failure on chronic dialysis were excluded. For this analysis patients were also excluded if A) they presented with ST-elevation myocardial infarction as biomarkers are considered of less importance in these patients or B) the final diagnosis remained unclear after adjudication. Among the remaining, patients were eligible for analysis if measurements at presentation as well as at 1 hour of hs-cTnT and hs-cTnI were available. The most common reasons for missing values at 1 hour were early transfer to the catheterization laboratory or coronary care unit and diagnostic procedures around the 1 hour window that precluded blood draw at 1 hour.

The study was carried out according to the principles of the Declaration of Helsinki and approved by the local ethics committees. The authors designed the study, gathered and analysed the data, vouch for the data and analysis, wrote the paper, and made the decision to submit it for publication. The assays were donated by the manufacturers, who had no role in the design of the study, data analysis, manuscript, or decision to submit for publication.

Clinical Assessment

All patients underwent a clinical assessment that included standardized and detailed medical history including detailed assessment of 32 predefined chest pain characteristics, vital signs, physical examination, 12-lead ECG, continuous ECG rhythm monitoring, pulse oximetry, standard blood test, and chest radiography if indicated. Levels of cTn were measured at presentation and serially thereafter as long as clinically indicated. Diagnostic uncertainty at 90 minutes in the ED was quantified by a visual analogue scale (VAS) documenting clinical judgment of the treating physician for the presence of an ACS. Heart failure was defined as a history of chronic heart failure or a B-type natriuretic peptide level of at least 100 pg/ml. [19][20] Chronic heart failure was defined, clinically, as a syndrome in which patients have typical symptoms (e.g. breathlessness, ankle swelling, and fatigue) and signs (e.g. elevated jugular venous pressure, pulmonary crackles, and displaced apex beat). Treatment of patients was left to discretion of the attending physician.

Reference Standard: Adjudicated Final Diagnosis

Two independent cardiologists reviewed all available medical records - patient history, physical examination, results of laboratory testing, radiologic testing, ECG, echocardiography, cardiac exercise stress test, lesion severity and morphology in coronary angiography - pertaining to the patient from the time of ED presentation to 90-days follow up. In situations of disagreement about the diagnosis, cases were reviewed and adjudicated in conjunction with a third cardiologist. Adjudication of the final diagnosis was performed centrally in a core lab (University Hospital Basel) and included two sets of serial cTn measurements: serial cTn measurements obtained as part of routine clinical care locally (several cTn assays), and serial measurements of

hs-cTnT from study blood draws performed centrally in a core laboratory in order to take advantage of the higher sensitivity and higher overall diagnostic accuracy offered by the hs-cTnT assays.[21]

AMI was defined and hs-cTn levels interpreted as recommended in current guidelines [4]. In brief, AMI was diagnosed when there was evidence of myocardial necrosis in association with a clinical setting consistent with myocardial ischemia. Myocardial necrosis was diagnosed by at least one hs-cTnT value above the 99th percentile together with a significant rise and/or fall. Absolute changes in hs-cTnT were used to determine significant changes based on the diagnostic superiority of absolute over relative changes. [22][23] Based on studies of the biological variation of cTnT [24][25], as well as on data from previous chest pain cohort studies [26][27][28] a significant absolute change was defined as a rise or fall of at least 10ng/l within six hours, or 6ng/l within three hours.

Blood sampling and laboratory methods

Blood samples for determination of hs-cTnI (Architect) and hs-cTnT (Elecsys) were collected at presentation to the ED, and 1, 2, 3 and 6 hours after presentation. After centrifugation, samples were frozen at -80°C until assayed in a blinded fashion in a dedicated core laboratory.

