



Evidence based interpretation of biomarkers in patients with chest pain - WESTCOR: Study design

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Keywords:	Chest pain, acute coronary syndrome, cardiovascular biomarkers, rule in/rule out algorithms;, troponin, NSTEMI, unstable angina pectoris
Abstract:	Objectives: The main aim of the Aiming toWards Evidence baSed

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	<p>Interpretation of Cardiac biomarkers in patients presenting with chest pain (WESTCOR-study) (Clinical Trials number NCT02620202) is to improve diagnostic pathways for patients presenting to the Emergency department (ED) with acute chest pain.</p> <p>Design: The WESTCOR-study is a two center, cross-sectional and prospective observational study recruiting unselected patients presenting to the ED with suspected non-ST elevation acute coronary syndrome (NSTEMI-ACS). Patient inclusion started September 2015 and we plan to include 2250 patients, finishing in 2019. The final diagnosis will be adjudicated by two independent cardiologists based on all available information including serial high sensitivity cardiac troponin measurements, coronary angiography, coronary CT angiography and echocardiography. The study includes one derivation cohort (N=985) that will be used to develop rule out /rule in algorithms for NSTEMI and NSTEMI-ACS (if possible) using novel troponin assays, and to validate established NSTEMI algorithms, with and without clinical scoring systems. The study further includes one subcohort (n=500) where all patients are examined with coronary CT angiography independent of biomarker status, aiming to assess the associations between biomarkers and the extent and severity of coronary atherosclerosis. Finally, an external validation cohort (N=750) will be included at Stavanger University Hospital. Prospective studies will be based on the merged cohorts.</p> <p>Conclusion: The WESTCOR study will provide new diagnostic algorithms for early inclusion and exclusion of NSTEMI-ACS and insights in the associations between cardiovascular biomarkers, CT-angiographic findings and short and long-term clinical outcomes.</p>



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4 1 Aiming towards evidence based interpretation of cardiac
5 2 biomarkers in patients presenting with chest pain - the
6 3 WESTCOR study: Study design
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21 9 troponin; NSTEMI; unstable angina pectoris.
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24 10
25
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27
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29
30 13 and Stavanger University hospital.
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33 14
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35 15 **Disclosure statement**
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37 16 Kristin M Aakre has served on one advisory board for Roche Diagnostics. Torbjørn Omland
38
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40
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49 22 Care.
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1 **Abstract**

2 *Objectives:* The main aim of the **Aiming toWards Evidence baSed inTerpretation of Cardiac**
3 **biOmarkers in patients pREsenting with chest pain (WESTCOR-study)** (Clinical Trials number
4 NCT02620202) is to improve diagnostic pathways for patients presenting **to the Emergency**
5 **department (ED)** with acute chest pain.

6 *Design:* The WESTCOR-study is a two center, cross-sectional and prospective observational
7 study recruiting unselected patients presenting to the ED with suspected non-ST elevation acute
8 coronary syndrome (NSTEMI-ACS). Patient inclusion started September 2015 and we plan to
9 include 2250 patients, finishing in 2019. The final diagnosis will be adjudicated by two
10 independent cardiologists based on all available information including serial high sensitivity
11 cardiac troponin measurements, coronary angiography, coronary CT angiography and
12 echocardiography. The study includes one derivation cohort (N=985) that will be used to
13 develop rule out /rule in algorithms for NSTEMI and NSTEMI-ACS (if possible) using novel
14 troponin assays, and to validate established NSTEMI algorithms, with and without clinical
15 scoring systems. The study further includes one subcohort (n=500) where all patients are
16 examined with coronary CT angiography independent of biomarker status, aiming to assess the
17 associations between biomarkers and the extent and severity of coronary atherosclerosis.
18 Finally, an external validation cohort (N=750) will be included at Stavanger University
19 Hospital. Prospective studies will be based on the merged cohorts.

20 *Conclusion:* The WESTCOR study will provide new diagnostic algorithms for early inclusion
21 and exclusion of NSTEMI-ACS and insights in the associations between cardiovascular
22 biomarkers, CT-angiographic findings and short and long-term clinical outcomes.

1 **Introduction**

2 Despite reduced incidence and improved therapies non ST- elevation acute coronary syndrome
3 (NSTE-ACS) remains one of the leading causes of death in the industrialized world [1].
4 Internationally do 6-10% of patients who are admitted to the ED have symptoms suggestive of
5 acute coronary syndrome (ACS) [2, 3]. Only a minor proportion have ACS [4, 5], apparently 15-
6 20% are discharged with a final diagnosis of myocardial infarction, while another 10-15% are
7 diagnosed with unstable angina pectoris (UAP) [6, 7]. Numerous strategies to improve the
8 efficiency of the diagnostic pathway of patients presenting with acute chest pain have been
9 published [8, 9, 10, 11]. While ST elevation myocardial infarction (STEMI) is identified based
10 on specific **electrocardiogram** (ECG) changes, the European Society of Cardiology (ESC)
11 currently advocates specific troponin-based algorithms for early rule out and rule in of non-
12 STEMI (NSTEMI) [12]. Evaluation of these algorithms shows that a small percentage of
13 NSTEMI patients mistakenly are ruled out [13], and this percentage might be unacceptable high
14 to some clinicians [14]. Finally, UAP is diagnosed based on clinical history, laboratory results,
15 ECG and imaging [8]. UAP is associated with a more favorable prognosis compared to
16 NSTEMI, but still need in-hospital diagnosis and follow-up [15, 16, 17]. **Faster and more
17 accurate diagnostic pathways for UAP is beneficial from an individual patient and health care
18 provider perspective.**

