ECG-based Predictors of Re-infarction or Death on the Hospital Admission 12-Lead ECG among UA/NSTEMI Patients: A Protocol for a Systematic Review and Meta-Analysis

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Protocol

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Abstract

Background The incidence of unstable angina/ non-ST elevation MI (UA/NSTEMI) continues to rise. The electrocardiogram (ECG) remains the first-line assessment of cardiac conduction and myocardial ischemia, and is performed within the first 10-minutes of hospital presentation. Despite recent advances in treatment, in-hospital death and re-infarction continues as a result of delayed interventions. Since the ECG is a rapid test to guide treatment decisions, it is crucial emergency providers understand the prognostic value of characteristics on the admission 12-lead ECG to decide treatments which may reduce the risk of re-infarction and death. This is the first systematic review and meta-analysis to assess the significance of these ECG findings associated with in-hospital death and re-infarction.

Methods A systematic review and meta-analysis will be conducted to comprehensively assess the prognostic value of specific characteristics on the admission 12-lead ECG associated with re-infarction and death. This is the protocol for such review and meta-analysis. Electronic databases and specific cardiovascular journals will be searched using predefined search terms to identify relevant studies. Eligible studies will be peer-reviewed research articles with empirical findings on the risk re-infarction and death based on characteristics on the admission 12-lead ECG. The methodological quality of the included studies will be assessed with the Newcastle-Ottawa Quality Assessment Scale and GRADE. Citations will be managed using EndNote X9. A random effects meta-analysis will be conducted with the Meta-Essentials package and STATA.

Discussion This study will be among the first to systematically evaluate and quantitatively assess the evidence available on the prognostic value of characteristics on the admission 12-lead ECG for the risk of re-infarction and death. This study will inform clinicians about the significance of characteristics on the admission 12-lead ECG so better treatment decisions can be made, as well as inform new research opportunities in the field of cardiovascular risk stratification.

Registration This systematic review and meta-analysis is registered with the International Prospective Register of Systematic Reviews (PROSPERO; ID CRD42020158491).

Background

More than 65% of all myocardial infarctions in the United States are diagnosed as unstable angina/ non-ST elevation myocardial infarction (UA/NSTEMI), and the number increases annually [1]. UA/NSTEMI occurs due to the rupture or erosion of an atherosclerotic plaque causing either a partial occlusion of a coronary artery or a total occlusion of a coronary artery in the presence of collateral blood flow [2, 3]. The current diagnostic definition for UA/NSTEMI involves an emergent presentation with or without chest pain, but with electrocardiographic (ECG) changes consistent with ischemia (e.g. ST-segment changes) and elevation in cardiac biomarkers for NSTEMI only (e.g. troponin) [2]. Thus, UA/NSTEMI are similar conditions which only differ in the absence (i.e. UA) or presence (i.e. NSTEMI) of detectable cardiac biomarkers [2]. The majority of patients with UA/NSTEMI present heterogeneously with non-anginal
symptoms including arm pain and back discomfort, and normal initial cardiac biomarkers [4, 5,6]. The heterogeneity in patient presentation make decisions around timing of interventions susceptible to error despite the fact that timely interventions are needed to reduce the risk of re-infarction and death [6,7,8,9].

The risk of re-infarction and death is a serious concern among UA/NSTEMI patients, and initial treatment is based on this acute risk. In the Global Registry of Acute Coronary Events (GRACE) registry of over 16,000 patients from 14 countries between 2001 and 2007, the in-hospital mortality was 3.3% and the rate of in-hospital re-infarction was 2.4% [10]. In the United States, the Worcester Heart Attack Study reported a hospital post-admission case mortality rate of nearly 10% [11]. Despite a growing emphasis on early invasive strategy to prevent re-occurring myocardial ischemia, in-hospital mortality rates have not significantly decreased [12]. This may be due to an initial underestimation of ischemic injury at presentation [7,8,9].

