BMJ Open

Measuring Outcome Differences Associated with STEMI Screening and Diagnostic Performance: A Multi-centered Retrospective Cohort Study Protocol

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-022453
Article Type:	Protocol
Date Submitted by the Author:	01-Mar-2018
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Keywords:	Myocardial infarction < CARDIOLOGY, ACCIDENT & EMERGENCY MEDICINE, Cardiology < INTERNAL MEDICINE

TITLE: Measuring Outcome Differences Associated with STEMI Screening and Diagnostic Performance: A Multi-centered Retrospective Cohort Study Protocol

SHORT TITLE: STEMI Screening and Diagnostic Performance

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WORD COUNT: 3,935

SUBMITTED: February 28, 2018

ABSTRACT (Word Count: 244 words, max 300)

Introduction: Advances in ST-segment elevation myocardial infarction (STEMI) management have involved improving the clinical processes connecting patients with timely emergency cardiovascular care. Screening upon ED arrival for an early ECG to diagnose STEMI, however, is not optimal for all patients. In addition, the degree to which timely *screening* and *diagnosis* are associated with improved time-to-intervention and post-PCI outcomes, under more contemporary practice conditions, is not known.

Methods: We present the methods for a retrospective multi-center cohort study anticipated to include 1220 patients across seven EDs to 1) evaluate the relationship between timely screening and diagnosis with treatment and post-intervention clinical outcomes; 2) introduce novel measures for cross-facility performance comparisons of screening and diagnostic care team performance including: door-to-screening (D2S), door-to-diagnosis (D2D), and door-to-catheterization lab arrival (D2CAR) times; and 3) describe the use of electronic health record (EHR) data in tandem with an existing disease registry.

Ethics and Dissemination: The completion of this study will provide critical feedback on the quality of screening and diagnostic performance within the contemporary STEMI care pathway that can be used to 1) improve emergency care delivery for STEMI patients presenting to the ED, 2) present novel metrics for the comparison of screening and diagnostic care, and 3) inform the development of screening and diagnostic support tools that could be translated to other care environments. We will disseminate our results via publication and quality performance data sharing with each site. Institutional ethics review approval was received prior to study initiation.

KEY WORDS: STEMI, screening, diagnosis, door-to-ECG, door-to-treatment

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This study overcomes the lack of adequate data within existing national registries to study STEMI screening and diagnosis.
- It presents a structured approach to multi-centered retrospective data collection for a low frequency, but critical, emergency condition.
- Despite studying STEMI care in 7 tertiary care academic facilities, study result will inform the STEMI screening and diagnostic practices of more diverse emergency departments as well as other environments with patients reporting acute symptoms suggestive of STEMI.

INTRODUCTION

We can find opportunities to improve ST-segment elevation myocardial infarction (STEMI) care by exploring the timeliness of screening and diagnosis. Each year, approximately 258,000 patients present to an ED with STEMI.[1] Advances in STEMI care have involved improvements in the clinical processes connecting patients - experiencing this rapidly progressive pathophysiology - with timely emergency care.[2-10] The completion of screening upon ED arrival for an early ECG to diagnose STEMI, however, is not optimal for all patients.[11-14] This is particularly the case when studying the percutaneous coronary intervention (PCI) center affiliated ED sub-population, where variation attributed to inter-facility transfer is removed. Despite proximity to the location of intervention, timely care is highly dependent on the pre-existing screening, diagnosis, and treatment systems.[6,11,14] Here we present the methods for our multi-center investigation to 1) evaluate the relationship between timely screening and diagnosis with treatment time and clinical outcomes, 2) characterize generalizable screening and diagnostic measures that can be used for cross-facility performance comparisons, and 3) describe the use of electronic health record (EHR) data in tandem with an existing disease registry.

Given the European Heart Association, American College of Cardiology, and American Heart Association recommendation to obtain an early electrocardiogram (ECG) within 10 minutes for patients with symptoms suggestive of STEMI,[2,3,4] nearly 85% of EDs have protocols to guide the screen of all arriving patients for the need of an early ECG.[14] We define an early ECG as one performed upon ED arrival, typically well before physician evaluation to diagnose STEMI, in a timely fashion.[14-16] Our prior work identified 12.8% (95% CI [3.4-32.6%]) of patients with STEMI do not receive a timely ECG. The resulting diagnostic delay led to 14-80 minutes of additional myocardial ischemia time.[14] Earlier treatment has been historically associated with better outcomes.[2,3] The degree to which timely *screening* and *diagnosis* are associated with improved time-to-intervention and post-PCI outcomes, under more contemporary practice conditions, is not known. In addition, STEMI care pathway performance has not been explored in the ED population through a large multi-centered patient cohort.

METHODS

Study Design. This is a multi-center retrospective cohort study designed to quantify the potential impact of improving ED screening and diagnostic care performance on timely STEMI treatment and post-PCI outcomes. The results are intended to inform the design of a future EHR embedded algorithm to screen for STEMI upon ED arrival. We aim to describe our approach to quantifying the associations between 1) time-to-diagnosis, and 2) time-to-treatment (PCI) between patients who do and do not receive an early ECG within 10 minutes. We seek to understand variability in achieving timely PCI, hospital length of stay (LOS), subsequent heart failure, and mortality by patient characteristics (i.e., age, gender, race, language) and care process factors (i.e, achieving timely screening, time of day, distance between ED and cath lab) through these pre-specified sub-group analyses. We received institutional review board (IRB) approval from all participating facilities prior to study initiation. A shared IRB approval process was used for this National Institute of Health funded study.

Study Setting. Participating sites are tertiary care center EDs within a hospital designated as a PCI Center where the ED physician can activate the cath lab for emergency STEMI intervention (Code STEMI) with a single phone call.[10]

Process Measures. Exploring STEMI process measures includes quantifying time intervals associated with STEMI screening and diagnosis. *Door-to-Screening* (D2S) and defined as the time from ED arrival to the completion of the first ECG (Table 1). The time of ECG completion was selected to mark the end of screening because it is the only retrospective clinical timestamp recorded to represent the completion of STEMI screening among those who screen positive. It is typical practice in EDs for ECGs to be taken directly to an emergency physician for interpretation.[14-17] *Door-to-Diagnosis* (D2D) is the interval from ED arrival to STEMI diagnosis (Table 1). STEMI diagnosis is defined as the time when the physician activates a cardiac lab team for emergent PCI. As a result we primarily measure the completion of diagnosis as door-to-cath-lab-activation. We found that cath lab activation time was rarely included in the medical record, maintained in an external telephone call center database, and inconsistently recorded. As a result, site PIs were permitted to export cath lab activation times from their local database for the National Cardiovascular Data Registries' (NCDR) Acute Coronary Treatment and Intervention Outcomes Network (ACTION) Get with the Guidelines Registry supported by the American College of Cardiology (NCDR-ACTION®, Table 2). We also included the time-to-diagnostic ECG as a secondary measure for diagnostic time.

These definitions are a necessary change from the traditional use of door-to-ECG as the starting point for STEMI performance measures and reflect how screening and diagnosis require separate metrics for appropriate diagnostic performance evaluation. Delayed STEMI screening and diagnosis are barriers to effective treatment access. By limiting our population to patients screened by the ED, we limit the variation in point-of-first-medical contact to those brought in by emergency medical services (EMS) or self-transport.

Patient and Public Involvement. The study research question and outcome measures were developed from a desire to evaluate how well ED STEMI screening and diagnosis are performed for individual patients. We seek to better understand the demographics and presentations of patients who may experience differential outcomes potentially associated with sub-optimal STEMI screening. Patients, however, were not directly involved in the design or conduct of this study.

Inclusion/Exclusion Criteria. We will include all 2014 to 2016 ED patients with a final hospital diagnosis of STEMI. To reduce misclassification bias, STEMI will be defined by International Classification of Disease (ICD) 9 codes previously validated in the literature and the corresponding ICD-10 diagnosis codes (Table 3).[1] Data abstractors, familiar with the EHR of their institution, will review electronic patient charts for study data and to determine if the course of care is consistent with acute STEMI. Care is considered inconsistent with acute STEMI if at least two of the following apply: STEMI is not mentioned in the context of a diagnosis, the discharge summary does not include STEMI as a final diagnosis, there is no cath lab intervention, cath lab findings are not consistent with STEMI anatomy or intervention, and an alternative diagnosis is present for which care is most consistent (including non-STEMI, unstable angina, and coronary vasospasm amongst others). It is recognized that some of these patients' anatomy and physiology may generate ECG findings consistent with an appropriate diagnosis of STEMI from the ED. We opted to exclude these patients because the ultimate goal of STEMI screening from the ED is to identify patients who have STEMI and will benefit from emergent removal of an acute thrombus within a coronary artery. This would be the objective of a precision-oriented approach to screening ED patients upon arrival for possible STEMI. We retained patients who received care in the ED but had a diagnostic ECG acquired prior to hospital arrival. Their door-to-diagnostic-ECG time would be negative and reflect an opportunity for an alternative care pathway, such as pre-hospital arrival cath lab activation. Cases inconsistent with acute STEMI are referred to the site-principal investigator (PI) for chart review. All excluded cases are shared with the Vanderbilt Emergency Care Health Services Research Data Coordinating Center (HSR-DCC) central study PI (M.Y.Y.) for approval. Patients for exclusion are flagged for exclusion by the HSR-DCC but not removed.