19 **Aims of the WESTCOR study**

20 First, we will develop algorithms for rule out and rule in of NSTEMI using novel troponin
21 assays and possibly also new myocardial necrosis biomarkers. We will investigate whether
22 already published troponin based algorithms used alone or in combination with clinical risk
23 scores might reduce the number of incorrectly ruled out NSTE-ACS patients, and incorrectly
24 ruled in patients with non-coronary chest pain. Second, we will search for and validate novel
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1 biomarkers or algorithms for diagnosing UAP. Third, we will investigate if novel biomarkers
2 may predict significant obstructive coronary artery disease as diagnosed with coronary
3 computed tomography angiography (CCTA). The fourth and last aim is to investigate the ability
4 of different biomarkers to predict long-term mortality and cardiovascular risk.

6 **Study organization and ethics**

7 The WESTCOR study is a collaborative project including Haukeland University Hospital
8 (Bergen) and Stavanger University Hospital (*Stavanger*). The study is chaired by a steering
9 committee. The Regional Committees for Medical and Health Research Ethics in Norway has
10 approved the study and biobank (2014/1365 REK vest and 2014/1905 REK vest), and the study
11 is registered at Clinical Trials (NCT02620202).

13 **Materials and methods**

14 *Study design*

15 The study is a two-center, cross-sectional prospective observational study. The study plans to
16 include 2250 patients, divided into three different cohorts (figure 1). The WESTCOR derivation
17 cohort (WESTCOR-D) will include approximately 1000 patients. The data will be used to
18 develop novel algorithms (see Supplemental data, table 1) and for validation of already
19 suggested rule out/rule in algorithms (see Supplemental data, table 2) for NSTEMI, NSTEMI-ACS
20 and short-term major adverse cardiovascular events (MACE) [9, 18], and for prediction of long-
21 term cardiovascular endpoints. The second cohort is the WESTCOR-CT cohort including 500
22 patients who will have a CCTA performed as part of the study protocol, unless clinically
23 contraindicated, (contrast allergy, decompensated heart failure and a eGFR below 30
24 ml/min/1.73m²). The pulse frequency needs to be below 60 beats per minute.

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3 1 The data will be used for investigation and validation of novel biomarkers for diagnosing
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5 2 significant coronary artery stenosis and arteriosclerosis. The WESTCOR-D and WESTCOR-
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7 3 CT cohorts are recruited at Haukeland University Hospital using high-sensitive c-TnT (5th gen,
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9 4 Roche Diagnostics) as routine clinical test. The last subcohort (the WESTCOR validation
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11 5 cohort (WESTCOR-V)) will recruit 750 patients at Stavanger University Hospital and utilize
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13 6 hs-cTnI (Abbott Diagnostics) as the clinical routine test for adjudication. Finally, we will merge
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15 7 the three cohorts and validate different algorithms in subgroups of patients. Prediction of long-
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17 8 term endpoints may also be undertaken based on the total data set.
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23 24 10 *Study enrollment and bio-banking*

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26 11 Norway has large rural areas and a general practitioner (GP) commonly evaluates patients with
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28 12 acute conditions before they are referred to the ED, while other patients come directly to ED
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30 13 after contacting the emergency service. A Norwegian study showed that most chest pain
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32 14 patients who present to the GP are referred to the hospital [19]. All patients with suspected
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34 15 NSTEMI-ACS are potentially eligible for inclusion in the study (Table 1), and receive oral
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36 16 information about the study upon arrival. After oral consent is given blood is drawn for the
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38 17 biobank at arrival, and after 1 (approximately 2/3 of the patients), 3 and 8-12 hours. Troponin
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40 18 results obtained after 1 hour are by design not reported to the attending clinicians. Full study
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42 19 information and written consent are obtained when the clinical situation is stabilized. Patients
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44 20 who do not wish to participate after reading the study information (less than 1% of those
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46 21 enrolled to date) are immediately withdrawn from the study and their samples destroyed.
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54 23 Recruitment started in September 2015. Up to October 2018 1280 patients has been enrolled at
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56 24 Haukeland University Hospital and 250 patients at Stavanger University Hospital, this
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3 1 corresponded to 8 patients per week for Haukeland University Hospital, approximately 20-25%
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5 2 of the anticipated recruitment rate. Low inclusion rate is due to competing pressures on staff.
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12 5 *Diagnosis*

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14 6 Two independent cardiologists adjudicate the final diagnosis based on all available clinical,
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16 7 routine laboratory, ECG, ultrasound and imaging findings, including CCTA and conventional
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18 8 angiography. A third adjudicator resolves disagreements.
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21 9 Specific diagnostic criteria are predefined for 22 different medical conditions based on current
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23 10 guidelines (See supplemental data). NSTEMI and UAP are defined according to the third
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25 11 universal definition for MI [20], and a 20-50% change in troponin concentration is regarded as
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27 12 a significant change as suggested by ESC in 2012 [21] (supplemental data). Clinical information
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29 13 needed to calculate a large number of risk scores (e.g. HEART, EDAC, GRACE, TIMI) are
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31 14 retrospective collected from the patients files.
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38 16 *Follow-up and end points*