The admission 12-lead ECG is known to carry similar or even better prognostic information than cardiac biomarker measurements for UA/NSTEMI [13]. The 12-lead ECG is inexpensive, noninvasive and completed within the first 10 minutes of patient presentation per current American Heart Association/American College of Cardiology (AHA/AACC) guidelines [2]. This means the ECG can be used to rapidly risk stratify patients. Frontline emergency care provider can quickly and efficiently use characteristics on the admission 12-lead ECG to risk stratify suspected UA/NSTEMI patients for risk of re-infarction and death. Emergency care providers are in a unique position to initiate efforts to decrease time to initial treatment for UA/NSTEMI patients and quickly determine those at highest risk whom require more invasive interventions [14,15]. However, emergency care providers need information on the prognostic significance of specific characteristics on the admission 12-lead ECG in order to guide these initiatives.

This protocol aims to conduct a systematic review and meta-analysis to identify specific characteristics on the admission 12-lead ECG prognostic of re-infarction and death among patients presenting to the emergency department for UA/NSTEMI, and summarize the research in this field. This would be the first systematic review and meta-analysis on this topic. This systematic review and meta-analysis will inform emergency care providers about the prognostic value of the admission 12-lead ECG, and advance the science of risk stratification in UA/NSTEMI.

Methods

The following protocol has been written in accordance to the Guidelines for Meta-Analyses and Systematic Reviews of Observational Studies (MOOSE) and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA-P) guidelines [16, 17]. The PRISMA-P checklist is seen in Figure 1. The protocol is registered at the International Prospective Register of Systematic Reviews (PROSPERO; ID CRD42020158491) [18].

The proposed systematic review and meta-analysis is part of a larger project entitled “Development and Validation of TIB: A Total Ischemic Burden Score for the Rapid Risk Stratification of NSTEMI.” The aims of research are (1) to assess the prognostic value of characteristics on the admission 12-lead ECG for in-
hospital re-infarction and death; and, (2) to build a rapid risk stratification tool called Total Ischemic Burden (TIB) based solely on significant characteristics on the admission 12-lead ECG for risk assessment of in-hospital re-infarction and death; and, (3) to evaluate the impact of TIB on emergency triage, pre-hospital ECG interpretation and, ultimately, patient care at a large academic medical center.

**Research Question**

The PIOT (Population, Indicator, Outcome, Time) research question guiding this systematic review and meta-analysis is: Among UA/NSTEMI patients (Population), do specific characteristics on the admission 12-lead ECG (Indicator) for the prediction of re-infarction and death (Outcome) in the first 24 hours of patient presentation (Time)? No comparison component will be used.

**Independent Variables**

The independent variables for this protocol are specific characteristics on the 12-lead ECG. Previous research and medical expertise in this area of inquiry hypothesize the following characteristics will most likely be included: ST-segment depression, T-wave inversion, and pathological Q waves. However, we will not limit our search to just these three well known characteristics. It is also important to recognize that there may be measurement differences across studies. Although these characteristics have standardized measurements and corresponding normal values, individual studies may deviate from these published standards [19]. We will record details on the measurement of these characteristics in this review and meta-analysis.

**Dependent Variable**

The dependent variable of interest for this systematic review and meta-analysis is in-hospital re-infarction and death after initial presentation for UA/NSTEMI. In-hospital re-infarction will be defined in accordance to the forth universal definition of myocardial infarction, and is defined as an acute myocardial infarction that reoccurs dependent of ST-elevation or depression ≥ 1 mm, new pathognomonic Q waves appear in at least two contiguous leads, particularly when associated with ischemic symptoms, and a >20% increase of the cardiac troponin biomarker value in the second sample compared to the first sample collected at initial presentation [20]. If there is a difference in the definition in re-infarction in individual studies, we will record this difference as this may introduce bias and heterogeneity in this study.

**Moderator Variables**

Age and sex are important potential moderating variables which may influence the presenting ECG [1,19,23]. Thus, we will collect information on the age and sex distribution of the samples used in individual studies.