Primary Outcomes. The primary outcome (Table 1) is time-to-treatment, i.e. time from ED arrival to STEMI treatment. An early ECG is defined per existing clinical practice guidelines[2,3,14] as the time between ED arrival (the patient's first recorded presence in the ED) to the completion of the first ECG in the ED intended to permit the early diagnosis of STEMI. ED arrival, or "door" time, is defined as the patient's first recorded presence in the ED.[11,14,18] Our definition for time-to-treatment includes two outcome measures. The first measure is door-to-cath lab arrival (D2CAR) a diagnostic team oriented measure (Table 1). Patient cath lab arrival marks the last point in the STEMI care pathway the diagnostic team can influence. The second measure is door-to-balloon (D2B) time, the more traditionally used PCI treatment time measure (Figure 1). During the study design phase we found that D2B time was not consistently documented in the EHR at any of our seven hospitals. Thus, we modified definitions for this timestamp after considering the use of alternative data as established by the NCDR-ACTION® registry. The registry includes proxies for this outcome in a hierarchy such that D2B time can be measured primarily as balloon inflation time, yet the time the guidewire crosses the coronary lesion can be used when this time is missing.[10,19]

Secondary Outcomes. Secondary outcomes include ED LOS, hospital LOS, change in cardiac ejection fraction (EF) after the acute STEMI, and one year mortality. ED LOS is defined as the time from ED arrival to ED departure.[18] Change in EF is calculated as the difference between the last EF measured prior to the patient's STEMI and the first documented after hospital discharge. Hospital LOS is the time from hospital admission to hospital discharge. Mortality at one year was assessed by assigning one of three categories to a patient's survival status one year after the STEMI ED visit: deceased (with date, time, and cause noted), alive (based on evidence of contact with the health system via EHR documentation), and lost to follow up.

Risk Factors. The independent variable of primary interest is time-to-screening defined as door-to-first-ECG ($D2E_{1st}$) (Table 1). This is the screening (D2S) time interval measured as both

a continuous variable and dichotomized (D2S ≤ 10 minutes vs D2S >10 minutes) per existing clinical practice guidelines.[2,3] Additional risk factors of interest include information often known about a patient upon ED arrival which will be examined in exploratory analyses as adjusting variables. These include age, gender, race, primary language, arrival time (time of day), arrival mode (EMS, self-transport, or other), and chief complaint.

Secondary Subgroup Analysis. We also included patient characteristics known to increase the risk for STEMI and to be associated with outcome differences.[3,14] These include symptom onset,[19,20-21] as well as a history of diabetes (pre-diabetes was not included), hypertension, dyslipidemia, tobacco use, heart failure, prior myocardial infarction, prior coronary artery bypass graft, and prior PCI procedure. In defining variables we balanced maximizing co-variate granularity with medical informatics best practice for data integration and data standardization. For example, tobacco use status is recorded by NCDR as a dichotomous variable. In order to obtain more detail, we collected these data primarily from the EHR. During the study design phase we evaluated the smoking history data available in each EHR and found the degree of tobacco exposure was variably categorized across our seven sites. We developed the following categories to maximize variability while standardizing data reporting: current smoker, prior smoker but quit, and non-smoker. Tobacco exposure fields in the shared database were limited to only accept one of these 3 smoking status designations for each patient.[22-23]

Recognizing the impact of EHR user access and data use context,[21] we only include information available to the diagnostic care providers at the time of the initial encounter. These providers are typically the ED team but can include an interventional cardiology consultant for rare presentations or complex patients. The NCDR-ACTION® registry permits the inclusion of all data available upon review of the full medical record. The structure of the ED interface with EHRs varies between hospitals with some having more or less data available upon patient arrival. As a result, we opted for data collection directly from the EHR using what is accessible during the early phases of the diagnostic clinical encounter.

Sample Size. We estimate our analysis will require 1220 patients from our 7 study sites. This was based our plan for a non-parametric Wilcoxon rank sum test comparing door-to-balloon (D2B) time between dichotomized door-to-first-ECG (D2E) groups (early ECG: D2E ≤ 10 minutes vs missed screening: D2E >10 minutes) of STEMI patients. An aggregation of ICD 9/10 code counts within each hospital from a prior studies suggests approximately 444 ED STEMI patients are seen in these 7 EDs annually with 87.2% captured with a timely early ECG and 12.8% in the missed screening cases.[14,24] This is the effective sample size required to detect a standardized difference of 0.35, with a type I error rate of 0.05 and power of 80% in two-tailed tests. This is a small to medium effect size by Cohen's nomenclature.[25] This translates to 596 patients and a detectable door-to-balloon (D2B) time difference of 5.2 minutes.[26] Due to potential correlation in D2B between patients seen at the same ED, we calculated a cluster design effect of 1.84 assuming an inter-cluster correlation coefficient of 0.01. This required us to include a minimum of 1220 patients. With an anticipated ICD coding misclassification exclusion rate of 5-10%, this patient sample size is achievable with 3 years of data.

Data Collection. Cohort data for patients meeting study year, ED care, and ICD diagnosis code inclusion criteria are extracted from each hospital's EHR using a pre-programmed report to identify the study cohort. These data are sent securely to the data coordinating center (HSR-DCC) using the HIPPA and research data security "Sendit" function of Research Electronic Data Capitulation (REDCap). REDCap is a secure, web-based application designed exclusively to support data capture for research studies.[27-29] The cohort data for each site is uploaded into a

sub-section of the larger study database built and maintained by the HSR-DCC. The coordinating study PI and HSR-DCC staff have access to all study data, but individual sites only see their patient records. The use of a centrally designed database with built-in variable definitions and quality control checks ensured data harmonization across sites.[27,30]

At a minimum, cohort data include a patient identifier (typically the medical record number), ED date of service, and final hospital ICD diagnosis codes. Each patient record is reviewed by a data abstractor associated with each institution's ED. A REDCap-based data collection form is completed with existing EHR data that, as noted above, would have been available to diagnostic providers in the ED during the clinical encounter. Prior to data collection, each site PI completed a training case form (TCF, Table 4) in which data were collected for the first patient of record for study inclusion. The location of each variable within the EHR, including the location within specific documents, was recorded and used as a guide for the local data abstractors. The resultant data dictionary was used to verify data definitions were standardized across sites. In total, we had 11 data abstractors from the seven EDs. All data abstractors received a minimum of two hours of training to further ensure standardized data collection. Training was via a two-part module developed and delivered by the HSR-DCC. Part 1 involved a 90 minute session via video conference introducing the study design, the data abstractors' role in the project, study data definition, and practice using all fields of the study database for the TCF patient. Part 2 involved repeating the data entry process for the TCF patient with direct use of the associated EHR record (Table 5).

We verified that all participating ED sites submit STEMI patient data to the NCDR-ACTION® Registry. Despite the presence of this existing data registry, we undertook primary data collection for additional information on ED-level STEMI care variables. Site PIs, however, were permitted to send select variables with identical data definitions to HSR-DCC data from their local NCDR-ACTION® Registry database (Table 2). These data were uploaded directly into the database by the HSR-DCC to reduced data entry time, and verified by data abstractors upon chart review.

The data collection form within the study database has alerts for values outside of the expected range and instructions for uniform units of measure. The HSR-DCC staff review all completed entries for accuracy with the use of data cleaning checks run via R statistical code (www.r-project.org, available at http://biostat.mc.vanderbilt.edu/wiki/Main/JenkinsEMCode) on data contained in the study database after the completion of 2014 data, 2015 data, and study close. The data cleaning code identifies missing values, patterns of missing-ness, and inconsistent data entries (e.g., an ED arrival date that occurs before date of birth is likely a data entry error in the year for the ED visit or birth). Results of the first data cleaning checks are communicated to the site PI and data abstractors at the end of 2014 data collection, discussed via telephone conference call, with a response verified by the HSR-DCC staff. Subsequent data checks are run upon request and at a minimum of every 30 days. Results for follow up data checks are run for each site, then communicated to each collaborating team via email. The full report is then saved on a shared secure drive (vanderbilt.box.com) managed by the HSR-DCC with specific sub-folders for each site. Access permissions are set such that data for each site are only seen by the site PI and local data abstractors. Site PIs are asked to clarify ambiguous entries. The HSR-DCC study coordinator follows up on all requests for data clarification.

Data Analysis. Descriptive statistics for screening, diagnosis and treatment time-intervals including D2S (time-to-screening), D2D (time-to-diagnostic test completion), D2CLA (time-to-diagnosis communication), D2CAR (time-to-ED-to-cardiology care transition), D2B (time-to-intervention) and patient characteristics, will be calculated using mean, standard deviations, and

quartiles for continuous variables and proportions for categorical variables. They will be compared between the two primary exposure STEMI patient groups: early ECG and missed screening cases using non-parametric Wilcoxon rank sum test for continuous variables and Chi-square test for categorical variables.

For the primary adjusted analysis, we will first use a linear mixed effects regression model with D2B, as the outcome. The primary independent variable of interest is D2S status ($D2E_{1st}$ ≤10 minutes vs. $D2E_{1st}$ >10min) with a random effect for the ED providing care. We will adjust for ED screening methods (e.g., point of first patient contact in the ED, dedicated space for early ECGs, etc.), care process factors (e.g., time of day, distance between ED and cath lab, etc.), and individual patient characteristics. Since D2S is a portion of D2B, we will use the first-ECG-to-balloon time interval[26] calculated by subtracting D2S from D2B as the primary outcome in this model. Results from those adjusted analyses will help quantify differences in timely care between early ECG and missed screening case STEMI patients and reduction in time-to-treatment (D2B) for every minute saving in time-to-screening (D2E). These analyses will be repeated with D2CAR as the outcome, then D2D as the independent variable of interest.[31]

We will then perform a time-to-event analysis using the Cox proportional hazard model stratified by ED for each secondary outcome event (Hospital LOS, and one year mortality), and a linear mixed effects regression model with ED random effect for continuous outcomes (change in cardiac EF after acute STEMI) with the same adjustments and independent variables as the primary analysis.

Lastly, we will use our adjusted data to construct a summary of the care course (the sequence of median STEMI process intervals) by age, gender, race, language, presenting symptom and ED subgroups to identify differences in the following time intervals: symptom onset-to-arrival, arrival-to-first ECG, first ECG-to-diagnostic-ECG, diagnostic-ECG-to-cath lab activation, activation-to-PCI balloon, PCI-to-hospital discharge (see Figure 1).

DISCUSSION

Despite the limitations of retrospective EHR data, we selected this approach over a prospective study for several reasons. First, the time and financial cost of the prospective approach would make the study impracticable. Prospective enrollment would require four years to complete data collection and continued screening of ED patients. The cost would outweigh the enrollment yield given the relative infrequency of STEMI events within the larger ED patient population. These logistics would significantly slow our ability to generate knowledge to inform an important study question for a deadly disease. Second, our targeted screening intervention will use EHR data available to the ED care team upon arrival, therefore the use of existing EHR data will be subject to similar data conditions during intervention implementation.