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40 17 Three months after admission, all patients receives a letter inviting them to have a blood
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42 18 sample drawn and to fill out a questionnaire (including Seattle Angina Score, Rose Dyspnoea
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44 19 Score, RAND-12 and Hospital Anxiety and Depression Scale). Further follow-up is
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46 20 undertaken through national health care registers; the Norwegian Patient Register and
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48 21 Norwegian Cause of Death Registry. The following end points will be recorded 1 and 5 years
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50 22 after admission: total mortality, and the incidence of MACE defined as cardiovascular death,
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52 23 MI, UAP, stable angina (requiring hospitalization), revascularization, stroke, heart failure and
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54 24 cardiac arrhythmias.
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1 *Statistics*

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5 2 The baseline characteristics will be analyzed using ordinary descriptive statistics, including
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8 3 parametric (Student's t-test) and non-parametric (Mann Whitney U test) statistical tests for
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11 4 continuous variables and Chi-square or Fisher Exact test for categorical variables, as
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13 5 appropriate. The efficiency and safety of different biomarkers or biomarker panels as rule out
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15 6 and rule in markers will be compared using ordinary descriptive statistics. Statistical analyses
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17 7 will include calculation of sensitivity, specificity, positive and negative predictive value, and
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19 8 likelihood ratios, as well as area under the receiver operating characteristics curve (AUC-ROC).
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21 9 Differences in AUC-ROC will be evaluated using the Delong test. C-statistics will be used to
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24 10 measure the incremental prognostic information of different biomarkers by multivariate logistic
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26 11 and Cox proportional hazard regression analysis adjusting for established risk indices and
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28 12 biomarkers for prognosis. When applicable we will also calculate net reclassification index and
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30 13 a risk score that include established risk indices for prognosis.
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33 34 35 15 *Sample size and power calculations*

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37 16 Sample size and power calculations were targeted towards the ability of biomarkers or
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39 17 algorithms to diagnose NSTEMI or NSTEMI-ACS with a power of at least 80%. A difference
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41 18 between two different methods of 5% for sensitivity, 5% for specificity [22] and 0.03 in AUC
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43 19 was thought to be clinically meaningful. To be able to discover a 5 % difference in sensitivity
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45 20 or specificity, a total of 355 patients must be included (McNemar's test). To have a power of
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47 21 80% to detect a difference in AUC of 0.03 (e.g. from 0.92 to 0.95) (Delong test; rank correlation
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49 22 between tests set to 0.9, ratio between negative and positive subjects set to 8) 92 patients with
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51 23 the condition (NSTEMI or NSTEMI-ACS) and 736 subjects without the condition, a total of 828
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53 24 patients need to be included. To do a subgroup analysis e.g. in a cohort of acute chest pain
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55 25 patients with chronic kidney disease (CKD) we estimated that the prevalence of NSTEMI in a
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3 1 CKD population would be 35% [23]. To have a power of 80% to detect a difference in AUC of
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5 2 0.03 (i.e. from 0.87 to 0.90) (DeLong test; rank correlation between tests set to 0.9, ratio between
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7 3 negative and positive subjects set to 1.9) 141 NSTEMI and 263 patients without NSTEMI
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9 4 needed to be included (totally 404). If the prevalence of CKD in the total population is 18%,
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11 5 totally 2250 patients must be included.
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17 **Results**

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19 8 The first 985 of the included patients have been adjudicated, baseline characteristic are shown
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21 9 in table 2.
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26 **Discussion**

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29 12 The high sensitivity troponin assays have improved the diagnostic pathways for NSTEMI, with
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31 13 faster identification and better sensitivity as the main outcome [11, 24, 25, 26]. Even so, there
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33 14 are still important challenges that limit the efficiency of acute investigations of possible NSTEMI-
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35 15 ACS.
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41 17 The first challenge is that patients with myocardial ischemia without necrosis (UAP) cannot be
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43 18 accurately identified using troponin measurement or the ECG alone or in combination. The
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45 19 second challenge is that troponin is not a specific marker of ischemic myocardial injury. Stable
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47 20 increases are seen in chronic diseases like kidney disease and multi-morbid conditions.
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49 21 Transient increases are seen in a range of conditions including atrial fibrillation, exacerbation
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51 22 of chronic obstructive pulmonary disease, sepsis, acute stroke, burn injury and strenuous
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53 23 physical activity [27]. Many of these conditions have clinical symptoms resembling acute
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55 24 coronary ischemia. Consequently, large proportions of patients are in need of additional
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57 25 investigations (often imaging) to distinguish NSTEMI-ACS from non-coronary chest pain or non-
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3 1 coronary myocardial injury [28, 29]. The last challenge is that although troponins are specific
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5 2 for myocyte necrosis in the clinical setting of coronary ischemia, they provide no information
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7 3 of the underlying pathophysiology causing ischemia and necrosis. Even in NSTEMI patients,
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9 4 troponins cannot distinguish between atherosclerosis, and other often more rare causes of
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11 5 ischemia like spontaneous coronary dissection, coronary spasm or oxygen supply/demand
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13 6 imbalance as the cause of the MI. Improved knowledge of the underlying mechanisms for
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15 7 ischemia in general and atherosclerosis in particular is necessary to develop new and targeted
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17 8 treatments for both acute and stable coronary artery disease.
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10 *Different diagnostic algorithms currently suggested for early rule out/rule in of NSTEMI*