**Data Sources, Search Terms, and Search Strategy**
This literature review and meta-analysis will be based on systematic searches in multiple electronic literature databases, including Medline/PubMed, Web of Science, Embase, and CINAHL. Since ECG research appears in cardiovascular specific journals, specific searches to expand capture of relevant studies will be performed using the same key words in over 20 other cardiology and emergency medicine journals including: Circulation, Heart Rhythm, Journal of Electrocardiology, Annals of Noninvasive Electrocardiology, Journal of Cardiovascular Nursing, Journal of Emergency Nursing, European Heart Journal, The American Journal of Cardiology, EP Europace, and American Journal of Emergency Medicine (Table 1). Lastly, we will search ClinicalTrials.gov for potential grey literature. All journals and search terms are listed in Table 1. Systematic searches will be conducted by combining every possible combination of five categories of keywords. The librarian and principal investigator will be responsible for conducting searches in electronic literature databases. The librarian will be responsible for conducting searches in the electronic databases and ClinicalTrials.gov. The principal investigator will be responsible for conducting searches in cardiovascular journals. Reference lists included articles will be checked to identify any potentially eligible studies. This in-depth and librarian guided systematic procedure substantiates that the literature search comprises all published studies [33]. The use of a librarian and the search of grey literature will also help reduce the risk of selection and detection bias [31]. The search results will be exported to Endnote X9 (Clarivate Analytics, PA, USA). The librarian will save the search results in an Endnote file on an encrypted, frequently backed-up computer system as a historical record.

Inclusion and Exclusion Criteria

The inclusion criteria for this study will be: 1) full-text peer-reviewed publications; 2) English language; 3) adult (> 18 years) patient presenting with confirmed UA/NSTEMI to the emergency department; 4) standard, resting 12-lead ECG performed in the supine position at time of admission, only, and 5) use of odds ratio (ORs) or risk ratio (RR) and the corresponding 95% confidence interval as the statistical outcome measure or the data necessary to calculate these measures. The 12-lead ECG must be in the supine position due to position effects which may distort the accuracy of the tracing [21].

For the meta-analysis portion additional inclusion criteria will be a quality score of \( \geq 5 \) on the Newcastle-Ottawa Quality Assessment Scale and a moderate rating on the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) score described below [22-24]. We used two scales in this systematic review because of their two different objectives. The objective of the Newcastle-Ottawa Quality Assessment Scale is to evaluate the quality of individual case-control or cohort design studies, whereas GRADE is for the systematic appraisal of research with the goal to advise evidence-based recommendations. Since the aims of this systematic review and meta-analysis was two-part: summarize the existing literature and develop guidelines for frontline emergency care providers, we felt two quality scales were necessary. The Newcastle-Ottawa Quality Assessment Scale varies from 0 to 9 and rates studies as poor (score of 0) to excellent quality (score of 9), correlating to the Agency for Healthcare Research and Quality (AHRQ) standards [22]. For this study, inclusion in the meta-analysis will require an overall score of \( \geq 5 \) which corresponds to good quality research [22]. GRADE is a widely recommended transparent framework for developing and presenting summaries of evidence and provides a systematic
approach for making clinical practice recommendations [23,24]. A score of moderate will be necessary for inclusion [24]. Moderate is defined as the authors of this review believe that the true effect is probably close to the estimated effect, thus filtering out erroneous results [25].

Exclusion criteria will include: 1) serial, 12-lead ECG; and continuous 3-lead, 5-lead or 12-lead ECG monitoring. There will be no upper restrictions on age or sex distribution for this study; however, age and sex will be moderators in the meta-analysis portion of this study (see below). There is no limitation in terms of geographic region or racial background. The search period will be from the beginning of the computerization of the ECG, January 1st, 1990 to June 1, 2020 [26].

Participants

The study population will be adults (18 years or older) presenting to emergency departments with suspected UA/NSTEMI. No restrictions will be placed on participants' gender, ethnicity, or other demographic characteristics. Since the aim of the study is to determine associations between characteristics on the admission 12-lead ECG and in-hospital re-infarction and death, factors influential on patient outcomes including age and sex will be recorded and used as moderators in meta-analyses (see below) [25,31].

