RACE-IT - Rapid Acute Coronary Syndrome Exclusion using the Beckman Coulter Access high-sensitivity cardiac troponin I: A stepped-wedge cluster randomized trial

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ABSTRACT

Background: Protocols utilizing high-sensitivity cardiac troponin (hs-cTn) assays for the evaluation of suspected acute coronary syndrome (ACS) in the emergency department (ED) have been gaining popularity across the US and the world. These protocols more rapidly rule-out ACS and more accurately identify the presence of acute myocardial injury. At this time, few randomized trials have evaluated the safety and operational impact of these assays, resulting in limited evidence to guide the use and implementation of hs-cTn in the ED.

Objective: The main study objective is to test the effectiveness of a rapid ACS rule-out pathway using hs-cTnI in safely discharging patients from the ED for whom clinical suspicion for ACS exists.

Design: This prospective, implementation trial (n = 11,070) will utilize a stepped wedge cluster randomized trial design. The design will allow for all participating sites to capture benefit from the implementation of the hs-cTnI pathway while providing data evaluating the effectiveness in providing safe and rapid evaluation of patients with clinical suspicion for ACS.

Summary: Demonstrating that clinical pathways using hs-cTnI can be effectively implemented to rapidly rule-out ACS while conserving costly hospital resources has significant implications for the care of patients with possible acute cardiac conditions in EDs across the US.

Clinicaltrials.gov identifier: NCT04488913.

1. Introduction

Cardiovascular disease is the leading cause of mortality in the United States [1]. Amongst patients with acute coronary syndrome (ACS), cardiac biomarkers are critical in detecting acute myocardial infarction (AMI). Newly approved for use in the US high sensitivity cardiac troponin (hs-cTn) biomarkers are increasingly being used in emergency departments (ED) to rapidly rule out ACS with the promise of expediting patient disposition while reducing hospital resource utilization [2-9].

In an effort to more efficiently diagnose and triage patients with possible ACS, Henry Ford Health System (HFHS) is implementing the Beckman Coulter Access hs-cTn assay across 9 EDs. Paired with the introduction of the new hs-cTn assay, we have developed a new clinical decision-making pathway, titled “Rapid Acute Coronary Syndrome Exclusion using the Beckman Coulter Access high-sensitivity I Troponin” (RACE-IT), to quickly identify patients with AMI and rule-out low risk patients utilizing hs-cTnI values in combination with a HEAR score [10, 11].

Prior studies have established the safety of such an approach, including the RAPID-TnT study which utilized a 0/1-h hs-cTnT protocol and had a negative predictive value of 99.6% for 30-day death or AMI [12]. Additionally, this study showed the hs-cTnT approach was non-inferior to standard care, associated with a shorter ED length of stay, and patients were more likely to be discharged from the ED [12].
They were also less likely to undergo functional cardiac testing.

However, while there is significant promise for hs-cTn protocols to reduce healthcare utilization while preserving patient safety, international trials in healthcare settings other than the US have suggested that adherence can be difficult to achieve with unguided implementation of such protocols [5,12-15]. To ensure both effective implementation and to study the operational impact, HFHS will utilize a modified stepped wedge cluster design to evaluate the new RACE-IT pathway.

This implementation trial will directly evaluate the primary outcome of safe discharge from the ED and multiple secondary endpoints such as overall patient safety and cost-effectiveness [14]. Additionally, assessment of outcomes in patients with minimally elevated hs-cTnI values who require further testing will provide rich data for phenotypic analysis, allowing us to evaluate specific patient phenotypes based on their hs-cTnI values. Publication of these results will provide important data to other health systems considering similar implementation and will help guide clinical decision making.

2. Methods and analysis

2.1. Main objectives and hypotheses

The primary objective of this study is to compare safe ED discharge to home rates among patients receiving standard of care (SOC) evaluation for ACS and the new RACE-IT pathway. We hypothesize that patients evaluated under the new pathway who have ED hs-cTnI values \( \leq 18 \) ng/L will have higher rates of safe discharge home. A safe discharge constitutes a discharge to home in which a patient has no all-cause death or AMI within 30 days of their ED presentation.

