DIagnostic accuracy oF electrocardiogram for acute coronary OCClUsion resuLTing in myocardial infarction (DIFOCCULT Study)* Study Protocol

*ACO-MI, acute coronary occlusion; MI, myocardial infarction; STE, ST-segment elevation.

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Abbreviations

ACO, acute coronary occlusion

CABG, Coronary artery by-pass grafting

ECG, electrocardiogram

LVEF, left ventricular ejection fraction

MI, myocardial infarction

NSTEMI, non-ST-segment elevation myocardial infarction

PCI, percutaneous coronary intervention

STE, ST-segment elevation

STEMI, ST-segment elevation myocardial infarction

Study Project Summary

The underlying conceptual flow of the study as follows:

- Universally recommended STEMI criteria come from the studies designed for discriminating biomarker-positive MI (mainly CK-MB) from benign-variant STE.
- In these studies, neither coronary angiography had been utilized nor acute coronary occlusion (ACO) had been sought for.
- Now, the term STEMI is used synonymously with ACO.
- However, it restricts our thinking to the point that it is only the ST-segment that matters for the reperfusion decision, there is no need for taking any other ECG variable into account, such as preceding QRS-complex, following T-wave or even the morphology of ST-segment itself.
- Recent studies clearly indicated that any STE should be interpreted in context of other ECG variables.[1] Some ACO localizations may not show STE in contagious leads and some may not show any STE at all (hyperacute T-waves, DeWinter's pattern etc.).
- In reality, STEMI criteria have a limited diagnostic accuracy for ACO, causing a substantial amount of false catheterization laboratory activations.
- More importantly, they miss nearly one-third of ACO and causing this unfortunate group of patients, labeled as non-STEMI, to be deprived of emergent reperfusion therapy, as in the old days of Q-wave/non-Q-wave MI approach.
- Additionally, the term STEMI is somewhat self-contradictory, since a patient without STE on ECG, but ACO on angiogram, still classified as non-STEMI. But ACO-MI/non-ACO-MI terminology is not limited by ECG signs and permits retrospective reclassification of these patients.

- Several authors called for a new paradigm shift from STEMI/non-STEMI to ACO-MI/non-ACO-MI, as ACO can be reliably recognized with the help of many other ECG findings, however, it is uncertain whether this new approach would result in better identification of the patients who need acute reperfusion therapy and/or ECG has sufficient diagnostic power to go beyond established STEMI criteria.
- The objective of this study is to provide answers to these critical questions.

Study General Procedures

1. Application for Institutional Review Board (IRB)/Ethics board approval

IRB/Ethics board approval will be obtained from Dr. Siyami Ersek Thoracic and Cardiovascular Surgery Training and Research Hospital.

2. Patient selection

We planned to enroll 1000 patients in each of the STEMI, NSTEMI and control groups.

Considering Dr. Siyami Ersek Thoracic and Cardiovascular Surgery Training and Research Hospital has a large local network for primary with around 1000-1500 STEMI patients per year referred for primary PCI, it will take approximately one-year period to collect 1000 STEMI patients. This institution also receives STEMI and NSTEMI patients with a 2:1 ratio, which corresponds well to the reported incidences of these two entities. Therefore, we expected to enroll 1000 NSTEMI patients before STEMI group is completed. Another 1000 patients with a clinical picture compatible with an acute coronary event, but without any ECG changes during serial follow-up and negative and unchanging troponin levels within the first 24 hours will be enrolled. As these patients were so much in frequency, and this group would be completed at the beginning of the study, if we started at the same time with

STEMI/NSTEMI enrollment (May 1, 2017); we decided to select these patients from a computer-generated random list. Therefore, the patients in these group was enrolled after first two groups were completed (December 31, 2018). The total admission counts will also be calculated for the weighted analysis of diagnostic accuracy indexes; such as sensitivity, specificity, negative and positive predictive value. After this enrollment period we will have three cohorts.