11 A substantial number of algorithms are published for early rule out and rule in of NSTEMI (See
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13 supplemental tables, table 2A, B and C). Of these, the rule-out algorithms are the most
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15 important to validate, since early, correct discharge of non-diseased individuals will have a
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17 large impact on health care expenditure, and erroneous rule-out of NSTEMI patients may cause
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19 serious harm to the patient. An earlier study found that clinicians would accept a false rule out
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21 rate for MACE of 0.5 to 1% [14], meaning that rule-out algorithms should have a sensitivity
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23 for NSTEMI of at least 99%, and high negative predictive value. The different algorithms for
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25 ruling out NSTEMI have a sensitivity ranging from 89.5% to 100% when tested in different
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27 populations.
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47 20 Lower sensitivity for ischemic coronary artery disease should be expected if troponins were
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49 21 used in an algorithm developed to diagnose UAP, NSTEMI-ACS or short-term MACE compared
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51 22 to diagnosing NSTEMI. **However, using troponin assays with improved analytical sensitivity**
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53 **and/or lower analytical variation combined with optimally adapted clinical scoring systems,**
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55 **may show improved sensitivity.**
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3 1 Rule in algorithms are intend to route critically ill NSTEMI-ACS patients directly to coronary care
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5 2 units and should consequently have high specificity and positive predictive value. Usually they
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7 3 are less accurate compared to rule out pathways, with specificity ranging from 75% to 100%
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9 4 (See supplemental data, table 2C). When tested in different populations the rule out and rule in
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11 5 algorithms have very different efficiencies for diagnostic clarification of patients, ranging
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13 6 between a total of 21% to 80% [30, 31, 32]. The reason for this is probably the heterogeneity
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15 7 of the chest pain populations included in the different studies.
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9 *Different biomarkers used for identification of NSTEMI, UAP and coronary artery disease*

10 High sensitivity troponin assays have been available since 2009 [33, 34], and novel assays are
11
12 still released. Another recently available biomarker of myocardial necrosis is cardiac Myosin
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14 binding protein C [35]. Whether this marker is superior to troponins for diagnosing MI and
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16 confers incremental prognostic information, needs further investigation. Recently, a
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18 multimarker approach including midkine, adiponectin, apolipoprotein C-I, and kidney injury
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20 molecule-1 could predict obstructive coronary artery disease $\geq 70\%$ stenosis with a positive
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22 predictive value of 90% [36]. Furthermore, different microRNAs have been suggested as
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24 potential diagnostic biomarkers for NSTEMI-ACS [37]. Analysis of components of Neutrophil
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26 Extracellular Traps has shown promising results for investigation of the pathophysiology and
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28 mechanisms that lead to atherosclerosis [38]. Measurement of these and other novel biomarkers
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30 may be possible in the WESTCOR-study.
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53 *Strengths and limitations of the WESTCOR-study*

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55 23 An important strength of the WESTCOR-study is that the patients have three to four troponin
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57 24 measurements, ensuring a minimum observational time in hospital of 8 hours, increasing the
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59 25 validity of the clinical diagnosis. The study closely mirrors clinical practice, by not excluding
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1 patients with end stage renal disease or patients with more than a 12 hour history of symptoms
2 suspicious of NSTEMI-ACS. Further, investigations with CCTA are scheduled in a high
3 proportion of included patients, which also adds certainty to the clinical diagnosis and
4 furthermore enables us to investigate biomarkers that may predict coronary artery stenosis. The
5 follow-up blood sample and clinical data registered 3 months after admission, permits
6 monitoring of long-term dynamics in troponin concentrations. The study takes advantage of the
7 high quality health care registers that are available in Norway, and register follow-up data at
8 least up to five years after inclusion.

9 The limitations are that only Norwegian centers are included. A Norwegian study showed that
10 13% of the patients admitted to the ED had chest pain [39]. This is higher than internationally
11 (e.g. 6-10%) [2, 3]. The reason is probably that Norwegian GPs will treat some non-cardiac
12 acute conditions locally while most chest pain patients are referred [19], increasing the
13 proportion of chest pain patients in Norwegian EDs. Another limitation is the relatively low
14 inclusion rate due to ward personal not being able to priority the study during busy periods in
15 the ER. This indicates that not all eligible patients are recruited. This is a common problem for
16 this type of study, however the ACS rate and patient characteristics in WESTCOR are similar
17 to comparable studies [11, 40]. **The last limitation is that not all patients in the WESTCOR-CT
18 cohort will be able to undergo CCTA since clinical contraindications prevent performing the
19 investigation for some individuals.**

21 *Conclusion*

22 Most previous studies has not explored the abilities to diagnose UAP, NSTEMI-ACS or short-term
23 MACE. We are conducting a cross-sectional and prospective observational study with wide
24 inclusion criteria in order to reflect chest pain patients admitted to the ED in routine clinical
25 practice. This study will provide new diagnostic algorithms for early inclusion and exclusion

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3 1 of NSTEMI-ACS and insights in the associations between cardiovascular biomarkers, CT-
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5 2 angiographic findings and short and long-term clinical outcomes Adjudication of the NSTEMI-
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7 3 ACS diagnoses, and the ability to assess long-term prognosis utilizing one follow-up sample
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9 4 and high-quality health care registers are important strengths of the WESTCOR-study.
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19 8 **Figure legends**

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21 9 Figure 1: *Flow chart outlining the study design.*
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Table 1. Inclusion and exclusion criteria.