Our main secondary objectives are to assess AMI and death rates for one year after each patient’s initial encounter, to create a registry of patients with quantifiable hs-cTnI values \( \leq 18 \) ng/L who are placed in observation, and to assess the cost-effectiveness of the RACE-IT pathway. This registry will allow for exploratory analysis of phenotypes that may confer low risk for death and MI at 30-days. We hypothesize that the implementation of the RACE-IT pathway will result in reduced hospital resource utilization and associated operational costs.

2.2. Study design

This is a pragmatic, implementation study testing the implications of a rapid evaluation pathway for suspected ACS using a hs-cTnI assay. A modified stepped wedge cluster design will take a phased approach to implementation across all nine HFHS EDs. This approach will result in all sites being exposed to both the control and novel protocol (SOC vs RACE-IT pathway). This design was chosen for this study because the proposed RACE-IT pathway has presumed benefit and does not withhold that benefit from any participating sites. We have designed the trial in concordance with the most recent CONSORT recommendations for modified stepped wedge cluster randomized trials [16]. Each of the sites will have three phases as detailed in Fig. 1, which include current SOC with data collection, an implementation phase where the RACE-IT pathway is started but no data are collected, and the RACE-IT pathway where it is active and data are being gathered. The planned implementation will take place over seven months with each phase lasting three weeks and each site randomly being allocated to enter the treatment condition at different time periods. We will trace rates of adherence to the RACE-IT pathway for each cluster over the course of the trial. Table 1 details inclusion and exclusion criteria for study participants. The planned sample size is 11,070 patients. Data analysis is expected to be completed within one year.

2.3. Setting

HFHS has nine associated EDs which will serve as sites for this study. These include Henry Ford Main, a quaternary care, level-1 trauma center in the heart of Detroit that cares for a primarily urban population, in addition to four suburban community hospital EDs (Allegiance, West Bloomfield, Macomb, and Wyandotte) and four free-standing EDs in metro-Detroit (Fairlane, Sterling Heights, Brownstown, and Cottage).

2.4. Intervention arm: RACE-IT pathway

The primary intervention, the implementation of the RACE-IT pathway, will be rolled out in phases according to the modified stepped wedge cluster randomized trial design. This pathway is substantively different from the current SOC pathway used at all participating EDs. Appendix A details the RACE-IT pathway. All patients with a first hs-cTnI value \( < 4 \) ng/L will be deemed very low risk and, if appropriate, eligible for immediate discharge. Patients with an initial value equal to \( 4 \) ng/L will have repeat testing in 1 h and if the increase is \( < 4 \) ng/L.

Table 1

| Cluster | Study Weeks |
|---------|-------------|
| HFH     | 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 |
| FRL     |             |
| WYH     |             |
| HMH     |             |
| HSH     |             |
| WBH     |             |
| HAH     |             |
| HFB     |             |
| HFC     |             |

Fig. 1. Stepped Implementation Design Matrix. Each segment represents a 3-week period. Blue segments indicate enrollment under the standard of care protocol, and orange cells indicate enrollment under RACE-IT pathway. Green cells indicate 3-week implementation periods for clinician education and time to accommodate practice change, during which patient enrollment does not occur. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)
(delta <4 ng/L), those patients will also be eligible for discharge home. Patients with an initial hs-cTnI ≥5 ng/L and <18 ng/L will receive repeat testing at one and 3 h, and if all levels are ≤18 ng/L, the HEAR score (also called the modified HEART score or HEART pathway) [11, 17] will be used to make a disposition decision. Patients in the prior group who have a HEAR score of <4 will be eligible for discharge home while observation will be recommended to these patients who have a HEAR score of ≥4 [11]. The management of patients with hs-cTnI >99th percentile upper reference limit (18 ng/L) is no different within the RACE-IT pathway compared to SOC. A figure demonstrating the full pathway is available in the supplementary material (Appendix A).