The Abbott hs-cTnI assay used was the final pre-commercial release version of the ARCHITECT High Sensitive STAT Troponin I assay (Abbott Laboratories, IL). Samples were thawed, mixed, and centrifuged prior to analysis and according to manufacturer's instructions. The hs-cTnI assay has a 99th percentile concentration of 26.2ng/l with a corresponding co-efficient of variation (CV) of <5% and a limit of

detection (LoD) of 1.9ng/l. [29] Long-term stability of Tnl and very high correlation between plasma and serum has been demonstrated.[29][30]

The limit of blank (LoB) and LoD of the Roche hs-cTnT (Elecsys 2010, Roche Diagnostics) assay were determined to be 3ng/l and 5ng/l respectively. The 99th-percentile of a healthy reference population was reported at 14ng/l with an imprecision corresponding to 10% CV at 13ng/l.[31]

Calculation of the estimated glomerular filtration rate (eGFR) was performed using the abbreviated Modification of Diet in Renal disease formula.[32]

hs-cTn 0h/1h-algorithm

The algorithms incorporate baseline hs-cTn levels and absolute hs-cTn changes within 1h. Selection of these two parameters was based on the previously published very high diagnostic accuracy of the combination of absolute levels and absolute changes.[23][33] The algorithms for hs-cTnT (Elecsys) and hs-cTnl (Architect) were derived and validated in recent studies. [7][8][9][23] The “rule-out” criteria were defined as an undetectable (<5ng/l) hs-cTnT at presentation or a baseline hs-cTnT level concentration of less than 12ng/l combined with an absolute change within the first 1 hour of less than 3ng/l. “Rule-in” is defined by a baseline hs-cTnT concentration of at least 52ng/l or an absolute change in hs-cTnT within the first 1 hour of at least 5ng/l. The remaining patients were classified in the “observe” zone.

The “rule-out” criteria for hs-cTnl were defined as undetectable levels (<2ng/l) at presentation or baseline hs-cTnl concentrations of less than 5ng/l combined with an absolute change within the first 1 hour of less than 2ng/l. “Rule-in” is defined by a baseline hs-cTnl concentration of at least 52ng/l or an absolute change in hs-cTnl within the first 1 hour of at least 6ng/l (Figure 1)

Patients suitable for CCTA

We used established criteria[34] to define patients suitable for CCTA. These include absence of pre-existing CAD and absence of a condition in which the use of intravenous beta-blockers to achieve a heart rate of 50 to 60 beats per minute (bpm) might harm patients such as asthma, acute pulmonary embolism peripheral artery disease and heart failure and other contraindications for CCTA like eGFR <30ml/min/1.73 m², atrial fibrillation (AF) or BMI >39kg/m².

Follow-up

After hospital discharge patients were followed after 3, 12 and 24 months by telephone or in written form. Major adverse cardiovascular events (including death, myocardial infarction, coronary artery bypass grafting, percutaneous coronary intervention) were recorded by establishing contact with the patient and the family physician. Information regarding death was also obtained from the national mortality registry. The primary prognostic end point was all-cause mortality.

Statistical analysis

The data are expressed as medians $\pm$ interquartile range (IQR) for continuous variables, and for categorical variables as numbers and percentages (%). All variables between the “rule-in”, “observe” zone and “rule-out” group were compared by Mann Whitney U Test between continuous variables or Pearson chi-square test for categorical variables. We used Cox proportional hazard models to compute hazard ratios (HRs) and 95% CIs for predictors of 720 days death or AMI for risk stratification within the “observe” patients. Variables for multivariable analysis were selected after significance ($p < 0.05$) in univariate analysis. Receivers operating

characteristic (ROC) curves were constructed to assess the sensitivity and specificity of hs-cTn for diagnosing AMI in “observe” patients. Survival during 720 days of follow-up according to the classification provided by both algorithms was plotted in Kaplan-Meier curves, and the log-rank test was used for comparison of survival between groups.

All hypothesis testing was two-tailed, and P values of less than 0.05 were considered to indicate statistical significance. All statistical analyses were performed with the use of IBM SPSS Statistics for Windows, version 22.0 (SPSS Inc Chicago, IL).