INCLUSION CRITERIA

Patients admitted with chest pain suspicious of NSTEMI-ACS

Age >18 years

EXCLUSION CRITERIA

Patients with STEMI

Patients transferred from other wards or hospitals for second opinion

Comatose or other reasons for not being able to consent

Terminal patients, short life expectancy

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10 4 Table 2. Baseline characteristics of the 985 first included patients in the WESTCOR study.
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12 5 Continuous variables are reported as median values (25-75 percentiles in brackets) and
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14 6 categorical variables as number of patients (percentages in brackets).
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Baseline characteristics	Total N=985	ACS n=237	Non ACS n=748	P-value
Age in years	63 (52.0-74.0)	69 (59.0-78.0)	61 (50.0-73.0)	<0.001
Male gender	600 (60.6)	171 (72.2)	427 (57.1)	<0.001
Time from symptom onset to first troponin sample in hours	8.1 (3.4-46.0)	8.7 (3.2-47.2)	8.0 (3.4-46.1)	0.756
<i>Risk factors</i>				
Hypertension	409 (41.5)	120 (50.6)	289 (38.6)	0.003
Hypercholesterolemia	179 (18.5)	55(23.5)	124 (16.9)	0.002
Diabetes mellitus	121 (12.3)	51 (21.5)	70 (9.4)	<0.001
Current smoker	204 (20.7)	42 (17.5)	160 (21.7)	<0.001
History of smoking	410 (41.4)	127 (52.9)	283 (37.8)	<0.001
Family history of ischemic heart disease	192 (19.5)	42 (17.7)	150 (20.1)	0.479
Previous MI	205 (20.8)	76 (32.1)	129 (17.2)	0,001
Previous PCI	207 (21.0)	81 (34.2)	126 (16.8)	<0.001
Previous CABG	82 (8.3)	44 (18.6)	38 (5.1)	<0.001

Previous peripheral vascular disease	22 (2.2)	12 (5.1)	10 (1.3)	0.001
Previous Stroke	27 (2.7)	9 (3.8)	18 (2.4)	0.381
Baseline drugs				
Statins	382 (38.8)	115 (48.5)	267 (35.7)	<0.001
Diuretics	177 (18.0)	50 (21.1)	127 (17.0)	0.150
ACE inhibitor/A2 blocker	331 (33.6)	94 (39.7)	237 (31.7)	0.067
Beta-blocker	339 (34.4)	104 (43.9)	235 (31.4)	0.002
Aspirin	342 (34.7)	123(51.9)	219 (29.3)	<0.001
Oral Anticoagulant	118 (11.9)	22 (9.3)	96 (12.8)	0.142
Antithrombotic agents	72 (7.4)	30 (12.5)	42 (5.7)	<0.001
Baseline measurements				
BMI, kg/m ²	26.3 (24.2-29.5)	25.8 (24.1-29.1)	26.6 (24.2-29.7)	0.222
HEART score	4.0 (3.0-5.0)	6.0 (5.0-7.0)	3.0 (2.0-4.0)	<0.001
HbA1c, %	5.6 (5.4-5.9)	5.8 (5.3-5.9)	5.6 (5.3-5.9)	<0.001
eGFR, ml/min/1.73m ²	85.4 (70.3-97.1)	79.5 (64.0-79.6)	86.3 (72.0-98.5)	<0.001
cTnT, ng/L	7.0 (3.0-18.0)	22.0 (9.0-63.0)	6.0 (3.0-12.0)	<0.001

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SUPPLEMENTAL DATA

TABLES

Table 1. Examples of how different pre-specified single sample concentrations may be tested as rule out algorithm for NSTEMI using a novel high sensitive troponin assay. Percentage of patients ruled out for NSTEMI are calculated for each concentration (first column) and each diagnosis (first row). The **Limit of Detection (LoD)** rounded to the nearest whole number. The concentration yielding the lowest percentage of ruled out NSTEMI patients and the highest percentage of ruled out non-cardiac chest pain patients will be the most favourable.

Concentration tested	NSTEMI	UAP	Non-ACS cardiac disease	Non-cardiac chest pain	Other diseases	Total
LoD						
LoD + 1 ng/L						
LoD + 2 ng/L						
LoD + ... continuing up to 99 th percentile of the assay or further as applicable						

Table 2A. The table shows currently suggested single sample and two sample (i.e. 1 and 3 hour) rule out algorithms for AMI, acute coronary syndrome and 30-day MACE.