2.5. Control arm: SOC pathway

The existing SOC protocol includes evaluation of suspected ACS with 0- and 3-h hs-cTnI evaluation and use of the 99th percentile as the upper reference limit. The lab reports actual values above the 99th percentile (18 ng/L), but reports measurements below the 99th percentile as < “18 ng/L.” Clinicians can discharge patients from the ED if hs-cTnI values do not exceed the 99th percentile with a HEAR score <4. Patients with clinical concern for possible ACS and a HEAR score ≥4 are often placed in observation care in the hospital. Patients with very high suspicion for unstable angina or AMI, may be directly admitted to a cardiology unit. Physicians always can place patients in observation if the patients have low HEAR scores but there is still a residual concern for ACS. Patients with rising hs-cTnI levels above the 99th percentile who are concerning for AMI are admitted to a cardiology floor.

2.6. Screening and enrollment

Patients that meet the inclusion criteria will be identified through the electronic health record (EHR) across all 9 HFHS EDs. After exclusion criteria are applied, a master registry will be created of eligible study patients. A log of ineligible patients for standardized reporting will be maintained, including reasons for exclusion and other demographic information. The volume of eligible ED patients over the course of the planned study period may exceed our necessary sample size. Data collection will include all eligible patients over the study period. We will perform complete data collection on the eligible population for analysis. Further description of sample size planning is described below. The sponsoring institutional review board has granted waiver of consent for the trial.

2.7. Data collection and outcome measures

REDCap (Nashville, TN), a secure data management tool, will be used for data collection and management. Data elements outlined in Table 2 will be collected through electronic health record (EPIC, Verona, WI) report functions and standardized chart review. Prior to study initiation, a data dictionary will be finalized, and team members will be trained on any required data abstraction. Data to be collected will include patient demographics, laboratory results (CBC, BNP, D-dimer, and hs-cTnI), ED and hospital length of stay, disposition, primary and secondary diagnoses, and for those patients requiring observation or admission, results of further diagnostic testing (cardiac stress testing, echocardiography, cardiac CT, cardiac MRI, cardiac catheterization). In addition to health outcomes data, we will also collect operational data to evaluate the effect of the RACE-IT pathway on throughput, resource utilization, and cost effectiveness. The data to be collected include patient-level reimbursement data from each encounter, utilization of diagnostic testing, and consultation with in-hospital cardiology services.

For outcome assessment, we will utilize Michigan’s statewide health information exchange (MiHIN) to identify patients with suspected AMI or death. This MiHIN provides a comprehensive assessment of any healthcare encounter at an ED or hospital throughout Michigan and provides data directly to HFHS secure data warehouses. If a patient has no encounters within the MiHIN over 30 days after their index ED encounter, we will consider that patient to have no event during that time period. There is the possibility of incomplete reporting or events that occur out of state, though we do not anticipate a bias in outcome assessment between patients managed with SOC and the RACE-IT pathway due to this limitation.

For patients who have an encounter identified on the MiHIN that has no cardiovascular related diagnoses, we will also consider that patient to have no AMI. For patients that have a cardiovascular related diagnosis, our team will supplement the MiHIN information with any additional information available in the electronic health record. We will make this information available in a de-identified manner for an adjudication team. The adjudication team (described below) will use this data to determine if a patient had an AMI or death (cardiac or non-cardiac). Finally, we will supplement the above processes with the Centers for Disease Control and Prevention national death index to determine if any death occurred in the study population outside available records.

While AMI and death are the primary outcome considerations, we will also track all revascularization procedures (PCI or CABG) and any rehospitalization related to cardiovascular disease over 30 days. Cardiovascular rehospitalization includes readmission for coronary revascularization, peripheral artery disease, cerebrovascular accidents, congestive cardiac failure without AMI, and atrial and ventricular arrhythmias. Lastly, we will continue to track these outcomes through diagnostic codes in MiHIN out to one year following each patient’s initial encounter.