Substantial resources are allocated to assure screening and diagnosis within 10 minutes of patient arrival to achieve timely STEMI treatment. Yet no existing measures or databases have adequate granularity to measure screening and diagnostic practice or to guide performance optimization. Much of the resource investment reflects the major consequences and medicolegal gravity of a missed STEMI in the context of time limited interventions, high mortality, and significant morbidity. If interventions are to be developed to more precisely identify STEMI patients upon ED arrival, data on ED STEMI patients are critical. These interventions need to be balanced with appropriate use of resources for this infrequent but potentially deadly condition.

Current practices are often supported by data extrapolated from the more broad population of hospital STEMI patients who may be different from the ED sub-population. This study will increase our understanding of whether those missed by ED STEMI screening receive less timely interventional care (PCI) than those with timely STEMI screening and diagnosis. It will better characterize the care process, demographic profile and clinical outcomes for this subpopulation of STEMI patients. The primary results of this study will be a comparison of differences in the timeliness of treatment between those who experienced timely vs. delayed screening and diagnosis. Our subgroup analysis may identify risk factors for poor outcomes providing data to focus clinical interventions to deliver precise diagnostic care normalized for subgroup specific risk factors.

The American Heart Association recently called for growth in the use of linked registry and EHR data to understand the penetration of cardiovascular care guidelines and evidence within clinical practice.[32] Our methods present an applied approach to the use of EHR data for emergency care sensitive cardiovascular disease diagnoses. NCDR-ACTION® Registry is a robust risk-adjusted, outcomes-based, quality improvement program that focuses exclusively on high-risk STEMI and non-NSTEMI patients. The registry database has revolutionized our ability to study outcomes for these high risk conditions despite their relatively low prevalence at any given center. However, the NCDR-ACTION® Registry is focused on treatment performance, and it lacks variables (Table 5) to support evidence-based screening and diagnostic performance evaluation to improve clinical practice. In contemporary practice the existence of EHRs is more the norm than the exception.[33] EHRs provide a vehicle for not only source data but the potential application of dynamic clinical decision support to enhance risk stratification and mechanisms for evidence-based care delivery. In this study we used standardized multi-center primary data collection from seven hospital EHRs to enable our ability to study these early STEMI care performance targets.

The completion of this study will provide a more accurate appraisal and critical feedback on the quality of contemporary STEMI care pathway performance that can be used to improve

emergency care delivery for ED STEMI patients, and inform the development of screening and diagnostic support tools that can be translated to other care environments. Specifically, we will better understand the consequences of and risk factors for delayed screening and diagnosis. We anticipate our results will be extrapolated to other care delivery spaces that receive undifferentiated patients (non-PCI center EDs and urgent care). What is learned about differential risk may be applied in primary care clinics, intake processes for direct to floor admissions, and inter-service floor transfers. Tools developed to improve screening may be used for other emergency care sensitive conditions.

ETHICS DISSEMINATION

Manuscript publication is our most broad plan for results dissemination. Given the critical nature of STEMI, we plan to simultaneously share our study results with the participating institutions STEMI care quality improvement committees, Divisions of Cardiology as well as Emergency Department leadership. The study data will be available to other researchers on a case-by-case basis via the Vanderbilt University Emergency Care Health Services Research Data Coordinating Center (HSR-DCC). Statistical code will be made available on the HSR-DCC website.

AUTHOR CONTRIBUTIONS

Dr. Maya Yiadom designed and coordinates the logistics of the study and served as lead investigator via the data coordinating center. Drs. Bryn Mumma, Chris Baugh, Brian Patterson, Angela Mills, Gilberto Salazar and Mary Tanski are Site-Principal Investigators and coordinate study implementation within their institutions. Cathy Jenkins is the lead staff biostatistician, Karen F. Miller is the data coordinating center's Data Integrity Officer. Brittney Jackson is the Study Program Manager. Drs. Jennifer West and Stephen Dorner were site data abstractors who contributed to study methods development. Drs. Chris U. Lehmann, Thomas J. Wang, Sean P Collins, Alan B. Storrow and Robert S. Dittus provided content specific expertise advising study design and implementation. Drs. Tim Vogus and Bernard provided content specific data analysis guidance. Dandan Liu was the overseeing statistician who co-designed the study with Dr. Yiadom and will oversee final data analysis with Dr. Yiadom.

ACKNOWLEDGEMENTS

Special thanks to the data abstractors at the 7 study sites including: Caitlin Azzo, Oluyemi O. Olubowale, Alex Trinh, Shannon McNabb, Samita Kumar, Sean Harla, Dr. Margo Kaller, Dr. Jane Dyball, Dr. Daniel Steward, and Dr. Christopher Beck. We are appreciative of Christina Kampe (Vanderbilt Emergency Care Health Services Research Data Coordinating Center's IRB Regulatory and Compliance Specialist) for managing the multi-site IRB approval process that was critical to initiate this study.

FUNDING STATEMENT

Research reported in this publication was supported by the National Heart Lung and Blood Institute's (NHLBI) award numbers 5K12HL109019, 1K23HL133477, 5K08HL130546. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

COMPETING INTERESTS

Dr. Yiadom is Director of the Emergency Department Operations Study Group (EDOSG). Dr. Baugh is a member of the Advisory Board, consultant for Roche Diagnostics and Janssen Pharmaceuticals, and has received research funding from Boehringer Ingelheim. Dr. Storrow has also received grant support from Abbott Diagnostics and Roche Diagnostics. He is a consultant for Roche Diagnostics, Novartis Pharmaceuticals Corp, Alere Diagnostics, Trevena, Beckman Coulter and Siemens. Dr. Collins received grant research support from NIH/NHLBI, PCORI, Cardiorentis, Novartis, and Cardioxyl and consultant support/other from Novartis, Trevena, Cardiorentis, Cardioxyl, and Siemens. All other authors have no disclosures.

TABLES

Table 1 – Definition of Time Stamps and Intervals in STEMI Screening and Diagnosis

Time Stamp	Care Interval	Definition
Symptom Onset Time	Time of symptoms prior to arrival	Recalled patient reported time for when symptoms associated with the acute STEMI encounter began.
Time Zero		
Door Time	ED arrival time[19] (Primary analysis)	First recorded presence of the patient in the ED
Screening		
First (early) ECG Time	Door-to-Screening, **D2S** Door-to-first ECG time, **$D2E_{1st}$** (Primary Independent variable of interest)	ED arrival to completion of the first ECG. The first ECG is generally performed prior to the ED physician evaluation for the purpose of enabling the early identification of STEMI
Diagnostic		
Diagnostic ECG Time	Door-to-Diagnostic ECG, **$D2E_{Dx}$** (Secondary Independent Variable of Interest)	ED arrival to completion of ECG used to activate the cath lab
Cath Lab Activation Time	Door-to-Cath Lab Activation, **D2CLA**	ED arrival to the time when the cath lab was activated (Code STEMI)
Treatment		
Patient Arrives in Cath Lab	Door-to-Cath Lab Arrival Time, **D2CAR** Diagnostic team centric (Primary Outcome)	ED arrival to patient arrival in the cath lab
Balloon Time	Door-to-Balloon Time, **D2B** Intervention team centric outcome (Primary Outcome)	Time from ED arrival to time the catheterization guidewire crossed the culprit coronary lesion in patients receiving balloon angioplasty

Time Zero = Start time for the indication for ST-segment myocardial infarction (STEM) emergency care. ED = Emergency Department Cath Lab = Cardiac Catheterization Lab. Outcomes = Treatment times for STEMI patient directed to percutaneous coronary intervention.

Table 2 – Study Data Permitted for Import from Local NCDR-ACTION® Registry Databases

Study Variable	NCDR-ACTION® Variable Number
Birth date	2050
Sex	2060
Race	2070 (White) 2071 (Black) 2073 (American Indian/Alaskan Native) 2072 (Asian) 2074 (Native Hawaiian /Pacific Islander)
Ethnicity	2076 (Hispanic vs non-Hispanic)
Health Insurance	3300 (Private) 3301 (Medicare) 3302 (Medicaid) 3303+3304+3305+3306 (Other) 3307 (Uninsured/Self Pay)
Cath Lab Activation Time	3159
PCI (yes/no)	7100
ED Discharge Time	3222
Cath Lab Arrival Date	7101
Cath Lab Arrival Time	7102

*We did not permit the inclusion of any data that would be used for calculated time intervals, the primary outcome or risk factors/exposures.

Table 3 - STEMI International Classification of Disease Codes (ICD) for Inclusion by Final Hospital Diagnosis

Acute Myocardial Infarction (AMI) Diagnosis Codes Associated with STEMI					
ICD 9	Diagnosis	**LOCATION**	ICD 10	Diagnosis	**LOCATION**
410	AMI		I21	STEMI and NSTEMI	
410.21	AMI infero-lateral wall	Inferior	I21.11	STEMI RCA	Inferior
410.31	AMI infero-posterior wall	Inferior	I21.19	STEMI other coronary artery inferior	Inferior
410.41	AMI of other inferior wall	Inferior	I21.21	STEMI LCX	Inferior
410.01	AMI antero-lateral wall	Anterior	I21.01	STEMI Left Main	Anterior
410.11	AMI other anterior wall	Anterior	I21.02	STEMI LAD	Anterior
			I21.09	STEMI other coronary artery anterior	Anterior
410.51	AMI other lateral wall	Lateral			
410.61	AMI true posterior wall infarction	Posterior	I21.29	STEMI other site	Other specified
410.81	AMI other specified site*	Other Spec			
410.91	AMI unspecified site	Nonspecified	**I21.3**	STEMI Unspecified	Nonspecified

AMI = acute myocardial infarction, STEMI = ST-segment elevation myocardial infarction, NSTEMI = non-ST –segment elevation myocardial infarction, RCA = right coronary artery, LCX = left circumflex artery, LAD = left anterior descending artery, *410.81 includes papillary muscle rupture.