Rule-out method	Assay	Criteria	Sensitivity, %	NPV, %	Primary outcome	Study	Ref.
cTn _{0h} / cTn _{3h}	Abbott	TnI ₀₋₃ <26 ng/L	Not given	98-100	Rule out ACS	2015 ESC Guidelines	[1]
	Roche	TnT ₀₋₃ <14 g/L					
cTn _{0h} / cTn _{3h}	Abbott	TnI ₀₋₃ < 26 ng/L	93.2	99	Rule out AMI	ADAPT/ ADP/	[2]
	Roche	TnT ₀₋₃ < 14 ng/L	94.8	99		EDACS/ RING	
cTn _{0h} / cTn _{3h}	Abbot	Time from symptom onset > 2 h and TnI ₀ <5 ng/L and TnI _{Δ0-3} <3 ng/L	99.7	99,5	Rule out AMI and 30- day MACE	High- STEACS	[3]

cTn _{0h} / cTn _{1h}	Abbot	Time from symptom onset > 3 h and TnI ₀ <2 ng/L or TnI ₀ <5 ng/L and TnI _{Δ0-1} <2 ng/L	98.8	99.8	Rule out AMI	ADAPT/ ADP/ EDACS/ RING	[4]
	Roche	Time from symptom onset > 3 h TnT ₀ <5 ng/L or TnT ₀ <12 ng/L and TnT _{Δ0-1} <3 ng/L	97.1	99.5			
cTn _{0h} / cTn _{1h}	Abbot	TnI ₀ <5 ng/L and TnI _{Δ0-1} <2ng/L TnI ₀ <3 ng/L and TnI _{Δ0-1} <5 ng/L	98,8 97.8-100	99,6 98.8-100	Rule out AMI	APACE *	[5]
cTn _{0h} / cTn _{1h}	Siemens	TnI ₀ <5 ng/L and TnT _{Δ0-1} <2ng/L	100	100	Rule out AMI	APACE*	[6]
cTn _{0h} / cTn _{1h}	Abbott	Time from symptom onset > 3 h and TnI ₀ <2 ng/L Or TnI ₀ <5ng/L and TnI _{Δ0-1} <2ng/L	98.4 98.4	99.5 99.5	Rule out AMI	APACE	[7]

1	cTn _{0h}	Abbott	TnI ₀ <4 ng/L and glucose <6.6mmol/L	100	100	Rule out AMI within 7 days of presentation	ROMI-3	[8]
2			TnI ₀ <5 ng/l and glucose <6.6 mmol/L	99.2	99.7			
3			TnI ₀ <5 ng/l and glucose <6.6 mmol/L	99.2	99.7			
4			And HbA1c >6,5%					
5			TnI ₀ <5 ng/L	97.0	99.2			
6								
7	cTn _{0h}	Roche	TnT ₀ <24 ng/L and glucose <5.6 mmol/L.	99.2	99.6			
8			TnT ₀ <24 ng/L and glucose <5.6 mmol/L and	99.2	98.3			
9			HbA1c <6.5%					
10			TnT ₀ <14 ng/L	92.5	98.3			
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		TnT ₀ <14ng/L and glucose <5.6mmol/L	100	100			
cTn _{0h}	Roche	TnT ₀ <3 ng/L	97,4	96,9	Rule out AMI	Meta analysis	[9]
		TnT ₀ <5 ng/L	97,4	96,9			
		TnT ₀ <14 ng/L	89,5	96,5			
cTn _{0h}	Abbot	TnI ₀ <5 ng/L	98	99.5	Index Myocardial Infarction or Cardiac Death at 30 Days	Meta Analysis	[10]
cTn _{0h}	Abbot	TnI ₀ <LOD (2ng/L)	100	100	Rule out AMI	APACE	[7]
		TnI ₀ <5 ng/L	97.1	99.1			

cTn _{0h}	Abbott	TnI ₀ <LoD (1,9ng/L)	98,8	99,6	Rule out	UTROPIA	[11]
		TnI ₀ <LoD (1,9ng/L) + normal ECG	99,4	99,6	AMI	/ High-	
		High-STEACS <(5ng/L)	94,7	98,9	30- day	STEACS	
		High-STEACS < (5ng/l) + normal ECG	99,5	98,8	MACE		

*Validation cohort

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Table 2B. The table includes currently suggested rule out algorithms combining biomarkers and clinical risk scores for AMI, 30 days MACE and acute coronary syndrome.

Rule-out method	Assay	Criteria	Sensitivity, %	NPV, %	Primary outcome	Study	Ref.
cTn<LOD and TIMI score at 0 hours	Roche	TnT ₀ ≤ LoD (<5 ng/L) and TIMI score=0	98.7	99.6	30-day MACE	ADAPT/	[12]
		TnT ₀ ≤ LoD (<5 ng/L) and TIMI ≤1	98.4	99.5		IMPACT/	
		TnT ₀ ≤ LoD (<5 ng/L) and TIMI ≤2	97.4	99.3		ADAPT-ADP/	
	Abbot	TnI ₀ ≤ LoD (2 ng/L) and TIMI score=0	98.5	99.5		EDACS-ADP/	
		TnI ₀ ≤ LoD (2 ng/L) and TIMI ≤1	98.2	99.6		TRUST	
		TnI ₀ ≤ LoD (2ng/L) and TIMI ≤2	97.7	99.4			