In order to accurately determine the primary outcome (AMI or death), two independent adjudicators will review each case, and if there is disagreement a third adjudicator will review the case as well. All adjudicating physicians will be board-certified cardiologists or emergency medicine physicians. The diagnosis of AMI will be determined in accordance with the fourth Universal Definition after review of all available 30 day or one year clinical data and the serial individual hs-cTnI measurements utilized during the index or subsequent visit [18]. In the event that adjudicating physicians deem that too much data is missing to make an adequate determination for AMI, the outcome will be coded as unknown and incorporated into a sensitivity analysis.

2.8. Study funding

Beckman Coulter has funded an investigator-initiated grant to support this work.

2.9. Sample size determination

Sample size and power have both been determined based on guidelines for stepped wedge cluster randomized trials using PASS 2019
we will report the proportion of patients with hs-cTn analyses as described for the primary outcome above.

We also will perform sensitivity analyses to determine if stress tests, cardiology consultation, coronary CTA, coronary angiography, and PCI. We also will perform sensitivity analyses to determine if stress tests, cardiology consultation, coronary CTA, coronary angiography, and PCI.

The time-to-event curves will be calculated with the Kaplan-Meier survival analysis method. Multivariable analyses will adjust for the possible baseline variables listed in Table 2 where each center will be included as a random effect [19]. The primary analysis will adjust for the baseline hs-cTn values and delta values. This analysis will implement random forest techniques and could determine a clinical decision rule with superior performance using different hs-cTn cut-offs than are currently in clinical use. The primary outcome for this analysis will be 30-day rates of AMI or death.

2.10. Methods of statistical analysis

2.10.1. Primary analysis

The analysis will utilize generalized mixed models to evaluate the effect of RACE-IT to account for the clustering of patients within centers, where each center will be included as a random effect [19]. The primary analysis will adjust for the possible baseline variables listed in Table 2 which are known to affect cardiovascular outcomes. We will include a time-dependent variable to denote the change from SOC to the RACE-IT protocol phase as determined by the stepped wedge design and include time as an independent variable in all models. The effect of implementation of the RACE-IT protocol will be reported as an odds ratio with its 95% confidence interval (CI). The statistical nature of missing data will be assessed, and sensitivity analysis will be performed to analyze the impact of missing data on results in order to propose the most appropriate imputation method. Sensitivity analyses include an evaluation to assume the worst unknown primary outcome for the patient by the adjudication committee to in fact have AMI or death within 30-days. To account for the potential of significant convergence of the SOC and RACE-IT pathways for patients with an initial hs-cTn value of 6–18 ng/L, we will report the proportion of patients with hs-cTn < 5 ng/L in total and stratified by HEAR score. The primary analysis will be performed according to the intention-to-treat principle. All analyses will use SAS version 9.4 (SAS Institute Inc., Cary, NC). All tests will be two-sided with p-value < 0.05 as statistical significance.

2.10.2. Secondary analyses

We will also compare 30 day rates of AMI or death (binary outcome) among patients discharged home or placed in observation in both cohorts. We will use generalized mixed models to evaluate the extent of RACE-IT to account for the clustering of patients within centers, where center will be included as a random effect.

Using outcome assessment to one year, we will also compare survival curves between patients in the SOC or RACE-IT cohorts. If patients have no AMI or death, they will be censored one year following their index encounter. If they have AMI or death, they will be censored at the time of that initial event. Survival curves will additionally look at rates of revascularization (CABG or PCI) and rehospitalization for cardiovascular disease. The time-to-event curves will be calculated with the Kaplan-Meier method and compared, when appropriate, using marginal Cox proportional hazards regression model. Multilevel and multivariable Cox regression models are considered using the same patient covariates as the primary analysis and incorporating exposure to SOC or the RACE-IT pathway.