Table 4 – Data Abstractor Training Module

- PART 1 – 90 minute Video Conference
  Content
  1. Clinical Problem: What is known and unknown about STEMI and STEMI patient outcomes
  2. Study Questions
  3. Study Design
  4. Clinical Care Pathway for STEMI Care:
     Case Study: Beverly Hospital, Beverly, Massachusetts
     - https://www.youtube.com/watch?v=FkeH036oigo
       (View to 3 minutes and 50 seconds)
  5. Role of the Electrocardiogram (ECG)
  6. PCI Procedure:
  7. Clinical timestamps and care documentation in the electronic health record
     The Procedure: PCI care and Timestamps:
     - https://www.youtube.com/watch?v=I45kJJoCa6s:
       (View full video)
     - https://www.youtube.com/watch?v=-BuazAhs7uA:
       (View to 1 minute and 10 seconds)
  8. Outcome measure data definitions (similarities and differences with NCDR-GWTG ACTION Registry®
  9. Study procedures and timeline
  10. Introduction to study database
  11. Data entry with Training Case Form (TCF) example

- PART 2 – Independent data abstraction for TCF patient directly form the local Electronic Health Record (30 minutes)

- A Data Abstractor is approved to start data entry after Emergency Care Health Services Research Data Coordinating Center (HSR-DCC) staff review and confirm accurate and complete TCF data entry within the database for the TCF patient. Once confirmed, the Site-PI co-signs a delegation of authority (DOA) form certifying the Data Abstractor is trained and will collect data under their guidance.

Table 5 – Study Variables Not Available in the NCDR-ACTION® Registry

Variable Name	Comment
PATIENT DEMOGRAPHICS	
Primary Language	
EMERGENCY DEPARTMENT - ED	
Triage start time	
Triage end time	
Emergency Severity Index (ESI) score	Measure of anticipated care acuity assigned upon ED Triage (lower = higher acuity)
Onset of symptoms prior to arrival in your ED	Measured as hours prior to presentation, no assumptions made for patient reports of this morning, last night, yesterday, etc
Chief Complaint Reported Upon Arrival	Chest Pain (yes/no)
Chief Complaint Reported Upon Arrival	Chief Complaint 1-5
Final ED Diagnosis	Diagnostic Care Team's Diagnosis 1-5
ED discharge date	
HOSPITALIZATION	
Hospital Discharge Diagnosis ICD codes 1-5	Action includes the first 3 rather than 5
PCI Center Early ECG	
Was there a First PCI Center ED ECG? - First PCI Center ED ECG date - First PCI Center ED ECG time - First PCI Center ED ECG Clinical Interpretation - First PCI Center ED ECG Official ECG Interpretation	Yes/No
Receiving Hospital Follow Up ECG	
Was there a follow up ECG at the Receiving hospital? - Receiving Hospital Follow Up ECG date - Receiving Hospital Follow Up ECG time - Official ECG Interpretation - Clinical Interpretation of Receiving ED EKG	Yes/No
Prior ECG	
Was there a prior ECG from an outside facility or agency? If yes, - ECG from EMS Transferring to Receiving Hospital - ECG from Outside Hospital - ECG by EMS transporting to Outside Hospital - Referring Clinic Provider ECG	Yes/No If yes, date and time, clinical interpretation, official interpretation
Diagnostic ECG (select one)	
- PCI Center Early ECG - EMS Transferring from the Field to the PCI Center ED - Outside Hospital ED - EMS Transporting from OSH ED - Referring Clinic Provider	ECG with which the decision was made to activate the cath lab emergently
Change in Ejection Fraction (Pre, During Index Visit, Post Index Visit)	
Last EF Prior to Index Visit	EF measured before this current index visit? (Yes/No) If yes, - Prior EF Date - Prior EF % (lowest documented) - Prior EF Range
EF during Index Visit	EF measured during index visit? (Yes/No) If yes, - Index Visit EF Date - Index Visit EF % (lowest document) - Index Visit EF Range
EF after Index Visit	First post index visit discharge EF (Yes/No) - Post-Index-Visit EF Date - Post-Index-Visit EF % (lowest documented) - Post-Index-Visit EF Range

FIGURE LEGEND

Figure 1 – STEMI Patient Care Process Measures: Screening, Diagnosis and Treatment

D2E1st = Door-to-first ECG = Door-to-early ECG = Door-to-Screening (D2S). D2Ed = Door-to-Diagnostic ECG = one of 2 ways to measure Door-to-Diagnosis (D2D). More ideally, Door-to-Diagnosis (D2D) can be measured as Door-to-Cathlab-Activation (D2CLA). Note: Pre-hospital ECGs interpreted by the paramedic team as a STEMI would be represented as "negative" Door-to-Diagnostic ECG time. These patients would ideally bypass the ED care pathway in the absence of an overriding need for non-PCI (or pre-PCI) care (i.e., motor vehicle collision injuries requiring stabilization, witnessed cardiac arrest after pre-hospital ECG acquisition, etc). Thus negative D2S would indicate potential opportunity for an alternative care pathway.

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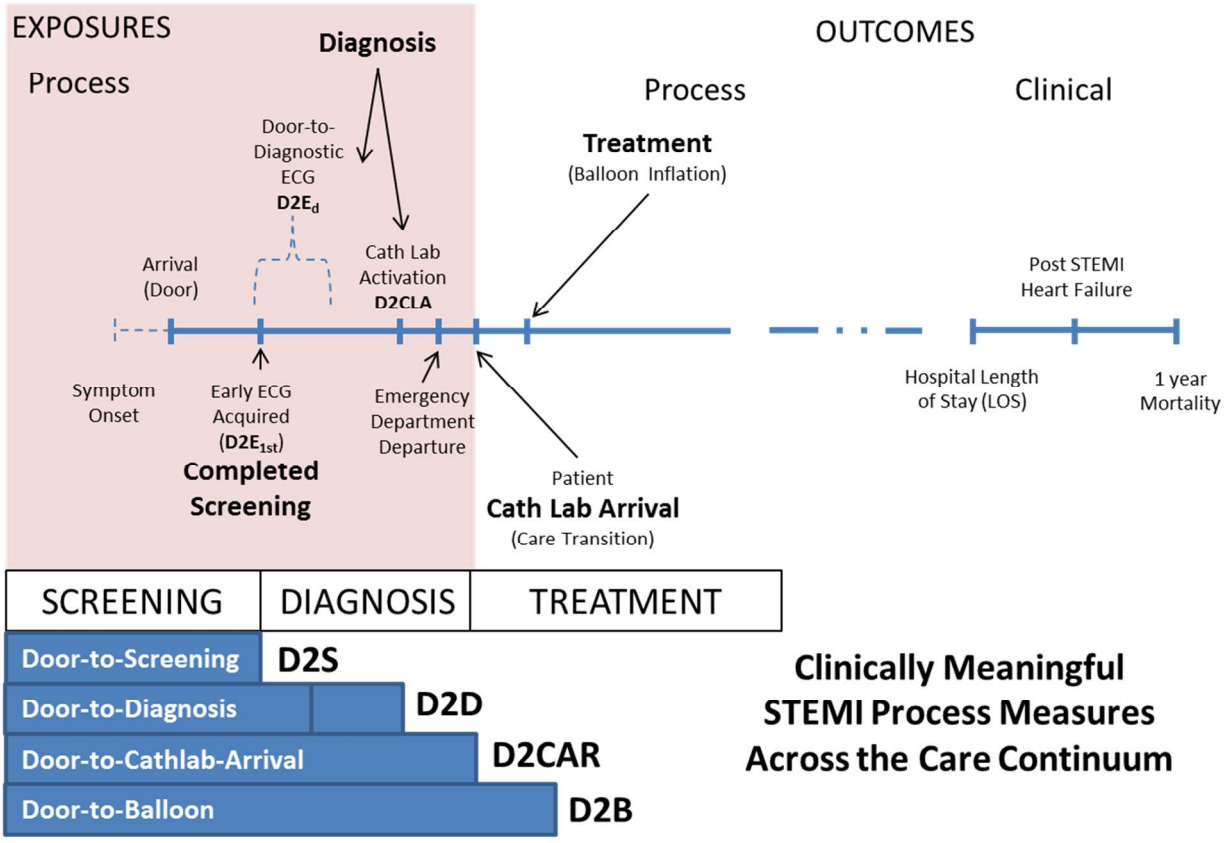
Figure 1 – STEMI Patient Care Process Measures: Screening, Diagnosis and Treatment



D2E1st = Door-to-first ECG = Door-to-early ECG = Door-to-Screening (D2S). D2Ed = Door-to-Diagnostic ECG = one of 2 ways to measure Door-to-Diagnosis (D2D). More ideally, Door-to-Diagnosis (D2D) can be measured as Door-to-Cathlab-Activation (D2CLA). Note: Pre-hospital ECGs interpreted by the paramedic team as a STEMI would be represented as "negative" Door-to-Diagnostic ECG time. These patients would ideally bypass the ED care pathway in the absence of an overriding need for non-PCI (or pre-PCI) care (i.e., motor vehicle collision injuries requiring stabilization, witnessed cardiac arrest after pre-hospital ECG acquisition, etc). Thus negative D2S would indicate potential opportunity for an alternative care pathway.