- STEMI group: These patients should have all of the following criteria: (1) New ST-segment elevation at the J-point in two contiguous leads with the cut-point: ≥ 1 mm in all leads other than leads V2–V3 where the following cut-points apply: ≥ 2 mm in men ≥ 40 years; ≥ 2.5 mm in men < 40 years, or ≥ 1.5 mm in women regardless of age. (2) a peak troponin level above 99th percentile and (3) a clinical picture compatible with acute coronary syndrome.

- NSTEMI group: These patients should have both of the following criteria: (1) a peak troponin level above 99th percentile and (2) a clinical picture compatible with acute coronary syndrome. But these patients should not have STEMI criteria ((1) New ST-segment elevation at the J-point in two contiguous leads with the cut-point: ≥ 1 mm in all leads other than leads V2–V3 where the following cut-points apply: ≥ 2mm in men ≥ 40 years; ≥ 2.5 mm in men < 40 years, or ≥ 1.5 mm in women regardless of age).

- Control group: These patients should have (1) a technically adequate ECG, (2) a clinical picture compatible with acute coronary syndrome, (3) a peak troponin level below 99th percentile or, if low-positive, change in the first 12-hours should

be less than 20%.

All of these patients may or may not have undergone catheterization during their hospital stay.

Estimated number of subjects to be submitted:

We estimated that the enrollment of 963 patients in non-STE-MI group would provide the study with a statistical power of 95% to detect a relative excess mortality rate of 5% in ACO-MI subgroup (from 10% to 15%) with the use of a two-sided test at the 0.05 level, with a frequency prediction of 25% for ACO-MI. Far less patients (267 and 383) would be necessary to detect a 10% difference in area under curve (AUC, from 0.700 to 0.770) for the comparison of diagnostic accuracy two approaches in predicting ACO and long-term mortality, respectively.

3. Personnel

1) *Patient and data collection:* Barış Şimşek
2) *ECG Interpreters*: Emre Aslanger, Mustafa Aytek Şimşek (referee: Muzaffer Değertekin)
3) *Angiogram Reviewers*: Özlem Yıldırımtürk, Emrah Bozbeyoğlu (referee: Can Yücel Karabay).

Study roles are detailed in the following sections describing the study process.

4. Data Collection

1) Starting from May 1, 2017 hospital database will be screened for STEMI and NSTEMI admissions.
2) Following will be checked:

   - The presence of a technically adequate (pre-cath) ECG.
   - A peak troponin level over 99 th percentile.

3) ECGs will be printed and handed over to ECG reviewers after all groups are completed.
4) Following baseline variables will be entered to the study Excel spreadsheet: Enrollment no., protocol no., cohort, age, gender, prior history of MI, prior history of PCI or CABG, presence or absence of diabetes (medication use or HbA1c>6.5), hypertension (medication use or average blood pressure over 140/90 mmHg during hospital stay), dyslipidemia (medication use), smoking (current smoker or past smoker with in 1 year), admission systolic blood pressure, admission heart rate, admission creatinine level, admission hemoglobin level, Killip class on admission, admission troponin I level (from a blood sample collected before, during or just after coronary angiography or at admission to the emergency department), peak troponin level (the maximum troponin level during hospital stay), 24-to-48 hour troponin level (the highest troponin level during this time window), ejection fraction from echocardiogram report, time from ECG to PCI (will be calculated from system recordings), in-hospital mortality, in-hospital resuscitation, in-hospital intubation.
5) From these parameters, baseline GRACE risk score, the change within troponin value in the first 24 hours will be calculated.

6) Angiograms will be reviewed by angiogram reviewers from hospital digital database. Following points will be noted: (1) the presence of total occlusion. The presence of collaterals to distal vessel, appearance of the total occlusion, easiness of guidewire crossing will also be assessed to determine if the total occlusion is acute in nature. If necessary, primary operator will also be contacted. (2) The presence of culprit lesion, which was defined based on several angiographic properties including appearance, presence of angiographic thrombus, critical stenosis with less than Thrombolysis in Myocardial Infarction 3 flow.