We will perform exploratory analyses on patients placed in observation both under SOC and RACE-IT. We will compare utilization of stress tests, cardiology consultation, coronary CTA, coronary angiography, and PCI. We also will perform sensitivity analyses to determine if phenotypes based on HEAR score, age, gender, race, and different hs-cTnI value/delta cut-offs are associated with low rates of AMI or death at 30 days and one year. We will use a similar mixed model for these analyses as described for the primary outcome above.

We also plan analysis to derive and validate a new clinical decision rule using clinical characteristics, HEAR score, and different cutoffs with the baseline hs-cTnI values and delta values. This analysis will implement random forest techniques and could determine a clinical decision rule with superior performance using different hs-cTnI cut-offs than are currently in clinical use. The primary outcome for this analysis will be 30-day rates of AMI or death.

2.10.3. Health economics analysis

In addition to the clinical effectiveness of RACE-IT, we propose to evaluate the economic justification of the pathway compared to SOC protocol. In fact, we hypothesize the RACE-IT will result in a lower overall cost of treatment, capitalizing on avoided admissions, reduced length of stay, fewer resources used, and lower rate of AMI, death, readmission, and overall hospital charges at 30 days.

To assess the cost-effectiveness of the RACE-IT pathway compared to the SOC protocol, we will measure resource utilization, length of stay, rates of admission, AMI, death, and hospital charges at 30 days to compare operational cost and quality associated with patient care under both protocols. Resource utilization will include detailed CPT billing code information on all performed cardiovascular procedures both in the ED and hospital setting, regardless of whether a patient is discharged home from the ED or brought into observation or inpatient care.

Within-trial incremental costs associated with the SOC and RACE-IT protocols will be estimated using hospital reported reimbursements from insurers received for ED and inpatient hospital costs. Incremental cost effectiveness will be defined with respect to the primary clinical outcome, either as avoided adverse outcomes or improved patient outcomes [20]. The length of study does not allow a trial-based evaluation of the quality-adjusted life years (QALYs); however, we will use the incidence of AMI and other adverse outcomes combined with estimates from literature to compute the expected QALY for rate of occurrence of such outcomes. In addition to linear multivariate and two-part estimation models, we will also estimate mean difference in cost and effects using nonparametric bootstrapping techniques with patient-level data to account for uncertainty due to sampling variation in cost-effectiveness. We will incorporate relevant data sources and literature to extrapolate the longer-term costs and benefits derived from observed differences in cardiovascular events to generate full estimates of the cost-effectiveness of the new protocol [21,22].

3. Ethical considerations

The proposed study will be taking place during a change in routine medical care and all participating sites will move to the RACE-IT pathway during the study period. As such, the protocol change falls within an overall quality improvement project and does not constitute a research intervention. Hence, the anticipated risk for patients participating in data collection during this transition in clinical care is primarily limited to a loss of confidentiality. Data collection through secure servers will safeguard against this threat. Potential benefits include earlier discharge from the ED, avoidance of costly observation stays or hospital admission, and possible reduction of invasive cardiac testing.

4. Discussion

This trial comparing the RACE-IT pathway utilizing the hs-cTnI, compared to SOC with conventional cTn evaluation (only reporting values > 99th%), will provide essential data regarding operational impacts and safety of hs-cTnI implementation. The aim for this study is to form a workflow that gives ED physicians the ability to quickly determine which patients will require admission for further evaluation of ACS versus those that can be safely discharged home based on hs-cTnI values and risk stratification with HEAR scores. Should the data reveal an effective, safe, and cost-effective algorithm, the implications on decreased ED length of stay, patient morbidity, and systems operations could be significant. The study results will have implications for EDs
well beyond HFHS as many ED sites around the world are in the process of implementing hs-cTn protocols.