Results

Patient's characteristics and diagnostic uncertainty

Twenty-four percent (n=523) of patients were assigned to “observe” by the hs-cTnT (ElecSys) 0h/1h-algorithm (Table 1A). “Observe” patients differed significantly in multiple characteristics from “rule-out” and “rule-in” patients: they were older (mean age 74 years), in 75% male, had more often impaired renal function, very often (57%) pre-existing CAD, chronic use of nitrates, and substantial diagnostic uncertainty regarding the presence of an ACS at 90 minutes (Figure 2A). IQR of the clinical judgement for the presence of an ACS was 20% to 70%. In only 24% of patients with an adjudicated diagnosis of AMI/unstable angina (UA) the treating physician were certain of ACS being the cause of acute chest discomfort, defined as likelihood for ACS >80% at 90 minutes after ED presentation.

Among “observe patients”, 75% of those with an adjudicated final diagnosis of ACS had pre-existing CAD. (Table 2A). Overall, due to the various relative and absolute contraindications for CCTA only 208 patients (39%) of all “observe” patients seemed to be appropriate candidates for CCTA. (online supplement; Figure 6)

Final adjudicated diagnoses

Among “observe” patients the most common final adjudicated diagnoses were non-cardiac disease (38%), non-coronary, cardiac disease including Tako-Tsubo cardiomyopathy, myocarditis, tachyarrhythmias and heart failure (24%), UA (21%), and AMI (15%; Figure 3A).

Resource Use including Imaging

Resource use characteristics are shown in Table 3A. Coronary angiography was performed in 28% of “observe” patients and coronary revascularization was performed in 17%. Stress ECG and stress myocardial perfusion scanning were performed in about 50% of “observe” patients.

Diagnostic performance of 2h and 3h hs-cTnT blood concentrations

The diagnostic accuracy for 2h and 3h hs-cTnT and its changes from ED presentation are shown in Figure 4A. Absolute hs-cTnT-changes within 3h had the highest diagnostic accuracy for AMI (AUC 0.86; 95% CI 0.78 - 0.94).

Major adverse cardiovascular events and risk stratification during follow-up

There were 64 deaths and 44 future AMIs within 720 days in the “observe” zone. Long-term mortality in the “observe” zone was similar to that of the “rule-in” zone ($p=0.277$ by log-rank test; Figure 5A). Results of univariate and multivariate Cox proportional hazard analysis for prediction of all-cause death and future AMI are shown in Table 4A. Higher age, lower BMI, lower systolic blood pressure and previous AMI remained independent predictors for death/future AMI.

Validation using the hs-cTnI 0h/1h-algorithm

Twenty-eight percent ($n=515$) of patients were assigned to “observe” by the hs-cTnI (Architect) 0h/1h-algorithm in the validation cohort. The “observe” group according to the hs-cTnI (Architect) 0h/1h-algorithm had similar characteristics as the “observe” group according to the hs-cTnT (Elecsys) 0h/1h-algorithm (online supplement, Table 1B, Table 3B, Figure 2B). Among “observe” patients the most common final adjudicated diagnoses were non-cardiac disease (46%), non-coronary, cardiac

disease including Tako-Tsubo cardiomyopathy, myocarditis, tachyarrhythmias and heart failure (19%), UA (19%), and AMI (12%; online supplement, Figure 3B). Absolute hs-cTnI-changes within 3h had the highest diagnostic accuracy for AMI (AUC 0.85; Figure 4B).

There were 59 deaths and 36 future AMIs within 24 months in the “observe” zone. Long-term mortality in the “observe” zone was similar to that of the “rule-in” zone ($p=0.159$ by log-rank test; online supplement, Figure 5B). Higher age and previous AMI remained independent predictors for death/future AMI. (Table 4B).

DISCUSSION

The new 2015 ESC hs-cTn 0h/1h-algorithm [13] accelerates and simplifies the management of patients with suspected AMI, however, only in patients assigned to “rule-out” or “rule-in”. Early diagnosis of AMI remains challenging for patients assigned to the “observe” zone, where hs-cTn testing at 3h and imaging are deemed necessary. This analysis from a large multicentre study aimed to better characterize “observe” patients and provide insights which diagnostic modalities would be best suited.