Data Extraction and Assessment of Methodological Quality

Following the search, all identified citations will be collected and uploaded into EndNote X8 to remove duplicates. After removing all duplicates, titles and abstracts the articles will be screened against the inclusion and exclusion criteria. The full text and citation of potential studies will be retrieved and imported into EndNote X8 with the corresponding citation. Potential articles will be assessed in detail against the inclusion criteria by the principal investigator and the senior investigator. Any disagreements that arise between the reviewers will be resolved through discussion and, when deemed necessary, a content expert (PhD-prepared cardiac nurse) will be invited as a third reviewer to make the ultimate decision. Reasons for excluded studies will be recorded and reported in the final manuscript.

After deciding which articles to include, all data entry will be completed by the principal investigator and verified by the senior investigator of this protocol who is a PhD-prepared research nurse scientist with background in ECG. The principal investigator and senior investigator will use a standardized data extraction form to ensure consistent data retrieval from the included studies (Table 2). The data extracted will include specific details about the population, context, study methods, and critical statistical findings relevant to the purpose of this review. The data extraction was piloted tested using 5 articles with an intrarater reliability of 95% between the principal investigator and the senior investigator. A third reviewer was not necessary during this pilot testing. If necessary, modifications to the standardized data extraction form will be reported in detail in the full report. If required, we will contact the authors of included studies to request missing or additional data. We will record attempts to contact authors for missing or additional data. Periodic data checking and entry will be conduct to ensure accuracy.
To assess quality of articles, the Newcastle-Ottawa Quality Assessment Scale and the GRADE score will be used. The Newcastle-Ottawa Quality Assessment Scale was developed to assess the quality of non-randomized studies such as case-control and cohort studies [22]. The following characteristics will be assessed: (1) representativeness of the cohort; (2) selection of the non-exposed cohort; (3) ascertainment of exposure; (4) demonstration that outcome of interest was not present at the start of the study; (5) comparability of cohorts on the basis of the design or analysis; (6) assessment of outcomes; (7) follow-up period sufficiently long for outcomes to occur; (8) adequacy of follow-up of cohorts [22]. This scale varies from 0 to 9 indicating that studies were graded as poor to good quality, and correlates to the AHQR standards [22]. The principal investigator and senior investigator will score each article independently using the scale. Afterwards, the two will discuss their independent evaluations and provide a justification. If a discrepancy between quality score arises, a third independent reviewer (a PhD-prepared cardiac registered nurse) will provide a score and the average of all three reviewer scores will be used to determine study inclusion in the meta-analysis section of this study. Inclusion in the meta-analysis will require an overall score of ≥5 which corresponds to good quality research. Kappa will be calculated to quantify the level of inter-rater agreement (e.g. Kendall's tau) [22].

GRADE is a recommended transparent framework for examining existing evidence in a systematic approach for making clinical practice recommendations [23,24]. The domains of GRADE include risk of bias, imprecision, inconsistency, indirectness, and publication bias [23,24]. We will use the GRADE handbook published by Cochrane to inform our evaluation of individual studies. The same protocol as described above will be followed for determine a GRADE score.

Meta-Analytic Approach

A random-effects meta-analytic power analysis was conducted to determine the necessary number of studies and study participants to answer the research question and achieve the specific aims of this protocol [27]. Though, some have argued that a minimum number of studies to be included in a meta-analysis is two [27]. Assuming a small effect size (Cohen's d of 0.2), average number of participants per group (n=150 participants), and high study heterogeneity, a minimum of 1,050 study participants distributed across 7 individual studies will be necessary to achieve a type I and type II error rate of 5% and 10%, respectively [27]. A small effect size was assumed because each individual ECG characteristics will be evaluated individually in this meta-analysis reducing the overall ES. This proposal will target 12 individual studies for inclusion. This meta-analysis will calculate RR as the main ES estimate. RR is a total and stable measure of hazard functions; however, many studies will report an OR which can overestimate the risk ratio when the incidence of an outcome is common in a study population (>10%) [28]. For this reason, we will convert OR to RR as described by Zhang and Yu [28]. This is a simple method to approximate a RR and derive an estimate of an effect size that better represents the true RR not dependent on the frequency of the outcome [28]. All RR values will be log transformed to satisfy normal distribution assumptions. Confidence interval of each outcome measure resembles the precision of the RR estimate as an indirect measure of sample size. To correct for precision, primary studies will be weighted by the inverse of their variance. To account for known methodological differences among
included studies, the heterogeneity of RR measures will be treated as a covariate by using a random-effect model. Heterogeneity between studies will be determined using Cochran Q, which is calculated as the weighted sum of squared differences between individual study effects and the pooled ES across studies.