The modified stepped wedge cluster design with the phased approach for implementation will allow for streamlined integration of the proposed RACE-IT pathway without restricting benefits from any patient that visits an ED with suspected ACS. The current timeline for implementation as well as data analysis is to be completed within one year. The nine participating EDs altogether care for approximately 464,000 patient encounters each year. Building a trial in a health system that evaluates large volumes of patients presenting with possible ACS provides an organic environment within which to test the algorithm without significant concern for meeting the goal sample size of 11,070.

The RACE-IT pathway uses clinical risk stratification with the HEAR score (HEART score without troponin component [11]) in addition to hs-cTn testing to determine which patients with suspected ACS and quantifiable hs-cTnI values below the 99th percentile should be placed in observation for further testing or sent home. Previous studies have shown that by including a clinical risk score, the safety involving the hs-cTnI threshold at 99th percentile is greatly improved for ruling in and ruling out the need for further evaluation [3,23]. Additionally, this trial is unique as it will also look at quantifiable hs-cTnI values that fall below the 99th percentile (<18 ng/L) to allow for exploratory analysis of phenotypes that may confer low risk. Altogether, this clinical trial has the ability to create a novel clinical workflow regarding ACS using the hs-cTnI assay along with the HEAR score.

One limitation of our trial design is reliance on there being a significant prevalence of patients with hs-cTnI ≤5 ng/L and reliance on clinician adherence to the RACE-IT protocol for these patients. While our preliminary data estimates that approximately 40% of eligible patients will fall in this group, it could be smaller and negatively impact the trial’s statistical power. The estimated 60% of patients with a hs-cTnI of 6–18 ng/L are included in the trial but have similar clinical treatment pathways in both the RACE-IT and SOC protocols. Poor clinical adherence to the protocol, particularly for patients with hs-cTnI values ≤5 ng/L will also impact statistical power and bias results towards the null hypothesis.

5. Conclusion

Accurately and efficiently evaluating ACS in the ED has significant implications for patient outcomes and health system operations. The thoughtful implementation of hs-cTn assays have great potential to more quickly rule-out ACS while preserving patient safety and reducing hospital resource utilization. This trial utilizes a modified stepped wedge cluster randomized design to evaluate these potential benefits in a large health system operating nine EDs that could have significant implications for other sites around the world considering similar protocols.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.conctc.2021.100773.

References

[1] E.J. Benjamin, P. Muntner, et al., American heart association council on epidemiology and prevention statistics committee and stroke statistics subcommittee. Heart disease and stroke statistics-2019 update: a report from the American heart association, Circulation 139 (10) (2019) e56–e528, https://doi.org/10.1161/CIR.0000000000006559.

[2] Anda Bularga, et al., High-sensitivity troponin and the application of risk stratification thresholds in patients with suspected acute coronary syndrome, Circulation 140 (19) (2019) 1557–1568, https://doi.org/10.1161/circulationaha.119.042860.

[3] Andrew R. Chapman, et al., High-sensitivity cardiac troponin i and clinical risk scores in patients with suspected acute coronary syndrome, Circulation 138 (16) (2018) 1654–1665, https://doi.org/10.1161/circulationaha.118.036426.

[4] Robert H. Christenson, et al., Pivotal findings for a high-sensitivity cardiac troponin assay: results of the HIGH-US study, Clin. Biochem. 78 (2020) 52–59, https://doi.org/10.1016/j.clinbiochem.2019.10.013.

[5] Judd E. Hollander, High-sensitivity troponin: time to implement, Ann. Emerg. Med. 72 (6) (2018) 665–667, https://doi.org/10.1016/j.annemergmed.2018.07.525.

[6] Tobias Reichlin, et al., Early diagnosis of myocardial infarction with sensitive cardiac troponin assays, N. Engl. J. Med. 361 (9) (2009) 858–867, https://doi.org/10.1056/nejmoa090428.

[7] Shubham Thapa, et al., Implementation of rapid rule out of myocardial infarction using high-sensitivity troponin: cross-sectional survey of English hospitals, Emerg. Med. J. 37 (4) (2020) 229–231, https://doi.org/10.1136/emermed-2019-209100.