We hereby reported seven major findings, which apply to both hs-cTnT and hs-cTnI 0h/1h-algorithms: First, “observe” patients were older, and more than half had pre-existing CAD, therefore ischemic preconditioning may have contributed to the only moderate increase of hs-cTn. [35] Second, diagnostic uncertainty at 90 minutes in the ED was still very high, clearly highlighting the unmet clinical need. Third, one-third of “observe” patients did have an adjudicated diagnosis of AMI or UA, while non-cardiac disorders and other cardiac disorders including Tako-Tsubo cardiomyopathy, myocarditis, tachyarrhythmias and heart failure were present in 40% and 25% of patients. Forth, the majority of “observe” patients had relative or absolute contraindications for the use of CCTA such as pre-existing CAD, severe renal dysfunction, atrial fibrillation, BMI>39, and contraindications to the use of intravenous B-Blockers. [34] Only 39% of “observe” patients seemed to be suitable candidates for CCTA. Fifth, diagnostic accuracy of 2h and 3h hs-cTn, particularly absolute changes in plasma concentration from ED presentation was high, providing further support for current guidelines recommending a 3h hs-cTn measurement in these patients. **Sixth, higher age, lower BMI, lower BP and history of MI were associated with the risk of death and future AMI in the hs-cTnT 0h/1h-algorithm, and higher age and history of**

MI were associated with the risk of death and future AMI in the hs-cTnI 0h/1h-algorithm. Seventh, mortality during 24 months in “observe” patients was as high as in patients “ruled-in” for AMI, and much higher as compared to patients in the “rule-out” zone.

These findings corroborate and extend previous studies,[8][9][10][11][12][13] and have major clinical implications. Due to the characteristics of “observe” patients, CCTA does seem a suitable imaging modality in only a small minority. [18][28] For the vast majority of “observe” patients either coronary angiography (in those with high pre-test probability for AMI or UA) or functional stress imaging seem to be the preferred tests. Stress tests, such as stress echocardiography, stress myocardial perfusion scanning, and stress cardiac magnetic resonance imaging in those with low-to-moderate pre-test probability for AMI or UA seem to be the most appropriate imaging modalities. Functional testing is mandatory to differentiate coronary lesions resulting in myocardial ischemia and acute chest pain at rest from lesions that are innocent bystanders regarding the acute chest pain episode leading to ED presentation.

Potential limitations of the present study merit consideration. Our study was conducted in ED patients with symptoms suggestive of AMI. While the multicentre design ensures that our findings are widely applicable in this setting, additional studies are required to investigate diagnostic strategies in patients presenting in settings with much lower pre-test probability for AMI such as a general practitioner. Second, while recruitment was independent from renal dysfunction, this study did not include patients with terminal kidney failure on chronic haemodialysis; therefore no statement can be made regarding imaging in these patients.

In conclusion, “observe” patients are typically elderly men with pre-existing CAD, a considerable diagnostic uncertainty regarding the presence of AMI or UA and high long-term mortality. Absolute hs-cTn-changes within 3h, functional stress imaging and coronary angiography are key diagnostic modalities.

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Figure Legends

Figure 1 **hs-cTnT and hs-cTnI 0h/1h-algorithm**

hs-cTnT and hs-cTnI 0h/1h-algorithm classifying patients into “rule-out”, “observe” and “rule-in”. hs-cTn values are presented in ng/l. 0h/1h = hs-cTn at presentation and after 1 hours. Delta 1h = absolute change of hs-cTn within the first hour.

Figure 2A **Boxplots for initial likelihood assessment**

hs-cTnT 0h/1h-algorithm for likelihood assessment by the emergency physician splitted for the “rule-in“, “observe“ and “rule-out“ and subdivided for the male and female. Boxes represent interquartile ranges (IQRs), while whiskers display ranges (without outliers further than 1.5 IQRs from the respective end of the box) and rings represent the outliers.

Figure 3A **Bars for final adjudicated diagnoses**

hs-cTnT 0h/1h-algorithm, bars for the five adjudicated diagnoses (AMI, unstable angina (UA), cardiac, not coronary, non-cardiac and unknown) according to the classification into “rule-in”, “observe” and “rule-out” in percent.