This analysis will assess whether or not the variation in effect sizes among pooled studies falls within expected sampling error. If this assumption is violated, then age and sex subgroup moderator analysis will be conducted. Age and sex were chosen to be moderators because they are important risk factors for UA/NSTEMI outcomes [25, 31]. If this occurs, studies will be coded as either (1) younger population (mean age<65 years) or older population (mean age >65 years) and (2) male-dominant (≥65% men) or female-dominant (≥65% women) [25,31]. The subgroup moderator analysis will inform whether age and sex influence prognostic ability of the ECG for death and mortality in UA/NSTEMI [25,31]. If the study fails to report a mean age, we will not be able to include it in this moderator analysis due to the skewed nature of the data. Instead, an additional data and analysis table will be used for studies which report medians. Depending on the number of studies, a subgroup comparison analysis will be completed between UA and NSTEMI to determine if there are ECG characteristics which differ between the two conditions. This will better inform about ECG changes specific to UA and NSTEMI.

Additionally, the I² statistic from the standard X² test will be computed to describe the percentage of variability across studies that is due to heterogeneity rather than chance alone. Lastly, to evaluate publication bias stemming from missing studies or search limitations, the trim-and-fill funnel plot method will be used. This method evaluates for the asymmetry of distribution of studies around their weighted mean. All analyses will be performed using Meta-Essentials in Excel, and STATA 16 (STATA Software, TX) [29,30].

**Discussion**

This systematic review and meta-analysis will evaluate and analyze the evidence available on the prognostic characteristics on the 12-lead ECG for in-hospital re-infarction and death. We believe this systematic review and meta-analysis will inform frontline emergency care providers on the prognostic significant of specific characteristics on the admission 12-lead ECG and result in more informed clinical decision making to reduce the incidence of in-hospital re-infarction and death. Moreover, this study will provide a much-needed overview of existing studies to inform future research in this area including our existing project which aims to

We hypothesize that multiple investigators have reported significant findings of common (e.g. ST-segment changes) and novel (e.g. QRS complex duration) characteristics which can predict in-hospital re-infarction and death, though this will be the first to summarize and synthesize these individual findings. Most of the studies may be older secondary due to well-known large and robust cardiovascular clinical trials such as GRACE [10]. We also hypothesize that there will be differences between males and females because cardiovascular studies tend to recruit more males [27]. Our protocol adjusts for this potential
limitation by including *a priori* subgroup analyses. In addition to informing frontline emergency care providers, this systematic review and meta-analysis will also inform our current project “Development and Validation of TIB: A Total Ischemic Burden Score for the Rapid Risk Stratification of NSTEMI.” The aims of this work are to (1) to assess the prognostic value of characteristics on the admission 12-lead ECG for in-hospital re-infarction and death; and, (2) to build a rapid risk stratification tool called TIB based solely on significant characteristics on the admission 12-lead ECG for in-hospital re-infarction and death. By knowing the current state of the science, we will have a better direction in assessing the importance and relevancy of specific characteristics on the admission 12-lead ECG, and how it may be weighted for clinical decision making. Finally, to our knowledge, this is the only systematic review and meta-analysis on characteristics on the admission 12-lead ECG, and one of the few in ECG overall.

**Limitations**

This systematic review will only include full-text peer reviewed published articles and will exclude other types of scholar works such as presentation abstracts, non-published studies and doctoral dissertations. Although some researchers have encouraged the inclusion of unpublished literature in systematic reviews and meta-analyses, the inclusion of data from unpublished studies can introduce bias [32]. Unpublished studies may provide insufficient data to be extracted for a systematic review and meta-analysis to be conducted, and may be of lower methodological quality than published studies [32]. In a study of 60 meta-analyses that included published and unpublished studies it was found that unpublished studies were more likely to be less rigorous compared to their published counterparts [33]. Moreover, a 2017 study concluded that the inclusion of non-published data had a non-significant effect on effect size estimates [32]. As the planned review will be based on a comprehensive literature search of studies published in peer reviewed journals and be accompanied by a librarian, the scientific quality of the included studies will be ensured. The robustness of the findings will also be indicated by publication bias analyses. The inclusion of a librarian to this systematic review also decreases bias, improves robustness, and correlates with a higher score in the literature searching component of systematic reviews [33, 34].