[8] K. Thyesen, et al., How to use high-sensitivity cardiac troponin in acute cardiac care, Eur. Heart J. 33 (18) (2012) 2252–2257, https://doi.org/10.1002/ehj3.1548.

[9] Christian Mueller, et al., Multicenter evaluation of a 0-hour/1-hour algorithm in the diagnosis of myocardial infarction with high-sensitivity cardiac troponin T, Ann. Emerg. Med. 68 (1) (1 July 2016), https://doi.org/10.1016/j.annemergmed.2015.11.013.

[10] Simon A. Mahler, et al., Safely identifying emergency department patients with acute chest pain for early discharge, Circulation 138 (22) (2018) 2456–2468, https://doi.org/10.1161/circulationaha.118.036528.

[11] James Mccord, et al., Propensity utility of a modified HEART score in chest pain patients in the emergency department, Circulation: Cardiovasc. Qual. Outcomes 10 (2) (2017), https://doi.org/10.1161/circoutcomes.116.003101.

[12] Derek P. Chew, et al., A randomized trial of a 1-hour troponin t protocol in suspected acute coronary syndromes, Circulation 140 (19) (2019) 1543–1556, https://doi.org/10.1161/circulationaha.119.042891.

[13] Jakob L. Forberg, et al., Direct hospital costs of chest pain patients attending the emergency department: a retrospective study, BMC Emerg. Med. 6 (1) (2006), https://doi.org/10.1186/1471-227x-6-6.

[14] Peter J. Pronovost, A. Christine, Goeschel. “Time to take health delivery research seriously. Jama 306 (3) (2011), https://doi.org/10.1001/jama.2011.1015.

[15] Jessica Laureano-Phillips, et al., HEART score risk stratification of low-risk chest pain patients in the emergency department: a systematic review and meta-analysis, Ann. Emerg. Med. 74 (2) (2019) 187–203, https://doi.org/10.1016/j.annemergmed.2018.12.010.

[16] Kari Hemming, et al., Reporting of stepped wedge cluster randomised trials: extension of the CONSORT 2010 statement with explanation and elaboration, BMJ (2018), https://doi.org/10.1136/bmj.k1614.

[17] Mahler Simon, et al., Safely identifying emergency department patients with acute chest pain for early discharge, Circulation 138 (22) (2018 Nov 27) 2456–2468, https://doi.org/10.1161/circulationaha.118.036528.

[18] Kristian Thysesen, et al., Fourth universal definition of myocardial infarction (2018), J. Am. Coll. Cardiol. 72 (18) (2018) 2231–2264, https://doi.org/10.1016/j.jacc.2018.08.1038.

[19] Michael A. Hussey, James P. Hughes, Design and analysis of stepped wedge cluster randomized trials, Contemp. Clin. Trials 28 (2) (2007) 182–191, https://doi.org/10.1016/j.cct.2006.05.005.

[20] Gillian D. Sanders, Matthew L. Maciejewski, Anirban Basu, Overview of cost-effectiveness analysis, J. Am. Med. Assoc. 321 (14) (2019) 1400–1401, https://doi.org/10.1001/jama.2019.1265.

[21] Anirban Basu, A welfare-theoretic model consistent with the practice of cost-effectiveness analysis and its implications, J. Health Econ. 70 (102287) (2020) 2021, https://doi.org/10.1016/j.jhealeco.

[22] Anirban Basu, Matthew L. Maciejewski, Choosing a time horizon in cost and cost-effectiveness analyses, J. Am. Med. Assoc. 321 (11) (2019) 1096–1097, https://doi.org/10.1001/jama.2019.1153.

[23] Louise Cullen, et al., Validation of high-sensitivity troponin i in a 2-hour diagnostic strategy to assess 30-day outcomes in emergency department patients with possible acute coronary syndrome, J. Am. Coll. Cardiol. 62 (14) (10 Apr. 2018) 1242–1249, https://doi.org/10.1016/j.jacc.2013.02.078.