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46	cTn _{0h} combined with five different risk scores	Roche	Hs-TnT ₀ ≤14 ng/L (99 percentile)	83.5	98.3	AMI within 30 days	Post hoc analysis of TRUST	[13]
			m-Goldman Score 0 and hs-TnT ₀ ≤14 ng/L	98.7	99.0			
			m-Goldman Score ≤1 and hs-TnT ₀ ≤14 ng/L	98.7	99.7			
			TIMI score 0 and hs-TnT ₀ ≤14 ng/L	100	100			
			TIMI score ≤1 and hs-TnT ₀ ≤14 ng/L	94.9	99.2			
			GRACE score <60(Incorporates hs-TnT)	100	100			
			GRACE score <80(Incorporates hs-TnT)	92.3	98.0			
			HEART score ≤2(Incorporates hs-TnT)	98.7	99.2			

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		HEART score ≤ 3 (Incorporates hs-TnT)	93.7	98.3			
		Vancouver Chest Pain Rule (Incorporates hs-TnT)	100	100			
cTn _{0h}	Abbot	hs-TnI ₀ ≤ 26.2 ng/L (99 percentile)	62.1	96.9	AMI within	Post hoc	[13]
combined with		m-Goldman Score 0 and hs-TnI ₀ ≤ 26.2 ng/L	98.5	99	30 days	analysis of	
five different risk		m-Goldman Score ≤ 1 and hs-TnI ₀ ≤ 26.2 ng/L	92.8	98.7		TRUST	
scores		TIMI score 0 and hs-TnI ₀ ≤ 26.2 ng/L	95.5	99.0			
		TIMI score ≤ 1 and hs-TnI ₀ ≤ 26.2 ng/L	87.9	98.3			
		GRACE score < 60 (Incorporates hs-TnI)	98.5	98.9			
		GRACE score < 80 (Incorporates hs-TnI)	89.4	97.5			

		HEART score ≤ 2 (Incorporates hs-TnI)	98.5	99.1			
		HEART score ≤ 3 (Incorporates hs-TnI)	97.0	99.3			
		Vancouver Chest Pain Rule (Incorporates hs-TnT)	100	100			
cTn _{0h} / cTn _{2h} combined with different risk scores	Abbot	ADAPT Pathway cTnI _{0-2h} ≤ 18 ng/L No new ischemia on ECG TIMI Score ≤ 1	92.8	99.1	30 day ACS	ADAPT IMPACT	[14]
		EDACS Pathway cTnI _{0-2h} ≤ 18 ng/L No new ischemia on ECG EDACS Score < 16	92.1	99.0			

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		HEART Pathway cTnI ₀₋₂ ≤18 ng/L HEART Score 0-3	95.0	99.2			
		Vancouver Chest Pain Rule NOT rule cTnI _{0-2h} ≤18 ng/L No new ischemia on ECG NOT Score =0	98.6	99.6			
cTn _{0h} / cTn _{2h}	Abbot	ADAPT Pathway cTnI _{0-2h} ≤18 ng/L No new ischemia on ECG TIMI Score ≤1	96.9	99.7	30 day	ADAPT	[14]
combined with					acute MI	IMPACT	
different risk							
scores							

1		EDACS Pathway	97.9	99.8			
2		cTnI _{0-2h} ≤18 ng/L					
3		No new ischemia on ECG					
4		EDACS Score <16					
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13							
14		HEART Pathway	97.9	99.8			
15		cTnI _{0-2h} ≤18 ng/L					
16		HEART Score 0-3					
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24		Vancouver Chest Pain Rule	100	100			
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26							
27							
28		NOT rule	100	100			
29		cTnI _{0-2h} ≤18 ng/L					
30		No new ischemia on ECG					
31		NOT Score =0					
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Table 2C. The table includes currently suggested single sample and two sample (i.e. 1 and 3 hour samples) rule in algorithms for AMI, 30 days and all-cause mortality. NC: not calculable. URL: Upper reference limit.

Rule- in method	Assay	Criteria	Specificity, %	PPV, %	Primary outcome	Study	Ref.
cTn _{0h} / cTn _{2h}	Roche	TnT _{0/2} >53 ng/L or TnT _{Δ0-2} >10 ng/L	99	85	30 days all- cause mortality	APACE*	[15]
cTn _{0h} / cTn _{1h}	Siemens	TnI ₀ >107 ng/L and TnI _{Δ0-1} >19 ng/L	95.6	70.4	Rule in AMI	APACE*	[6]
cTn _{0h} / cTn _{1h}	Abbot	TnI ₀ >52 ng/L or TnI _{Δ0-1} >6 ng/L	NC	75-80	Rule in AMI	ESC guide lines	[1]
	Roche	TnT ₀ >52 ng/L or TnT _{Δ0-1} >5 ng/L	NC	75-80			
cTn _{0h} / cTn _{1h}	Roche	TnT ₀ >52 ng/L or TnT _{Δ0-1} >5 ng/L	96.1	77.2	Rule in AMI	TRAPID- AMI	[16]

cTn _{0h}	Abbot	TnI ₀ >64 ng/L	97.5	72.8	Rule in AMI within 7 days	ROMI-3	[8]
		TnI ₀ >99 ng/L	99	85.3			
		TnI ₀ >82 ng/L and glucose >11 mmol/L	99.9	93.8			
	Roche	TnT ₀ >206 ng/L	99.5	80.8			
	TnT ₀ >206 ng/L and glucose >11 mmol/L	100	100				
		TnT ₀ >52 ng/L	92.5	46.8			

* Validation cohort

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3 1 SUPPLEMENTAL DATA
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6 2 **Diagnostic definitions**
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8