**Protocol amendments**

If the present protocol is substantially amended after an initiation that may impact on the conduct of the study (including eligibility criteria, study objectives, study design, study procedures, and analysis), then this amendment will be agreed upon by all collaborators prior to the implementation and will be documented in a note to a later publication or a report under the section titled “Differences between protocol and review”.

**Dissemination**

The results of this review will be submitted for peer-reviewed publication and will be presented at relevant cardiology conferences. The project team has commenced searching relevant studies in the relevant databases. This review is expected to be complete by December 2020.
List Of Abbreviations

ACC: American College of Cardiology
AHA: American Heart Association
AHQR: Agency for Healthcare Research and Quality
ECG: Electrocardiogram
GRACE: Global Registry of Acute Coronary Events
GRADE: Grading of Recommendations, Assessment, Development and Evaluations
MOOSE: Meta-Analyses and Systematic Reviews of Observational Studies
NSTEMI: Non-ST Elevation Myocardial Infarction
OR: Odds Ratio
PROSPERO: International Prospective Register of Systematic Reviews
PRISMA-P: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RR: Risk Ratio
TIB: Total Ischemic Burden (Score)
UA: Unstable Angina

Declarations

Ethical Approval and Consent to Participate

Not applicable.

Consent for Publication

Not applicable. Data and materials are available for reviewers upon request.

Availability of Data and Materials

The datasets created and analyzed during the current study will be available from the corresponding author upon reasonable request.

Competing Interests
The authors declare no competing interests.

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**Authors’ Contributions**

DJD is the principal investigator and responsible for conceiving the review, designing search strategy, modifying data extraction tool, selecting the appropriate tool for quality appraisal, conducting the journal-specific searches, and drafting the protocol. He is the guarantor of this review, and initiated the publication of this protocol. DHM is the librarian responsible for refining the search strategy, conducting the database searches, initially designing the data extraction tool, and providing librarian support. MGC is the senior investigator who provided content expertise on the topic, study assessment and appraisal, and reviewed the methodology. All authors read, reviewed, edited, and approved the final manuscript.

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Not applicable.

**Authors’ Information**

DJD is a registered nurse and PhD candidate at the University of Rochester School of Nursing. DHM is a librarian at the University of Rochester Medical Center. MGC is associate professor at the University of Rochester School of Nursing, and director of clinical nursing research center at the University of Rochester Medical Center.

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Tables

Table 1. Search Strategy for Protocol for ECG-based Predictors of Re-infarction or Death on the Hospital Admission 12-Lead ECG among UA/NSTEMI Patients.
Medline