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	n/a
	2b	All items from the World Health Organization Trial Registration Data Set	n/a
Protocol version	3	Date and version identifier	3
Funding	4	Sources and types of financial, material, and other support	5,6
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
	5b	Name and contact information for the trial sponsor	5
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	5
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	9-11
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	7

	6b	Explanation for choice of comparators	7 (mid pg), 8 (mid pg)
Objectives	7	Specific objectives or hypotheses	_8 (aims/seek__
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	_____8_____
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	_____8_____
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	__8 (sites- top, patients – bottom)
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	____n/a_____
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	____ n/a_____
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	_____n/a_____
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	_____n/a_____
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	_____9_____
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	__Figure 1____
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	____10_____

Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	n/a
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	n/a
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	n/a
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	n/a
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	n/a
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	10-11
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	n/a
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	10-11

Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	11
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	9-10
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	n/a
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	pgs 9-11 (data coordinating center, HSR-DCC)
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	n/a
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	n/a
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	11 (mid)
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	8 (top)
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	n/a
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	n/a

	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	10
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	6
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	5,15
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n/a
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	5,15
	31b	Authorship eligibility guidelines and any intended use of professional writers	16 (we use ICMJE criteria)
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	15
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	n/a
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1 – title, 3- abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	7
Objectives	3	State specific objectives, including any pre-specified hypotheses	7,8
Methods			
Study design	4	Present key elements of study design early in the paper	8
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	8
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	8
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	8 (sites- top, pts- bottom)
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	10-11
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	10
Bias	9	Describe any efforts to address potential sources of bias	8
Study size	10	Explain how the study size was arrived at	10
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8-11
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	11
		(*b*) Describe any methods used to examine subgroups and interactions	9-10
		(*c*) Explain how missing data were addressed	9,11
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	9

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	n/a
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	n/a
		(b) Give reasons for non-participation at each stage	n/a
		(c) Consider use of a flow diagram	n/a
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	n/a
		(b) Indicate number of participants with missing data for each variable of interest	n/a
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	n/a
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	n/a
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	n/a
		Cross-sectional study—Report numbers of outcome events or summary measures	n/a
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	n/a
		(*b*) Report category boundaries when continuous variables were categorized	n/a
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n/a
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	n/a
Discussion			
Key results	18	Summarise key results with reference to study objectives	n/a
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	n/a
Generalisability	21	Discuss the generalisability (external validity) of the study results	n/a
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	5,6

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.
Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Measuring Outcome Differences Associated with STEMI Screening and Diagnostic Performance: A Multi-centered Retrospective Cohort Study Protocol

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-022453.R1
Article Type:	Protocol
Date Submitted by the Author:	06-Mar-2018
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Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Emergency medicine, Evidence based practice
Keywords:	

TITLE: Measuring Outcome Differences Associated with STEMI Screening and Diagnostic Performance: A Multi-centered Retrospective Cohort Study Protocol

SHORT TITLE: STEMI Screening and Diagnostic Performance

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WORD COUNT: 3,935

SUBMITTED: February 28, 2018

ABSTRACT (Word Count: 244 words, max 300)

Introduction: Advances in ST-segment elevation myocardial infarction (STEMI) management have involved improving the clinical processes connecting patients with timely emergency cardiovascular care. Screening upon ED arrival for an early ECG to diagnose STEMI, however, is not optimal for all patients. In addition, the degree to which timely *screening* and *diagnosis* are associated with improved time-to-intervention and post-PCI outcomes, under more contemporary practice conditions, is not known.

Methods: We present the methods for a retrospective multi-center cohort study anticipated to include 1220 patients across seven EDs to 1) evaluate the relationship between timely screening and diagnosis with treatment and post-intervention clinical outcomes; 2) introduce novel measures for cross-facility performance comparisons of screening and diagnostic care team performance including: door-to-screening (D2S), door-to-diagnosis (D2D), and door-to-catheterization lab arrival (D2CAR) times; and 3) describe the use of electronic health record (EHR) data in tandem with an existing disease registry.

Ethics and Dissemination: The completion of this study will provide critical feedback on the quality of screening and diagnostic performance within the contemporary STEMI care pathway that can be used to 1) improve emergency care delivery for STEMI patients presenting to the ED, 2) present novel metrics for the comparison of screening and diagnostic care, and 3) inform the development of screening and diagnostic support tools that could be translated to other care environments. We will disseminate our results via publication and quality performance data sharing with each site. Institutional ethics review approval was received prior to study initiation.

KEY WORDS: STEMI, screening, diagnosis, door-to-ECG, door-to-treatment

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This study overcomes the lack of adequate data within existing national registries to study STEMI screening and diagnosis.
- It presents a structured approach to multi-centered retrospective data collection for a low frequency, but critical, emergency condition.
- Despite studying STEMI care in 7 tertiary care academic facilities, study result will inform the STEMI screening and diagnostic practices of more diverse emergency departments as well as other environments with patients reporting acute symptoms suggestive of STEMI.

INTRODUCTION

We can find opportunities to improve ST-segment elevation myocardial infarction (STEMI) care by exploring the timeliness of screening and diagnosis. Each year, approximately 258,000 patients present to an ED with STEMI.[1] Advances in STEMI care have involved improvements in the clinical processes connecting patients - experiencing this rapidly progressive pathophysiology - with timely emergency care.[2-10] The completion of screening upon ED arrival for an early ECG to diagnose STEMI, however, is not optimal for all patients.[11-14] This is particularly the case when studying the percutaneous coronary intervention (PCI) center affiliated ED sub-population, where variation attributed to inter-facility transfer is removed. Despite proximity to the location of intervention, timely care is highly dependent on the pre-existing screening, diagnosis, and treatment systems.[6,11,14] Here we present the methods for our multi-center investigation to 1) evaluate the relationship between timely screening and diagnosis with treatment time and clinical outcomes, 2) characterize generalizable screening and diagnostic measures that can be used for cross-facility performance comparisons, and 3) describe the use of electronic health record (EHR) data in tandem with an existing disease registry.

Given the European Heart Association, American College of Cardiology, and American Heart Association recommendation to obtain an early electrocardiogram (ECG) within 10 minutes for patients with symptoms suggestive of STEMI,[2,3,4] nearly 85% of EDs have protocols to guide the screen of all arriving patients for the need of an early ECG.[14] We define an early ECG as one performed upon ED arrival, typically well before physician evaluation to diagnose STEMI, in a timely fashion.[14-16] Our prior work identified 12.8% (95% CI [3.4-32.6%]) of patients with STEMI do not receive a timely ECG. The resulting diagnostic delay led to 14-80 minutes of additional myocardial ischemia time.[14] Earlier treatment has been historically associated with better outcomes.[2,3] The degree to which timely *screening* and *diagnosis* are associated with improved time-to-intervention and post-PCI outcomes, under more contemporary practice conditions, is not known. In addition, STEMI care pathway performance has not been explored in the ED population through a large multi-centered patient cohort.

METHODS

Study Design. This is a multi-center retrospective cohort study designed to quantify the potential impact of improving ED screening and diagnostic care performance on timely STEMI treatment and post-PCI outcomes. The results are intended to inform the design of a future EHR embedded algorithm to screen for STEMI upon ED arrival. We aim to describe our approach to quantifying the associations between 1) time-to-diagnosis, and 2) time-to-treatment (PCI) between patients who do and do not receive an early ECG within 10 minutes. We seek to understand variability in achieving timely PCI, hospital length of stay (LOS), subsequent heart failure, and mortality by patient characteristics (i.e., age, gender, race, language) and care process factors (i.e, achieving timely screening, time of day, distance between ED and cath lab) through these pre-specified sub-group analyses. We received institutional review board (IRB) approval from all participating facilities prior to study initiation. A shared IRB approval process was used for this National Institute of Health funded study.

Study Setting. Participating sites are tertiary care center EDs within a hospital designated as a PCI Center where the ED physician can activate the cath lab for emergency STEMI intervention (Code STEMI) with a single phone call.[10]

Process Measures. Exploring STEMI process measures includes quantifying time intervals associated with STEMI screening and diagnosis. *Door-to-Screening* (D2S) and defined as the time from ED arrival to the completion of the first ECG (Table 1). The time of ECG completion was selected to mark the end of screening because it is the only retrospective clinical timestamp recorded to represent the completion of STEMI screening among those who screen positive. It is typical practice in EDs for ECGs to be taken directly to an emergency physician for interpretation.[14-17] *Door-to-Diagnosis* (D2D) is the interval from ED arrival to STEMI diagnosis (Table 1). STEMI diagnosis is defined as the time when the physician activates a cardiac lab team for emergent PCI. As a result we primarily measure the completion of diagnosis as door-to-cath-lab-activation. We found that cath lab activation time was rarely included in the medical record, maintained in an external telephone call center database, and inconsistently recorded. As a result, site PIs were permitted to export cath lab activation times from their local database for the National Cardiovascular Data Registries' (NCDR) Acute Coronary Treatment and Intervention Outcomes Network (ACTION) Get with the Guidelines Registry supported by the American College of Cardiology (NCDR-ACTION®, Table 2). We also included the time-to-diagnostic ECG as a secondary measure for diagnostic time.

These definitions are a necessary change from the traditional use of door-to-ECG as the starting point for STEMI performance measures and reflect how screening and diagnosis require separate metrics for appropriate diagnostic performance evaluation. Delayed STEMI screening and diagnosis are barriers to effective treatment access. By limiting our population to patients screened by the ED, we limit the variation in point-of-first-medical contact to those brought in by emergency medical services (EMS) or self-transport.

Patient and Public Involvement. The study research question and outcome measures were developed from a desire to evaluate how well ED STEMI screening and diagnosis are performed for individual patients. We seek to better understand the demographics and presentations of patients who may experience differential outcomes potentially associated with sub-optimal STEMI screening. Patients, however, were not directly involved in the design or conduct of this study.

Inclusion/Exclusion Criteria. We will include all 2014 to 2016 ED patients with a final hospital diagnosis of STEMI. To reduce misclassification bias, STEMI will be defined by International Classification of Disease (ICD) 9 codes previously validated in the literature and the corresponding ICD-10 diagnosis codes (Table 3).[1] Data abstractors, familiar with the EHR of their institution, will review electronic patient charts for study data and to determine if the course of care is consistent with acute STEMI. Care is considered inconsistent with acute STEMI if at least two of the following apply: STEMI is not mentioned in the context of a diagnosis, the discharge summary does not include STEMI as a final diagnosis, there is no cath lab intervention, cath lab findings are not consistent with STEMI anatomy or intervention, and an alternative diagnosis is present for which care is most consistent (including non-STEMI, unstable angina, and coronary vasospasm amongst others). It is recognized that some of these patients' anatomy and physiology may generate ECG findings consistent with an appropriate diagnosis of STEMI from the ED. We opted to exclude these patients because the ultimate goal of STEMI screening from the ED is to identify patients who have STEMI and will benefit from emergent removal of an acute thrombus within a coronary artery. This would be the objective of a precision-oriented approach to screening ED patients upon arrival for possible STEMI. We retained patients who received care in the ED but had a diagnostic ECG acquired prior to hospital arrival. Their door-to-diagnostic-ECG time would be negative and reflect an opportunity for an alternative care pathway, such as pre-hospital arrival cath lab activation. Cases inconsistent with acute STEMI are referred to the site-principal investigator (PI) for chart review. All excluded cases are shared with the Vanderbilt Emergency Care Health Services Research Data Coordinating Center (HSR-DCC) central study PI (M.Y.Y.) for approval. Patients for exclusion are flagged for exclusion by the HSR-DCC but not removed.