Figure 4A **Area under the receivers operating characteristic curve for risk stratification**

Area under the receivers operating characteristic curve (ROC) displaying prognostic accuracy of 0h hs-cTnT, 1h hs-cTnT, delta 0h/1h hs-cTnT and the combination of 0h hs-cTnT and delta 0h/1h hs-cTnT for long-term (720 days) all-cause death and future AMI displaying area under the curves (AUC) with 95% confidence interval (95%CI).

Figure 5A

Kaplan-Meier curves for the cumulative survival according to the three groups

hs-cTnT 0h/1h-algorithm, Kaplan Meier Curves displaying survival during 720 days of follow-up in the cohort according to the classification into the “rule-in”, “observe” and “rule-out” group. Differences in survival were assessed using the log-rank test (p all < 0.001; p observe/rule-in =0.277; p observe/rule-out <0.001).

Figure 1

Figure 2A

Figure 3A

Figure 4A

Figure 5A

Tableg

Table 1A Baseline characteristics hs-cTnT 0h/1h-algorithm

	All patients (n=2213)		"rule-in" (n=382; 17%)		"observe" (n=523; 24%)		"rule-out" (n=1308; 59%)		P obs/rule-in	P obs/rule-out
Age, years, median (IQR)	62	(50 - 74)	70	(59 - 79)	74	(65 - 81)	54	(45 - 65)	<0.001	<0.001
Male, sex, n (%)	1512	68%	256	67%	392	75%	864	66%	0.009	<0.001
BMI, kg/m², median (IQR)	27	(24 - 30)	26	(24 - 29)	27	(25 - 30)	26	(24 - 30)	0.002	0.019
Risk factors, n (%)										
Hypertension	1356	61%	276	72%	445	85%	635	49%	<0.001	<0.001
Hypercholesterolemia	1121	51%	221	58%	361	69%	539	41%	0.001	<0.001
Diabetes	393	18%	86	23%	145	28%	162	13%	0.079	<0.001
Current smoking	554	25%	84	22%	78	15%	392	30%	0.005	<0.001
History of smoking	828	37%	160	42%	233	45%	435	33%	0.464	<0.001
History, n (%)										
Coronary artery disease	762	34%	145	38%	298	57%	319	24%	<0.001	<0.001
Previous myocardial infarction	525	24%	107	28%	209	40%	209	16%	<0.001	<0.001
Previous revascularization	617	28%	103	27%	240	46%	274	21%	<0.001	<0.001
Peripheral artery disease	128	5.8%	35	9.2%	58	11%	35	2.7%	0.346	<0.001
Previous stroke	126	5.7%	40	10%	47	9.0%	39	3.0%	0.454	<0.001
positive family history	295	15%	50	15%	52	18%	18	16%	0.061	0.003
Chest pain onset <6h	1285	58%	214	56%	296	57%	775	59%	0.863	0.298
Creatinine clearance, mL/min/m2, median (IQR)	85	(69 - 101)	73	(55 - 94)	71	(55 - 86)	92	(80 - 106)	0.242	<0.001
BNP pg/ml, median (IQR)	75	(26 - 209)	197	(75 - 783)	136	(57 - 329)	38	(17 - 86)	0.002	<0.001
ECG findings, n (%)										
Left bundle branch block	65	2.9%	21	5.5%	26	5.0%	18	1.4%	0.725	<0.001
ST-segment elevation	36	1.6%	8	2.1%	7	1.4%	21	1.6%	0.369	0.665
ST-segment depression	218	10%	110	29%	71	14%	37	2.9%	<0.001	<0.001
T-wave inversion	271	12%	92	24%	99	19%	80	6.1%	0.061	<0.001
No significant ECG abnormalities	1692	78%	193	51%	346	66%	1153	88%	<0.001	<0.001
Heart rate >70/min	1192	55%	243	65%	265	51%	684	53%	<0.001	0.469
Medication at entry n (%)										
Aspirin/Thienopyridin	873	39%	167	44%	318	61%	388	30%	<0.001	<0.001
B-blockers	759	34%	139	36%	283	54%	337	26%	<0.001	<0.001
ACE/AT2- Inhibitors	858	39%	168	44%	328	63%	362	28%	<0.001	<0.001
Calcium- Antagonists	320	14%	69	18%	121	23%	130	9.9%	0.064	<0.001
Nitrates	248	11%	57	15%	113	22%	78	6.0%	0.011	<0.001