ECG Interpretation

1. **Type 1 EGGs:** New ST-segment elevation at the J-point in two contiguous leads with the cut-point: ≥ 1 mm in all leads other than leads V2–V3 where the following cut-points apply: ≥ 2mm in men ≥ 40 years; ≥ 2.5 mm in men < 40 years, or ≥ 1.5 mm in women regardless of age.
    a. **Type 1a:** The amplitude, morphology, extent of STE and the presence of additional findings (hyperacute T waves, Q-waves, terminal QRS distortion) make ECG highly obvious for MI presumably due to acute, thrombotic occlusion. These ECGs will be included in both STEMI and ACO-MI groups.
    b. **Type 1b:** Does not meet recommended criteria for STEMI, but highly suggestive for MI, despite being subtle and difficult. Possible findings are minor STE with minor reciprocal ST-depression not fulfilling STEMI criteria, hyperacute T-waves or DeWinter's pattern, subtle anterior STE hard to differentiate from benign variant STE and nonconsecutive STE. These ECGs will be included in ACO-MI group but not in STEMI group.
    c. **Type 1c:** There is ST-segment elevation that meets criteria for STEMI, but it is

uncertain whether it is due to MI or to another condition, such as benign variant STE, left ventricular hypertrophy, left bundle branch block, prior MI, pericarditis, etc. These ECGs will be included in STEMI group but not in ACO-MI group, unless there are additional findings suspicious for acute coronary occlusion as follows:

i. Differential diagnosis for benign variant STE: Type 1c, if fulfills STEMI criteria. But re-classified as Type 1b, if Aslanger's formula is positive.
   - Aslanger's formula: (R-wave amplitude in lead V4 + QRS amplitude in V2) – (QT interval in millimeters + STE60 in V3) <12
   - *Reference:* Aslanger E, Yıldırımtürk Ö, Bozbeyoğlu E, et al. A Simplified Formula Discriminating Subtle Anterior Wall Myocardial Infarction from Normal Variant ST-Segment Elevation. Am J Cardiol 2018; 122: 1303-9.

ii. Differential diagnosis for left ventricular hypertrophy
   - Type 1c unless ST segment to R-S-wave magnitude is equal or greater than 25% (then indicates ACO, Type 1b).
   - *Reference:* Armstrong EJ, Kulkarni AR, Bhave PD, et al. Electrocardiographic criteria for ST-elevation myocardial infarction in patients with left ventricular hypertrophy. Am J Cardiol 2012; 110: 977-83.

iii. Differential diagnosis for isolated left bundle branch block:
   - Coded as Type 1c, unless one of the modified Sgarbossa criteria is positive (then indicates ACO, Type 1b):
   - ≥ 1 lead with ≥1 mm of concordant ST elevation

- ≥ 1 lead of V1-V3 with ≥ 1 mm of concordant ST depression
- ≥ 1 lead anywhere with ≥ 1 mm STE and proportionally excessive discordant STE, as defined by ≥ 25% of the depth of the preceding S-wave.
- *Reference:* Smith SW, Dodd KW, Henry TD, Dvorak DM, Pearce LA. Diagnosis of ST Elevation Myocardial Infarction in the Presence of Left Bundle Branch Block using the ST Elevation to S-Wave Ratio in a Modified Sgarbossa Rule. Ann Emerg Med 2012; 60: 766-76

iv. Differential diagnosis for prior MI:

- Type 1c, unless Smith's rule is positive (then indicates ACO, Type 1b):
- Smith's rule: If any 1 lead between V1-V4 has a T-wave amplitude to QRS amplitude ratio greater than or equal to 0.36.
- *Reference:* Klein LR, Shroff GR, Beeman W, Smith SW. Electrocardiographic criteria to differentiate acute anterior ST-elevation myocardial infarction from left ventricular aneurysm. Am J Emerg Med 2015; 33:786-90.

v. Differential diagnosis for pericarditis:

- Type 1c, unless there is ST-depression in aVL (then indicates ACO, Type 1b).
- *Reference:* Bischof JE, Worrall C, Thompson P, Marti D, Smith SW. ST depression in lead aVL differentiates inferior ST-elevation myocardial infarction from pericarditis. Am J Emerg Med. 2016; 34: 149-54.

d. **Type 1d:** There is ST-segment elevation that meets criteria for STEMI, but there is also T-wave inversion indicative of spontaneous reperfusion or QS waves and T-wave inversion indicative of subacute MI. These ECGs are not excluded by STEMI criteria, therefore will be included in STEMI group but not in ACO-MI group.