Primary Outcomes. The primary outcome (Table 1) is time-to-treatment, i.e. time from ED arrival to STEMI treatment. An early ECG is defined per existing clinical practice guidelines[2,3,14] as the time between ED arrival (the patient's first recorded presence in the ED) to the completion of the first ECG in the ED intended to permit the early diagnosis of STEMI. ED arrival, or "door" time, is defined as the patient's first recorded presence in the ED.[11,14,18] Our definition for time-to-treatment includes two outcome measures. The first measure is door-to-cath lab arrival (D2CAR) a diagnostic team oriented measure (Table 1). Patient cath lab arrival marks the last point in the STEMI care pathway the diagnostic team can influence. The second measure is door-to-balloon (D2B) time, the more traditionally used PCI treatment time measure (Figure 1). During the study design phase we found that D2B time was not consistently documented in the EHR at any of our seven hospitals. Thus, we modified definitions for this timestamp after considering the use of alternative data as established by the NCDR-ACTION® registry. The registry includes proxies for this outcome in a hierarchy such that D2B time can be measured primarily as balloon inflation time, yet the time the guidewire crosses the coronary lesion can be used when this time is missing.[10,19]

Secondary Outcomes. Secondary outcomes include ED LOS, hospital LOS, change in cardiac ejection fraction (EF) after the acute STEMI, and one year mortality. ED LOS is defined as the time from ED arrival to ED departure.[18] Change in EF is calculated as the difference between the last EF measured prior to the patient's STEMI and the first documented after hospital discharge. Hospital LOS is the time from hospital admission to hospital discharge. Mortality at one year was assessed by assigning one of three categories to a patient's survival status one year after the STEMI ED visit: deceased (with date, time, and cause noted), alive (based on evidence of contact with the health system via EHR documentation), and lost to follow up.

Risk Factors. The independent variable of primary interest is time-to-screening defined as door-to-first-ECG ($D2E_{1st}$) (Table 1). This is the screening (D2S) time interval measured as both

a continuous variable and dichotomized (D2S ≤ 10 minutes vs D2S >10 minutes) per existing clinical practice guidelines.[2,3] Additional risk factors of interest include information often known about a patient upon ED arrival which will be examined in exploratory analyses as adjusting variables. These include age, gender, race, primary language, arrival time (time of day), arrival mode (EMS, self-transport, or other), and chief complaint.

Secondary Subgroup Analysis. We also included patient characteristics known to increase the risk for STEMI and to be associated with outcome differences.[3,14] These include symptom onset,[19,20-21] as well as a history of diabetes (pre-diabetes was not included), hypertension, dyslipidemia, tobacco use, heart failure, prior myocardial infarction, prior coronary artery bypass graft, and prior PCI procedure. In defining variables we balanced maximizing co-variate granularity with medical informatics best practice for data integration and data standardization. For example, tobacco use status is recorded by NCDR as a dichotomous variable. In order to obtain more detail, we collected these data primarily from the EHR. During the study design phase we evaluated the smoking history data available in each EHR and found the degree of tobacco exposure was variably categorized across our seven sites. We developed the following categories to maximize variability while standardizing data reporting: current smoker, prior smoker but quit, and non-smoker. Tobacco exposure fields in the shared database were limited to only accept one of these 3 smoking status designations for each patient.[22-23]

Recognizing the impact of EHR user access and data use context,[21] we only include information available to the diagnostic care providers at the time of the initial encounter. These providers are typically the ED team but can include an interventional cardiology consultant for rare presentations or complex patients. The NCDR-ACTION® registry permits the inclusion of all data available upon review of the full medical record. The structure of the ED interface with EHRs varies between hospitals with some having more or less data available upon patient arrival. As a result, we opted for data collection directly from the EHR using what is accessible during the early phases of the diagnostic clinical encounter.

Sample Size. We estimate our analysis will require 1220 patients from our 7 study sites. This was based our plan for a non-parametric Wilcoxon rank sum test comparing door-to-balloon (D2B) time between dichotomized door-to-first-ECG (D2E) groups (early ECG: D2E ≤ 10 minutes vs missed screening: D2E >10 minutes) of STEMI patients. An aggregation of ICD 9/10 code counts within each hospital from a prior studies suggests approximately 444 ED STEMI patients are seen in these 7 EDs annually with 87.2% captured with a timely early ECG and 12.8% in the missed screening cases.[14,24] This is the effective sample size required to detect a standardized difference of 0.35, with a type I error rate of 0.05 and power of 80% in two-tailed tests. This is a small to medium effect size by Cohen's nomenclature.[25] This translates to 596 patients and a detectable door-to-balloon (D2B) time difference of 5.2 minutes.[26] Due to potential correlation in D2B between patients seen at the same ED, we calculated a cluster design effect of 1.84 assuming an inter-cluster correlation coefficient of 0.01. This required us to include a minimum of 1220 patients. With an anticipated ICD coding misclassification exclusion rate of 5-10%, this patient sample size is achievable with 3 years of data.

Data Collection. Cohort data for patients meeting study year, ED care, and ICD diagnosis code inclusion criteria are extracted from each hospital's EHR using a pre-programmed report to identify the study cohort. These data are sent securely to the data coordinating center (HSR-DCC) using the HIPPA and research data security "Sendit" function of Research Electronic Data Capitulation (REDCap). REDCap is a secure, web-based application designed exclusively to support data capture for research studies.[27-29] The cohort data for each site is uploaded into a

sub-section of the larger study database built and maintained by the HSR-DCC. The coordinating study PI and HSR-DCC staff have access to all study data, but individual sites only see their patient records. The use of a centrally designed database with built-in variable definitions and quality control checks ensured data harmonization across sites.[27,30]

At a minimum, cohort data include a patient identifier (typically the medical record number), ED date of service, and final hospital ICD diagnosis codes. Each patient record is reviewed by a data abstractor associated with each institution's ED. A REDCap-based data collection form is completed with existing EHR data that, as noted above, would have been available to diagnostic providers in the ED during the clinical encounter. Prior to data collection, each site PI completed a training case form (TCF, Table 4) in which data were collected for the first patient of record for study inclusion. The location of each variable within the EHR, including the location within specific documents, was recorded and used as a guide for the local data abstractors. The resultant data dictionary was used to verify data definitions were standardized across sites. In total, we had 11 data abstractors from the seven EDs. All data abstractors received a minimum of two hours of training to further ensure standardized data collection. Training was via a two-part module developed and delivered by the HSR-DCC. Part 1 involved a 90 minute session via video conference introducing the study design, the data abstractors' role in the project, study data definition, and practice using all fields of the study database for the TCF patient. Part 2 involved repeating the data entry process for the TCF patient with direct use of the associated EHR record (Table 5).

We verified that all participating ED sites submit STEMI patient data to the NCDR-ACTION® Registry. Despite the presence of this existing data registry, we undertook primary data collection for additional information on ED-level STEMI care variables. Site PIs, however, were permitted to send select variables with identical data definitions to HSR-DCC data from their local NCDR-ACTION® Registry database (Table 2). These data were uploaded directly into the database by the HSR-DCC to reduced data entry time, and verified by data abstractors upon chart review.

The data collection form within the study database has alerts for values outside of the expected range and instructions for uniform units of measure. The HSR-DCC staff review all completed entries for accuracy with the use of data cleaning checks run via R statistical code (www.r-project.org, available at http://biostat.mc.vanderbilt.edu/wiki/Main/JenkinsEMCode) on data contained in the study database after the completion of 2014 data, 2015 data, and study close. The data cleaning code identifies missing values, patterns of missing-ness, and inconsistent data entries (e.g., an ED arrival date that occurs before date of birth is likely a data entry error in the year for the ED visit or birth). Results of the first data cleaning checks are communicated to the site PI and data abstractors at the end of 2014 data collection, discussed via telephone conference call, with a response verified by the HSR-DCC staff. Subsequent data checks are run upon request and at a minimum of every 30 days. Results for follow up data checks are run for each site, then communicated to each collaborating team via email. The full report is then saved on a shared secure drive (vanderbilt.box.com) managed by the HSR-DCC with specific sub-folders for each site. Access permissions are set such that data for each site are only seen by the site PI and local data abstractors. Site PIs are asked to clarify ambiguous entries. The HSR-DCC study coordinator follows up on all requests for data clarification.

Data Analysis. Descriptive statistics for screening, diagnosis and treatment time-intervals including D2S (time-to-screening), D2D (time-to-diagnostic test completion), D2CLA (time-to-diagnosis communication), D2CAR (time-to-ED-to-cardiology care transition), D2B (time-to-intervention) and patient characteristics, will be calculated using mean, standard deviations, and

quartiles for continuous variables and proportions for categorical variables. They will be compared between the two primary exposure STEMI patient groups: early ECG and missed screening cases using non-parametric Wilcoxon rank sum test for continuous variables and Chi-square test for categorical variables.

For the primary adjusted analysis, we will first use a linear mixed effects regression model with D2B, as the outcome. The primary independent variable of interest is D2S status ($D2E_{1st}$ ≤10 minutes vs. $D2E_{1st}$ >10min) with a random effect for the ED providing care. We will adjust for ED screening methods (e.g., point of first patient contact in the ED, dedicated space for early ECGs, etc.), care process factors (e.g., time of day, distance between ED and cath lab, etc.), and individual patient characteristics. Since D2S is a portion of D2B, we will use the first-ECG-to-balloon time interval[26] calculated by subtracting D2S from D2B as the primary outcome in this model. Results from those adjusted analyses will help quantify differences in timely care between early ECG and missed screening case STEMI patients and reduction in time-to-treatment (D2B) for every minute saving in time-to-screening (D2E). These analyses will be repeated with D2CAR as the outcome, then D2D as the independent variable of interest.[31]

We will then perform a time-to-event analysis using the Cox proportional hazard model stratified by ED for each secondary outcome event (Hospital LOS, and one year mortality), and a linear mixed effects regression model with ED random effect for continuous outcomes (change in cardiac EF after acute STEMI) with the same adjustments and independent variables as the primary analysis.