Table Legend: BMI: body mass index; BNP: brain natiruretic peptide; ECG: electrocardiogram; ACE: angiotensin converting enzyme; AT1: angiotensin 1

Table 2A

Table 2A Characteristics of "observe" patients hs-cTnT 0h/1h-algorithm

	"observe" (n=523)		ACS (n=188; 36%)		no ACS (n=335; 64%)		P value
Age, years, median (IQR)	74	(65 - 81)	74	(66 - 79)	74	(64 - 81)	0.508
Male, sex, n (%)	392	75%	157	84%	235	70%	0.001
BMI, kg/m ² , median (IQR)	27	(25 - 30)	27	(25 - 30)	27	(25 - 30)	0.527
Risk factors, n (%)							
Hypertension	445	85%	175	93%	270	81%	<0.001
Hypercholesterolemia	361	69%	159	85%	202	60%	<0.001
Diabetes	145	28%	59	32%	86	26%	0.169
Current smoking	78	15%	25	13%	53	16%	0.437
History of smoking	233	45%	96	51%	137	41%	0.025
History, n (%)							
Coronary artery disease	298	57%	141	75%	157	47%	<0.001
Previous myocardial infarction	209	40%	102	53%	107	32%	<0.001
Previous revascularization	240	46%	123	65%	117	35%	<0.001
Peripheral artery disease	58	11%	30	16%	28	8.4%	0.008
Previous stroke	47	9.0%	9	4.8%	38	11%	0.012
positive family history	52	11%	24	14%	29	9.1%	0.115
ACS Likelihood >80%	65	12%	45	24%	20	6.0%	<0.001
Chest pain onset <6h	296	57%	112	60%	184	55%	0.303
Creatinine clearance, mL/min/m2, median (IQR)	71	(55 - 86)	71	(54 - 86)	71	(56 - 86)	0.573
BNP pg/ml, median (IQR)	136	(57 - 329)	136	(60 - 269)	138	(57 - 380)	0.431
ECG findings, n (%)							
Left bundle branch block	26	5.0%	7	3.7%	19	5.7%	0.325
ST-segment elevation	7	1.4%	4	2.2%	3	0.9%	0.234
ST-segment depression	71	14%	33	18%	38	11%	0.042
T-wave inversion	99	19%	47	25%	52	16%	0.008
No significant ECG abnormalities	346	67%	110	60%	236	71%	0.008
Heart rate >70/min	265	51%	81	44%	184	55%	0.011
Medication at admission n (%)							
Aspirin/Thienopyridin	318	61%	155	83%	163	49%	<0.001
B-blockers	283	54%	123	65%	160	48%	<0.001
ACE/AT2- Inhibitors	328	63%	130	69%	198	59%	0.023
Calcium- Antagonists	121	23%	68	36%	53	16%	<0.001
Nitrates	113	22%	60	32%	53	16%	<0.001

Table Legend: ACS: acute coronary syndrome; BMI: body mass index; BNP: brain natriuretic peptide; ECG: electrocardiogram