2. **Type 2 EGGs:** ECG that meets acute myocardial ischemia criteria recommended by fourth universal definition of MI. The ECG has "primary", i.e. cannot be completely explained as secondary to a depolarization disorder, ST-segment depression or T-wave inversion that is nondiagnostic of STEMI but is diagnostic of myocardial ischemia. These ECGs will not be included in neither STEMI nor ACO-MI groups.
3. **Type 3 ECGs:** Nonspecific ECG that is abnormal but nondiagnostic of any kind of acute coronary syndrome. Minor abnormalities including left ventricular hypertrophy without ST-T changes, arrhythmias, impulse generation and conduction diseases etc. These ECGs will not be included in neither STEMI nor ACO-MI groups.
4. **Type 4 ECGs:** Completely normal ECG. These ECGs will not be included in neither STEMI nor ACO-MI groups.

ACO Adjudication

Because the infarct-related artery may spontaneously open by the time of the angiogram or total occlusion may be chronic in nature, we defined a composite ACO using following criteria:

(1) total occlusion or presence of culprit lesion on angiography

PLUS

a peak troponin I level equal to or greater than 1.0 ng/ml

PLUS

at least 20% rise within 24 hours

(2) a highly elevated peak troponin, i.e., peak troponin I> 5.0 ng/mL, which was shown to be highly correlated with ACO

(3) cardiac arrest before any troponin rise has been documented with supporting clinical evidence of possible ACO.

Statistical Analysis

Baseline characteristics will be summarized using standard descriptive statistics. Comparisons of relevant parameters between groups will be performed by chi-square, Fisher's exact test, Mann-Whitney U, Kruskal-Wallis H test, one-way ANOVA and student t-test, as appropriate. Patients with missing values will be excluded pairwise from analyses. A Cohen's κ test will be used for determination of the intra- and inter-observer agreement for ECG classifications.

Kaplan-Meier analysis will be performed to determine the cumulative long-term mortality rates in different ECG subgroups. The mortality across groups will be compared using log-rank test. A Cox-regression model will be used to perform a survival analysis according to intervention timing and revascularization status. Baseline characteristics with a P value of 0.05 or less in the univariate analysis will be included and a step-down procedure will be applied for selection of final covariates.

Note: After data collection, we performed a univariate analysis for mortality and found that many of the baseline parameters, including age, systolic blood pressure, heart rate, baseline

creatinine etc., were significantly associated with long-term mortality. But when these were included in the Cox regression analysis alongside with baseline GRACE risk score, they all lost their statistical significance. Considering GRACE risk score already includes almost all of these variables, we only used GRACE risk score as a covariate in Cox regression model.

The sensitivity, specificity and diagnostic accuracy of STE/non-STE or ACO/non-ACO ECG approaches will be calculated using receiver operating characteristics analysis. As these parameters are highly dependent on the pre-test probability of the disease and pre-test probability of ACO and long-term mortality are closely associated with the presentation type, we will also repeat these analyses after weighing cases for the total number of hospital admissions in the study period.

Statistical analyses will be performed with SPSS (version 24.0; SPSS Inc., Chicago, IL) and MedCalc Software (version 18.2.1 [Evaluation version]; MedCalc Software, Ostend, Belgium).

Informed Consent form for patient.

This Informed Consent Form is for the patients who attend clinic Dr. Siyami Ersek Cardiothoracic Education and Research Hospital and who we are inviting to participate in research on ***DIagnostic accuracy oF electrocardiogram for acute coronary OCClUsion resuLTing in myocardial infarction (DIFOCCULT Study).***

This Informed Consent Form has two parts:

- **Information Sheet (to share information about the research with you)**
- **Certificate of Consent (for signatures if you agree to take part)**

You will be given a copy of the full Informed Consent Form

PART I: Information Sheet Introduction

I am Emre Aslanger, the chief researcher in the project DIFOCCULT. We are doing research on electrocardiogram in myocardial infarction. I am going to give you information and invite you to be part of this research. You do not have to decide today whether or not you will participate in the research. Before you decide, you can talk to anyone you feel comfortable with about the research.