9 3 *Myocardial infarction* was defined according to the third universal definition of myocardial
10 4 infarction.[1]

11 5 Detection of a rise and/or fall of cardiac biomarker values (preferably cardiac **troponins**
12 6 cTn) with at least one value above the 99th percentile upper reference limit (URL) and
13 7 with at least one of the following:

- 14 8 •Symptoms of ischemia
- 15 9 •Development of pathologic Q waves in the electrocardiogram (ECG)
- 16 10 •New or presumed new significant ST-segment-T wave (ST-T) changes or new left
17 11 bundle branch block (LBBB).
- 18 12 •Identification of an intracoronary thrombus by angiography or autopsy
- 19 13 •Imaging evidence of new loss of viable myocardium or a new regional wall motion
20 14 abnormality

21 15 *Unstable angina pectoris* — UAP: Defined as symptoms suggestive of an ACS without
22 16 elevation in biomarkers with or without ECG changes indicative of ischemia [2].

23 17 *Stable angina* was defined as typical angina symptoms lasting >1 month without an increase in
24 18 magnitude, duration or frequency of the pain and a known history of coronary artery disease
25 19 [3].

20 20 *Pericarditis* was diagnosed if at least two of four diagnostic criteria were present, as defined
21 21 in several studies: typical pleuritic chest pain, detection of a pericardial rub on auscultation,
22 22 typical ECG changes, new or increased amount of pericardial effusion on echocardiography
23 23 [4]. *Myocarditis* was diagnosed according to the position statement of ESC from 2013 [5].

24 24 *Takotsubo cardiomyopathy* was diagnosed with the modified criteria suggested by The Mayo
25 25 Clinic in 2008 [6].

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3 26 *Heart failure* was defined according to the ESC diagnostic criteria of 2016 [7] .
4
5 27 *Atrial fibrillation, atrial flutter* and other supraventricular arrhythmias were diagnosed by ECG
6
7
8 28 findings and the lack of symptoms and biochemical results supporting another disease.
9
10 29 *Aortic stenosis* and other valve diseases were diagnosed in accordance with echocardiographic
11
12 30 results and a history supporting the valve disease as cause of the symptoms [8].
13
14 31 *Myalgia* was defined as chest pain provoked by palpation in lack of cardiac disease.
15
16 32 *GERD* was based on gastroscopic findings, also in the lack of cardiac disease.
17
18 33 *Cholecystitis* were defined by the Tokyo Guidelines of 2006 while other abdominal diseases
19
20 34 were defined according to operative, endoscopic or radiological findings [9].
21
22 35 *Pneumonia* acquired typical symptoms and a chest X-ray supporting the disease, while the
23
24 36 diagnosis of both pulmonary embolism and pneumothorax was based on radiologic results and
25
26 37 the lack of concurrent cardiac disease.
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28 38 *COPD* was defined in accordance with the criteria by Stephens MB from 2008 [10], while chest
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30 39 pain without any specific clinical, radiologic or biochemical findings were defined as non-
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32 40 specific chest pain.
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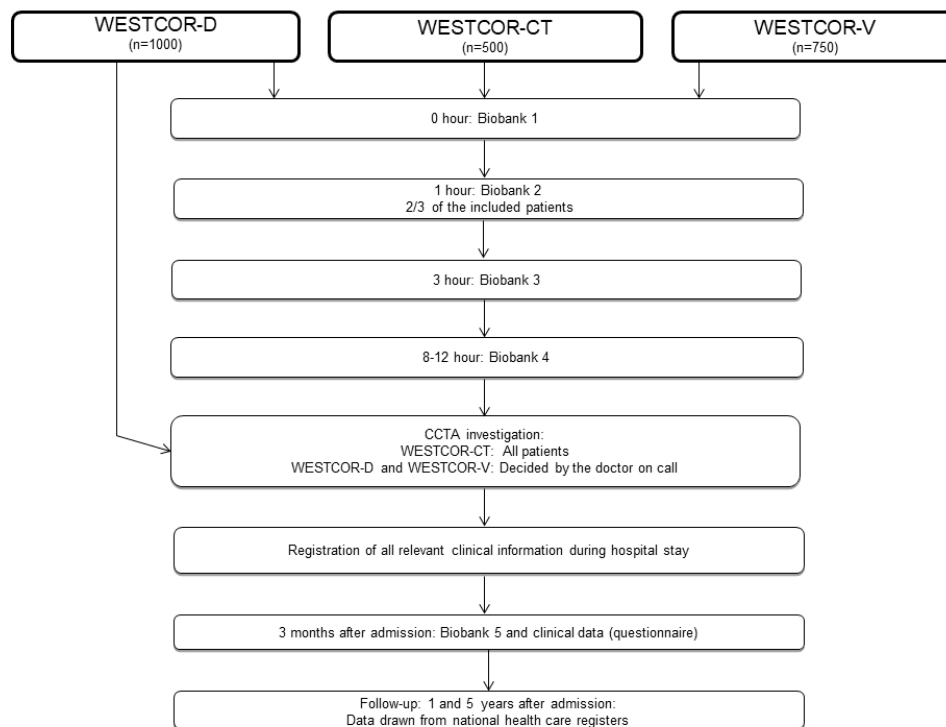


Figure 1: Flow chart outlining the study

254x190mm (96 x 96 DPI)