ACE: angiotensin converting enzyme; AT1: angiotensin 1

Table 3A

Table 3A Resource use hs-cTnT 0h/1h-algorithm

	All patients (n=2213)		"rule-in" (n=382; 17%)		"observe" (n=523; 24%)		"rule-out" (n=1308; 59%)		P Value	P Value
Coronary Angiography n (%)	512	23%	246	64%	148	28%	118	9.0%	<0.001	<0.001
one vessel disease	99	4.5%	47	12%	33	6.3%	19	1.5%	0.002	<0.001
two vessel disease	113	5.1%	64	17%	25	4.8%	24	1.8%	<0.001	<0.001
three vessel disease	213	9.6%	106	28%	71	14%	36	2.8%	<0.001	<0.001
Coronary Intervention n (%)	297	13%	161	42%	88	17%	48	3.7%	<0.001	<0.001
left main vessel	11	0.5%	5	1.3%	4	0.8%	2	0.2%	0.415	0.038
RIVA	127	5.7%	67	18%	36	6.9%	24	1.8%	<0.001	<0.001
RCX	92	4.2%	59	15%	22	4.2%	11	0.8%	<0.001	<0.001
ACD	94	4.2%	45	12%	32	6.1%	17	1.3%	0.003	<0.001
Bypass Intervention	18	0.8%	9	2.4%	6	1.1%	3	0.2%	0.160	0.011
more than one intervention	44	2.0%	25	6.5%	12	2.3%	7	0.5%	0.001	<0.001
CABG n (%)	42	1.9%	24	6.3%	13	2.5%	5	0.4%	0.004	<0.001
Stress ECG n (%)	593	27%	68	18%	142	27%	383	29%	0.001	0.363
clinically positive	99	4.5%	10	2.6%	34	6.5%	42	3.2%	0.004	<0.001
electrically positive	86	3.9%	12	3.1%	40	7.6%	47	3.6%	0.007	0.001
MPS n (%)	222	10%	23	6.0%	77	15%	122	9.3%	<0.001	0.001
Ischemia sign	139	6.3%	7	1.8%	38	7.3%	27	2.1%	0.001	<0.001
PCI/CABG 30days FU n (%)	234	11%	111	29%	80	15%	43	3.3%	<0.001	<0.001
MPS 30days FU n (%)	154	7.0%	36	9.4%	24	4.6%	93	7.1%	0.006	0.067
Ischemia sign 30days FU	26	1.2%	5	1.3%	6	1.1%	15	1.1%	0.826	0.999
AMI 30days FU n (%)	15	0.7%	9	2.4%	6	1.1%	0	0.0%	0.160	<0.001

Table Legend: RIVA: Ramus interventricularis anterior; RCX: Ramus circumflexus; ACD: Arteria coronaria dextra; CABG: coronary artery bypass graft

MPS: myocardial perfusion scanning; PCI: percutaneous coronary intervention; AMI: acute myocardial infarction

Table 4A

Table 4A Cox proportional hazard analysis for prediction of all-cause death and future AMI within 720 days for "observe" patients

Variables	Univariate analysis		Multivariate analysis	
	Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value
Age per 10 years	1.865 (1.479 - 2.352)	<0.001	1.736 (1.345 - 2.242)	<0.001
Female sex	1.412 (0.915 - 2.178)	0.119		
BMI per 10 kg/m2	0.476 (0.294 - 0.773)	0.003	0.555 (0.323 - 0.953)	0.033
eGFR per 10 ml/min/1.73 m2	0.884 (0.811 - 0.963)	0.005	0.999 (0.909 - 1.098)	0.978
systolic blood pressure per 10 mmHg	0.909 (0.840 - 0.984)	0.018	0.924 (0.855 - 0.999)	0.047
0h hs-cTnT per 10 ng/l	1.327 (1.111 - 1.586)	0.002	0.421 (0.132 - 1.347)	0.154
1h hs-cTnT per 10 ng/l	1.359 (1.135 - 1.627)	0.001	3.052 (0.937 - 9.946)	0.064
History of				
Hypertension	1.885 (0.913 - 3.890)	0.086		
Diabetes	1.336 (0.867 - 2.059)	0.189		
current smoking	0.767 (0.409 - 1.439)	0.409		
Coronary artery disease	1.904 (1.223 - 2.963)	0.004	0.997 (0.517 - 1.924)	0.993
Myocardial Infarction	2.056 (1.368 - 3.089)	0.001	2.052 (1.128 - 3.734)	0.019

Table Legend: CI: Confidence interval; BMI: body mass index; eGFR: estimated glomerular filtration rate