There may be some words that you do not understand. Please ask me to stop as we go through the information and I will take time to explain. If you have questions later, you can ask them of me, the study doctor or the staff.)

Purpose of the research

We believe that current understanding of electrocardiogram in myocardial infarction is below optimal level. Today, we perform emergent coronary angiography in patients with a specific sign on electrocardiogram, called ST-segment elevation. However, many other findings have been proved to show the need for emergent coronary angiography other than this. If we prove that a general approach to subtleties of electrocardiogram shows a better outcome in patients with myocardial infarction, current treatment paradigm will change in this direction.

Type of Research Intervention

This research will use your demographic data, blood tests, angiogram results and electrocardiograms stored in hospital system and no new study will be needed.

Participant selection

We are screening all adults with acute chest pain attend emergency department of Dr. Siyami Ersek Cardiothoracic Education and Research Hospital to participate in the research.

Voluntary Participation

Your participation in this research is entirely voluntary. It is your choice whether to participate or not. Whether you choose to participate or not, all the services you receive at this clinic will continue and nothing will change.

Procedures and Protocol

The data recorded in the hospital system during your stay in the hospital will be used and no new test will be done. After a period your survival status will be checked from national database.

Duration

The research takes place over 1 to 2 years.

Risks

As there is no intervention in this study, there is no added risk during the data collecting process. The healthcare workers will be looking after you and the other participants very carefully irrespective of your decision on giving consent about your data to be used in the study.

Benefits

There may not be any benefit for you, but your participation is likely to help us find the answer to the research question.

Reimbursements

Your participation is free. You will not be given any other money or gifts to take part in this research

Confidentiality

The information that we collect from this research project will be kept confidential. Information about you that will be collected during the research will be put away and noone but the researchers will be able to see it. Any information about you will have a number on it instead of your name.

Sharing the Results

The knowledge that we get from doing this research will be shared with you through community meetings before it is made widely available to the public. Confidential information will not be shared.

Right to Refuse or Withdraw

You do not have to take part in this research if you do not wish to do so. It is your choice and all of your rights will still be respected.

Who to Contact

If you have any questions you may ask them now or later, even after the study has started. If you wish to ask questions later, you may contact any of the following: [Dr Emre Aslanger, Chief Investigator, 02165784240)

This proposal has been reviewed and approved by local ethical committee of Dr. Siyami Ersek Cardiothoracic Education and Research Hospital, which is a committee whose task it is to make sure that research participants are protected from harm.

You can ask me any more questions about any part of the research study, if you wish to. Do you have any questions?

PART II: Certificate of Consent

I have read the foregoing information, or it has been read to me. I have had the opportunity to ask questions about it and any questions that I have asked have been answered to my satisfaction. I consent voluntarily to participate as a participant in this research.

Name of Participant_____

Signature of Participant _____

Date _____ Day/month/year

If illiterate

A literate witness must sign (if possible, this person should be selected by the participant and should have no connection to the research team). Participants who are illiterate should include their thumb-print as well.

I have witnessed the accurate reading of the consent form to the potential participant, and the individual has had the opportunity to ask questions. I confirm that the individual has given consent freely.

Print name of witness_____ AND

Signature of witness _____

Date _____ Day/month/year

Thumb print of participant

Statement by the researcher/person taking consent

I have accurately read out the information sheet to the potential participant, and to the best of my ability made sure that the participant understands that the following will be done:

1.
2.
3.

I confirm that the participant was given an opportunity to ask questions about the study, and all the questions asked by the participant have been answered correctly and to the best of my ability. I confirm that the individual has not been coerced into giving consent, and the consent has been given freely and voluntarily.

A copy of this ICF has been provided to the participant.

Print Name of Researcher/person taking the consent_____

Signature of Researcher /person taking the consent_____

Date _____ Day/month/year