Lastly, we will use our adjusted data to construct a summary of the care course (the sequence of median STEMI process intervals) by age, gender, race, language, presenting symptom and ED subgroups to identify differences in the following time intervals: symptom onset-to-arrival, arrival-to-first ECG, first ECG-to-diagnostic-ECG, diagnostic-ECG-to-cath lab activation, activation-to-PCI balloon, PCI-to-hospital discharge (see Figure 1).

DISCUSSION

Despite the limitations of retrospective EHR data, we selected this approach over a prospective study for several reasons. First, the time and financial cost of the prospective approach would make the study impracticable. Prospective enrollment would require four years to complete data collection and continued screening of ED patients. The cost would outweigh the enrollment yield given the relative infrequency of STEMI events within the larger ED patient population. These logistics would significantly slow our ability to generate knowledge to inform an important study question for a deadly disease. Second, our targeted screening intervention will use EHR data available to the ED care team upon arrival, therefore the use of existing EHR data will be subject to similar data conditions during intervention implementation.

Substantial resources are allocated to assure screening and diagnosis within 10 minutes of patient arrival to achieve timely STEMI treatment. Yet no existing measures or databases have adequate granularity to measure screening and diagnostic practice or to guide performance optimization. Much of the resource investment reflects the major consequences and medicolegal gravity of a missed STEMI in the context of time limited interventions, high mortality, and significant morbidity. If interventions are to be developed to more precisely identify STEMI patients upon ED arrival, data on ED STEMI patients are critical. These interventions need to be balanced with appropriate use of resources for this infrequent but potentially deadly condition.

Current practices are often supported by data extrapolated from the more broad population of hospital STEMI patients who may be different from the ED sub-population. This study will increase our understanding of whether those missed by ED STEMI screening receive less timely interventional care (PCI) than those with timely STEMI screening and diagnosis. It will better characterize the care process, demographic profile and clinical outcomes for this subpopulation of STEMI patients. The primary results of this study will be a comparison of differences in the timeliness of treatment between those who experienced timely vs. delayed screening and diagnosis. Our subgroup analysis may identify risk factors for poor outcomes providing data to focus clinical interventions to deliver precise diagnostic care normalized for subgroup specific risk factors.

The American Heart Association recently called for growth in the use of linked registry and EHR data to understand the penetration of cardiovascular care guidelines and evidence within clinical practice.[32] Our methods present an applied approach to the use of EHR data for emergency care sensitive cardiovascular disease diagnoses. NCDR-ACTION® Registry is a robust risk-adjusted, outcomes-based, quality improvement program that focuses exclusively on high-risk STEMI and non-NSTEMI patients. The registry database has revolutionized our ability to study outcomes for these high risk conditions despite their relatively low prevalence at any given center. However, the NCDR-ACTION® Registry is focused on treatment performance, and it lacks variables (Table 5) to support evidence-based screening and diagnostic performance evaluation to improve clinical practice. In contemporary practice the existence of EHRs is more the norm than the exception.[33] EHRs provide a vehicle for not only source data but the potential application of dynamic clinical decision support to enhance risk stratification and mechanisms for evidence-based care delivery. In this study we used standardized multi-center primary data collection from seven hospital EHRs to enable our ability to study these early STEMI care performance targets.

The completion of this study will provide a more accurate appraisal and critical feedback on the quality of contemporary STEMI care pathway performance that can be used to improve

emergency care delivery for ED STEMI patients, and inform the development of screening and diagnostic support tools that can be translated to other care environments. Specifically, we will better understand the consequences of and risk factors for delayed screening and diagnosis. We anticipate our results will be extrapolated to other care delivery spaces that receive undifferentiated patients (non-PCI center EDs and urgent care). What is learned about differential risk may be applied in primary care clinics, intake processes for direct to floor admissions, and inter-service floor transfers. Tools developed to improve screening may be used for other emergency care sensitive conditions.

ETHICS DISSEMINATION

Manuscript publication is our most broad plan for results dissemination. Given the critical nature of STEMI, we plan to simultaneously share our study results with the participating institutions STEMI care quality improvement committees, Divisions of Cardiology as well as Emergency Department leadership. The study data will be available to other researchers on a case-by-case basis via the Vanderbilt University Emergency Care Health Services Research Data Coordinating Center (HSR-DCC). Statistical code will be made available on the HSR-DCC website.

AUTHOR CONTRIBUTIONS

Dr. Maya Yiadom designed and coordinates the logistics of the study and served as lead investigator via the data coordinating center. Drs. Bryn Mumma, Chris Baugh, Brian Patterson, Angela Mills, Gilberto Salazar and Mary Tanski are Site-Principal Investigators and coordinate study implementation within their institutions. Cathy Jenkins is the lead staff biostatistician, Karen F. Miller is the data coordinating center's Data Integrity Officer. Brittney Jackson is the Study Program Manager. Drs. Jennifer West and Stephen Dorner were site data abstractors who contributed to study methods development. Drs. Chris U. Lehmann, Thomas J. Wang, Sean P Collins, Alan B. Storrow and Robert S. Dittus provided content specific expertise advising study design and implementation. Drs. Tim Vogus and Bernard provided content specific data analysis guidance. Dandan Liu was the overseeing statistician who co-designed the study with Dr. Yiadom and will oversee final data analysis with Dr. Yiadom.

ACKNOWLEDGEMENTS

Special thanks to the data abstractors at the 7 study sites including: Caitlin Azzo, Oluyemi O. Olubowale, Alex Trinh, Shannon McNabb, Samita Kumar, Sean Harla, Dr. Margo Kaller, Dr. Jane Dyball, Dr. Daniel Steward, and Dr. Christopher Beck. We are appreciative of Christina Kampe (Vanderbilt Emergency Care Health Services Research Data Coordinating Center's IRB Regulatory and Compliance Specialist) for managing the multi-site IRB approval process that was critical to initiate this study.

FUNDING STATEMENT

Research reported in this publication was supported by the National Heart Lung and Blood Institute's (NHLBI) award numbers 5K12HL109019, 1K23HL133477, 5K08HL130546. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

COMPETING INTERESTS

Dr. Yiadom is Director of the Emergency Department Operations Study Group (EDOSG). Dr. Baugh is a member of the Advisory Board, consultant for Roche Diagnostics and Janssen Pharmaceuticals, and has received research funding from Boehringer Ingelheim. Dr. Storrow has also received grant support from Abbott Diagnostics and Roche Diagnostics. He is a consultant for Roche Diagnostics, Novartis Pharmaceuticals Corp, Alere Diagnostics, Trevena, Beckman Coulter and Siemens. Dr. Collins received grant research support from NIH/NHLBI, PCORI, Cardiorentis, Novartis, and Cardioxyl and consultant support/other from Novartis, Trevena, Cardiorentis, Cardioxyl, and Siemens. All other authors have no disclosures.

TABLES

Table 1 – Definition of Time Stamps and Intervals in STEMI Screening and Diagnosis

Time Stamp	Care Interval	Definition
Symptom Onset Time	Time of symptoms prior to arrival	Recalled patient reported time for when symptoms associated with the acute STEMI encounter began.
Time Zero		
Door Time	ED arrival time[19] (Primary analysis)	First recorded presence of the patient in the ED
Screening		
First (early) ECG Time	Door-to-Screening, **D2S** Door-to-first ECG time, **$D2E_{1st}$** (Primary Independent variable of interest)	ED arrival to completion of the first ECG. The first ECG is generally performed prior to the ED physician evaluation for the purpose of enabling the early identification of STEMI
Diagnostic		
Diagnostic ECG Time	Door-to-Diagnostic ECG, **$D2E_{Dx}$** (Secondary Independent Variable of Interest)	ED arrival to completion of ECG used to activate the cath lab
Cath Lab Activation Time	Door-to-Cath Lab Activation, **D2CLA**	ED arrival to the time when the cath lab was activated (Code STEMI)
Treatment		
Patient Arrives in Cath Lab	Door-to-Cath Lab Arrival Time, **D2CAR** Diagnostic team centric (Primary Outcome)	ED arrival to patient arrival in the cath lab
Balloon Time	Door-to-Balloon Time, **D2B** Intervention team centric outcome (Primary Outcome)	Time from ED arrival to time the catheterization guidewire crossed the culprit coronary lesion in patients receiving balloon angioplasty

Time Zero = Start time for the indication for ST-segment myocardial infarction (STEM) emergency care. ED = Emergency Department Cath Lab = Cardiac Catheterization Lab. Outcomes = Treatment times for STEMI patient directed to percutaneous coronary intervention.

Table 2 – Study Data Permitted for Import from Local NCDR-ACTION® Registry Databases

Study Variable	NCDR-ACTION® Variable Number
Birth date	2050
Sex	2060
Race	2070 (White) 2071 (Black) 2073 (American Indian/Alaskan Native) 2072 (Asian) 2074 (Native Hawaiian /Pacific Islander)
Ethnicity	2076 (Hispanic vs non-Hispanic)
Health Insurance	3300 (Private) 3301 (Medicare) 3302 (Medicaid) 3303+3304+3305+3306 (Other) 3307 (Uninsured/Self Pay)
Cath Lab Activation Time	3159
PCI (yes/no)	7100
ED Discharge Time	3222
Cath Lab Arrival Date	7101
Cath Lab Arrival Time	7102

*We did not permit the inclusion of any data that would be used for calculated time intervals, the primary outcome or risk factors/exposures.