("Emergency Service, Hospital"[Mesh] OR emergency department*[tiab] OR emergency nursing*[tiab] OR emergency medicine*[tiab] OR triage*[tiab] OR "cardiovascular nursing*[tiab] AND "Myocardial Infarction"[Mesh] OR "Non-ST Elevated Myocardial Infarction"[Mesh] OR "Myocardial Ischemia"[Mesh] OR "Myocardial Reperfusion"[Mesh] OR "Myocardial Revascularization"[Mesh] OR "Ischemic Preconditioning"[Mesh] OR "Acute Coronary Syndrome"[Mesh] OR "Angina, Unstable*[Mesh] OR "Angina Pectoris*[Mesh] OR "Coronary Artery Disease*[Mesh] OR "Coronary Vessels*[Mesh] OR "Coronary Circulation*[Mesh] OR "myocardial infarction*[tiab] OR "Non-ST elevated myocardial infarction*[tiab] OR "myocardial ischemia*[tiab] OR "myocardial reperfusion*[tiab] OR "myocardial revascularization*[tiab] OR "ischemic pre-conditioning*[tiab] OR "acute coronary syndrome*[tiab] OR "unstable angina*[tiab] OR "chest pain*[tiab] OR "chest pains*[tiab] OR "angina pectoris*[tiab] OR "atherosclerosis*[tiab] OR "coronary artery disease*[tiab] OR "coronary arteries*[tiab] OR "coronary artery*[tiab] OR "coronary circulation*[tiab] OR "UA/NSTEMI*[tiab] AND "12 lead ECG*[tiab] OR "12 lead electrocardiogram*[tiab] OR "Electrocardiography*[Mesh] OR "ECG*[tiab] OR "EKG*[tiab] OR "electrocardiogram*[tiab] OR "electrocardiography*[tiab] OR "diagnostic tests, routine*[MeSH Terms] OR "diagnostic measure*[tiab] OR "diagnostic procedure*[tiab] OR "diagnostic procedures*[tiab] OR "diagnostic test*[tiab] OR "diagnostic techniques*[tiab] AND ("Death*[Mesh] OR "Fatal Outcome*[Mesh] OR "Cause of Death*[Mesh] OR "Mortality*[Mesh] OR "dead*[tiab] OR "death*[tiab] OR "fatality*[tiab] OR "fatal outcome*[tiab] AND ("Sensitivity and Specificity*[Mesh] OR "Prognosis*[Mesh] OR "risk ratio*[tiab] OR "risk*[tiab] OR "odds ratio*[tiab] OR "probability*[tiab] OR "harm reduction*[tiab] OR "populations at risk*[tiab] OR "population at risk*[tiab] ))

('emergency service, hospital'/exp OR 'emergency department'/exp OR 'emergency service'/exp OR 'emergency room'/exp OR 'emergency department*'/exp OR 'emergency nursing*/exp OR 'emergency medicine'/exp OR 'triage'/exp OR 'cardiovascular nursing'/exp OR 'coronary care nursing'/exp)

AND ('myocardial infarction'/exp OR 'non st segment elevation myocardial infarction'/exp OR 'chest pain'/exp OR 'myocardial ischemia'/exp OR 'acute coronary syndrome'/exp OR 'unstable angina'/exp OR 'angina pectoris'/exp OR 'atherosclerosis'/exp OR 'coronary artery disease'/exp OR 'coronary arteries'/exp OR 'coronary artery'/exp OR 'coronary circulation'/exp OR 'heart infarction'/exp OR 'heart muscle ischemia'/exp OR 'heart muscle reperfusion'/exp OR 'heart muscle revascularization'/exp OR 'ischemic preconditioning'/exp OR 'acute coronary syndrome'/exp OR 'unstable angina pectoris'/exp OR 'angina pectoris'/exp OR 'coronary artery disease'/exp OR 'coronary blood vessel'/exp AND ('12 lead ecg'/exp OR 'twelve lead ecg'/exp OR '12 lead electrocardiogram'/exp OR '12 lead electrocardiogram'/exp OR '12 lead electrocardiogram'/exp OR '12 lead electrocardiogram'/exp OR '12 lead electrocardiogram'/exp OR '12 lead electrocardiogram'/exp OR '12 lead electrocardiogram'/exp OR '12 lead 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AND ('sensitivity and specificity'/exp OR 'prognosis'/exp OR "risk ratio"/exp OR "risk"/exp OR "odds ratio"/exp OR "probability"/exp OR "harm reduction"/exp OR "populations at risk"/exp OR "population at risk"/exp)

(#5 AND #4 AND #3 AND #2 AND #1)
Table 2. Data Extraction Form for Protocol for ECG-based Predictors of Re-infarction or Death on the Hospital Admission 12-Lead ECG among UA/NSTEMI Patients.
Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)-P 2015 Checklist

Table 3. PRISMA-P 2015 Checklist for Electrocardiogram-based Predictors of Re-infarction or Death on the Admission 12-Lead ECG among UA/NSTEMI Patients: A Systematic Review and Meta-Analysis
## ADMINISTRATIVE INFORMATION

### Title

| Identification | 1a | Identify the report as a protocol of a systematic review | Yes | No | Line number(s) |
|----------------|----|--------------------------------------------------------|-----|----|----------------|
|                |    | X                                                      |     |    | 3, 4, 45, 139  |

### Update

| 1b | If the protocol is for an update of a previous systematic review, identify as such | Yes | No | Line number(s) |
|----|--------------------------------------------------------------------------------|-----|----|----------------|
|    | X                                                                              |     |    | NA             |

### Registration

| 2 | If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract | Yes | Line number(s) |
|---|--------------------------------------------------------------------------------------------------------|-----|----------------|
|   | X                                                                                                      |     | 60, 144        |

### Authors

### Contact

| 3a | Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author | Yes | Line number(s) |
|----|-----------------------------------------------------------------------------------------------------------------------------|-----|----------------|
|    | X                                                                                                                           |     | 6-21; 376-381  |

### Contributions

| 3b | Describe contributions of protocol authors and identify the guarantor of the review | Yes | Line number(s) |
|----|-----------------------------------------------------------------------------------|-----|----------------|
|    | X                                                                                |     | 366-374        |
| Section/topic | # | Checklist item | Information reported | Line number(s) |
|---------------|---|----------------|----------------------|---------------|
| **Amendments** | 4 | If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments | | X NA |
| **Support** | | | | |
| Sources 5a | | Indicate sources of financial or other support for the review | X | 334-337 |
| Sponsor 5b | | Provide name for the review funder and/or sponsor | X | |
| Role of sponsor/funder 5c | | Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol | X | 353-357 |
| **INTRODUCTION** | | | | |
| Rationale 6 | | Describe the rationale for the review in the context of what is already known | X | 95-134 |
| Section/topic  | #  | Checklist item | Information reported | Line number(s) |
|---------------|----|----------------|-----------------------|----------------|
| Objectives    | 7  | Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO) | X             | 150-154 |
| METHODS       |    |                |                       |                |
| Eligibility criteria | 8  | Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review | X             | 185-216 |
| Information sources | 9  | Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage | X             | 165-184 |
| Section/topic     | #    | Checklist item                                                                 | Information reported | Line number(s) |
|------------------|------|-------------------------------------------------------------------------------|----------------------|----------------|
| Search strategy  | 10   | Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated | X                    | Table 1        |
| **STUDY RECORDS**|      |                                                                                |                      |                |
| Data management  | 11a  | Describe the mechanism(s) that will be used to manage records and data throughout the review | X                    | 180,181        |
| Selection process| 11b  | State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis) | X                    | 209-217; 229-244 |
| Section/topic          | #   | Checklist item                                                                 | Information reported | Line number(s) |
|-----------------------|-----|-------------------------------------------------------------------------------|-----------------------|----------------|
| Data collection process | 11c | Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators | X                     | 218-228        |
| **Data items**        | 12  | List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications | X                     | 156-179        |
| Outcomes and prioritization | 13  | List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale | X                     | 166-175        |
| Section/topic | #  | Checklist item                                                                 | Information reported | Line number(s) |
|---------------|----|-------------------------------------------------------------------------------|----------------------|----------------|
| Risk of bias in individual studies | 14 | Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis | X                    | 209-226        |
| DATA          |    |                                                                               |                      |                |
| Synthesis     | 15a| Describe criteria under which study data will be quantitatively synthesized    | X                    | 190-208        |
|               | 15b| If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., $I^2$, Kendall’s tau) | X                    | 285-278; 307-324 |
| Section/topic | #   | Checklist item                                                                 | Information reported | Line number(s) |
|---------------|-----|---------------------------------------------------------------------------------|-----------------------|---------------|
|               |     |                                                                                 | Yes | No |               |
| 15c           |     | Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression) | X   |     | 307-324       |
| 15d           |     | If quantitative synthesis is not appropriate, describe the type of summary planned | X   | NA |               |
| Meta-bias(es) | 16  | Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies) | X   |     | 284-322       |
| Confidence in cumulative evidence | 17  | Describe how the strength of the body of evidence will be assessed (e.g., GRADE) | X   |     | 261-283       |