Table 3 - STEMI International Classification of Disease Codes (ICD) for Inclusion by Final Hospital Diagnosis

Acute Myocardial Infarction (AMI) Diagnosis Codes Associated with STEMI					
ICD 9	Diagnosis	**LOCATION**	IC10	Diagnosis	**LOCATION**
410	AMI		I21	STEMI and NSTEMI	
410.21	AMI infero-lateral wall	Inferior	I21.11	STEMI RCA	Inferior
410.31	AMI infero-posterior wall		I21.19	STEMI other coronary artery inferior	Inferior
410.41	AMI of other inferior wall		I21.21	STEMI LCX	Inferior
410.01	AMI antero-lateral wall	Anterior	I21.01	STEMI Left Main	Anterior
410.11	AMI other anterior wall		I21.02	STEMI LAD	Anterior
			I21.09	STEMI other coronary artery anterior	Anterior
410.51	AMI other lateral wall	Lateral	I21.29	STEMI another sites	Other specified
410.61	AMI true posterior wall infarction	Posterior			
410.81	AMI other specified site*	Other specified			
410.91	AMI unspecified site	Non-specified	I21.3	STEMI Unspecified	Non-specified

AMI = acute myocardial infarction, STEMI = ST-segment elevation myocardial infarction, NSTEMI = non-ST –segment elevation myocardial infarction, RCA = right coronary artery, LCX = left circumflex artery, LAD = left anterior descending artery, *410.81 includes papillary muscle rupture.

Table 4 – Data Abstractor Training Module

- PART 1 – 90 minute Video Conference
  Content
  1. Clinical Problem: What is known and unknown about STEMI and STEMI patient outcomes
  2. Study Questions
  3. Study Design
  4. Clinical Care Pathway for STEMI Care:
     Case Study: Beverly Hospital, Beverly, Massachusetts
     - https://www.youtube.com/watch?v=FkeH036oigo
       (View to 3 minutes and 50 seconds)
  5. Role of the Electrocardiogram (ECG)
  6. PCI Procedure:
  7. Clinical timestamps and care documentation in the electronic health record
     The Procedure: PCI care and Timestamps:
     - https://www.youtube.com/watch?v=I45kJJoCa6s:
       (View full video)
     - https://www.youtube.com/watch?v=-BuazAhs7uA:
       (View to 1 minute and 10 seconds)
  8. Outcome measure data definitions (similarities and differences with NCDR-GWTG ACTION Registry®
  9. Study procedures and timeline
  10. Introduction to study database
  11. Data entry with Training Case Form (TCF) example

- PART 2 – Independent data abstraction for TCF patient directly form the local Electronic Health Record (30 minutes)

- A Data Abstractor is approved to start data entry after Emergency Care Health Services Research Data Coordinating Center (HSR-DCC) staff review and confirm accurate and complete TCF data entry within the database for the TCF patient. Once confirmed, the Site-PI co-signs a delegation of authority (DOA) form certifying the Data Abstractor is trained and will collect data under their guidance.

Table 5 – Study Variables Not Available in the NCDR-ACTION® Registry

Variable Name	Comment
PATIENT DEMOGRAPHICS	
Primary Language	
EMERGENCY DEPARTMENT - ED	
Triage start time	
Triage end time	
Emergency Severity Index (ESI) score	Measure of anticipated care acuity assigned upon ED Triage (lower = higher acuity)
Onset of symptoms prior to arrival in your ED	Measured as hours prior to presentation, no assumptions made for patient reports of this morning, last night, yesterday, etc
Chief Complaint Reported Upon Arrival	Chest Pain (yes/no)
Chief Complaint Reported Upon Arrival	Chief Complaint 1-5
Final ED Diagnosis	Diagnostic Care Team's Diagnosis 1-5
ED discharge date	
HOSPITALIZATION	
Hospital Discharge Diagnosis ICD codes 1-5	Action includes the first 3 rather than 5
PCI Center Early ECG	
Was there a First PCI Center ED ECG? - First PCI Center ED ECG date - First PCI Center ED ECG time - First PCI Center ED ECG Clinical Interpretation - First PCI Center ED ECG Official ECG Interpretation	Yes/No
Receiving Hospital Follow Up ECG	
Was there a follow up ECG at the Receiving hospital? - Receiving Hospital Follow Up ECG date - Receiving Hospital Follow Up ECG time - Official ECG Interpretation - Clinical Interpretation of Receiving ED EKG	Yes/No
Prior ECG	
Was there a prior ECG from an outside facility or agency? If yes, - ECG from EMS Transferring to Receiving Hospital - ECG from Outside Hospital - ECG by EMS transporting to Outside Hospital - Referring Clinic Provider ECG	Yes/No If yes, date and time, clinical interpretation, official interpretation
Diagnostic ECG (select one)	
- PCI Center Early ECG - EMS Transferring from the Field to the PCI Center ED - Outside Hospital ED - EMS Transporting from OSH ED - Referring Clinic Provider	ECG with which the decision was made to activate the cath lab emergently
Change in Ejection Fraction (Pre, During Index Visit, Post Index Visit)	
Last EF Prior to Index Visit	EF measured before this current index visit? (Yes/No) If yes, - Prior EF Date - Prior EF % (lowest documented) - Prior EF Range
EF during Index Visit	EF measured during index visit? (Yes/No) If yes, - Index Visit EF Date - Index Visit EF % (lowest document) - Index Visit EF Range
EF after Index Visit	First post index visit discharge EF (Yes/No) - Post-Index-Visit EF Date - Post-Index-Visit EF % (lowest documented) - Post-Index-Visit EF Range

FIGURE LEGEND

Figure 1 – STEMI Patient Care Process Measures: Screening, Diagnosis and Treatment

D2E1st = Door-to-first ECG = Door-to-early ECG = Door-to-Screening (D2S). D2Ed = Door-to-Diagnostic ECG = one of 2 ways to measure Door-to-Diagnosis (D2D). More ideally, Door-to-Diagnosis (D2D) can be measured as Door-to-Cathlab-Activation (D2CLA). Note: Pre-hospital ECGs interpreted by the paramedic team as a STEMI would be represented as "negative" Door-to-Diagnostic ECG time. These patients would ideally bypass the ED care pathway in the absence of an overriding need for non-PCI (or pre-PCI) care (i.e., motor vehicle collision injuries requiring stabilization, witnessed cardiac arrest after pre-hospital ECG acquisition, etc). Thus negative D2S would indicate potential opportunity for an alternative care pathway.

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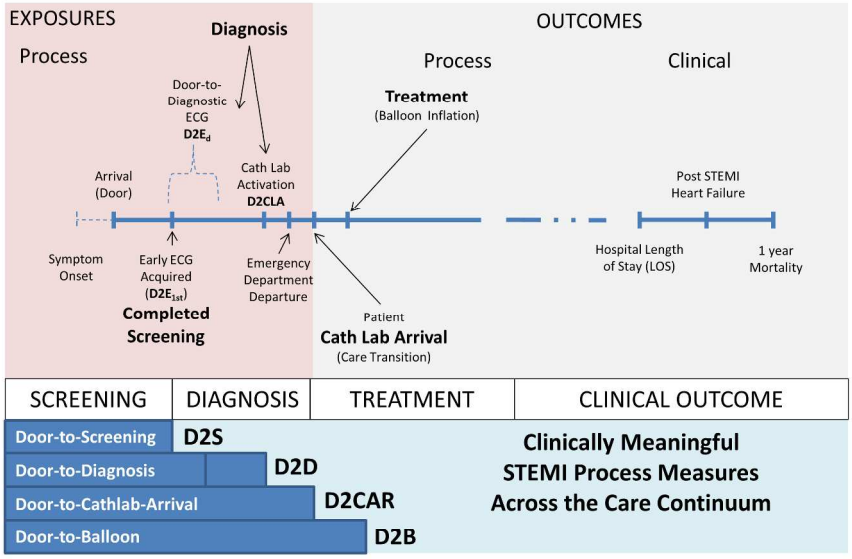

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254x190mm (300 x 300 DPI)

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	n/a
	2b	All items from the World Health Organization Trial Registration Data Set	n/a
Protocol version	3	Date and version identifier	3
Funding	4	Sources and types of financial, material, and other support	5,6
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
	5b	Name and contact information for the trial sponsor	5
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	5
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	9-11
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	7

	6b	Explanation for choice of comparators	7 (mid pg), 8 (mid pg)
Objectives	7	Specific objectives or hypotheses	_8 (aims/seek__
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	_____8_____
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	_____8_____
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	__8 (sites- top, patients – bottom)
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	____n/a_____
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	____ n/a_____
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	_____n/a_____
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	_____n/a_____
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	_____9_____
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	__Figure 1____
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	____10_____

Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	n/a
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	n/a
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	n/a
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	n/a
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	n/a
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	10-11
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	n/a
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	10-11

Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	11
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	9-10
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	n/a
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	pgs 9-11 (data coordinating center, HSR-DCC)
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	n/a
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	n/a
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	11 (mid)
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	8 (top)
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	n/a
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	n/a

	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	10
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	6
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	5,15
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n/a
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	5,15
	31b	Authorship eligibility guidelines and any intended use of professional writers	16 (we use ICMJE criteria)
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	15
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	n/a
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1 – title, 3- abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	7
Objectives	3	State specific objectives, including any pre-specified hypotheses	7,8
Methods			
Study design	4	Present key elements of study design early in the paper	8
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	8
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	8
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	8 (sites- top, pts- bottom)
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	10-11
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	10
Bias	9	Describe any efforts to address potential sources of bias	8
Study size	10	Explain how the study size was arrived at	10
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8-11
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	11
		(*b*) Describe any methods used to examine subgroups and interactions	9-10
		(*c*) Explain how missing data were addressed	9,11
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	9

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	n/a
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	n/a
		(b) Give reasons for non-participation at each stage	n/a
		(c) Consider use of a flow diagram	n/a
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	n/a
		(b) Indicate number of participants with missing data for each variable of interest	n/a
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	n/a
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	n/a
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	n/a
		Cross-sectional study—Report numbers of outcome events or summary measures	n/a
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	n/a
		(*b*) Report category boundaries when continuous variables were categorized	n/a
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n/a
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	n/a
Discussion			
Key results	18	Summarise key results with reference to study objectives	n/a
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	n/a
Generalisability	21	Discuss the generalisability (external validity) of the study results	n/a
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	5,6

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.
Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.