A feasibility study for CODE-MI: High-sensitivity cardiac troponin–Optimizing the diagnosis of acute myocardial infarction/injury in women

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Background CODE-MI is a pan-Canadian, multicentre, stepped-wedge, cluster randomized trial that evaluates the impact of using the female-specific 99th percentile threshold for high-sensitivity cardiac troponin (hs-cTn) on the diagnosis, treatment and outcomes of women presenting to the emergency department (ED) with symptoms suggestive for myocardial ischemia. A feasibility study was conducted to estimate the number of eligible patients, the rate of the study's primary outcome under control conditions, and the statistical power to detect a clinically important difference in the primary outcome.

Methods Using linked administrative data from 11 hospitals in Ontario, Canada, from October 2014 to September 2017, the following estimates were obtained: number of women presenting to the ED with symptoms suggestive of myocardial ischemia and a 24-hour peak hs-cTn value within the female-specific and overall thresholds (ie, primary cohort); the rate of the 1-year composite outcome of all-cause mortality, re-admission for nonfatal myocardial infarction, incident heart failure, or emergent/urgent coronary revascularization. Study power was evaluated via simulations.

Results Overall, 2,073,849 ED visits were assessed. Among women, chest pain (with or without cardiac features) and shortness of breath were the most common complaints associated with a diagnosis of acute coronary syndrome. An estimated 7.7% of women with these complaints are eligible for inclusion in the primary cohort. The rate of the 1-year outcome in the primary cohort varied significantly across hospitals with a median rate of 12.2% (95%CI: 7.9%-17.7%). With 30 hospitals, randomized at 5-month intervals in 5 steps, approximately 19,600 women are expected to be included in CODE-MI, resulting in >82% power to detect a 20% decrease in the odds of the primary outcome at a 0.05 significance level.

Conclusions This feasibility study greatly enhanced the design of CODE-MI, allowed accurate evaluation of the study power, and demonstrated the strength of using linked administrative health data to guide the design of pragmatic clinical trials. (Am Heart J 2021;234:60–70.)

Cardiac troponin (cTn) is a key biomarker for the evaluation of myocardial infarction (MI) or myocardial injury in patients presenting with suspected acute coronary syndrome (ACS). The new generation of high-sensitivity cTn (hs-cTn) assays allow accurate measurement of very low concentrations of circulating cTn. In healthy reference populations, women have lower hs-cTn concentration levels than men.(1,2) Although, the use of sex-specific diagnostic thresholds has been recommended for hs-cTn assays (1,2) in most clinical settings, the overall 99th percentile threshold, which is considerably higher than the female-specific threshold, is still being used.(3) This could be a contributing factor to the under-diagnosis and under-treatment of women presenting with signs and symptoms suggestive of ischemia.(4-6) However, there is a lack of clear evidence demonstrating the benefit of using hs-cTn with sex-specific thresholds. As such, the CODE-MI trial (hs-**c**Tn - **O**ptimizing the **D**iagnosis of **A**cute **M**yocardial **I**nfarction/Injury in Women; ClinicalTrials.gov identifier: NCT03819894) was designed to evaluate the impact of using the female-specific hs-cTn threshold, compared to the overall threshold, on the diagnosis, treatment and

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outcomes of females presenting to the emergency department (ED) with symptoms suggestive for ischemia. This feasibility study was conducted to inform the design of CODE-MI.

CODE-MI Trial

The study intervention is to introduce the female-specific hs-cTn threshold. As this is a system-wide process change, it is not feasible to randomize individual patients. Hence, a cluster randomized design, with phased implementation, is the most appropriate choice.(7-9) Therefore, CODE-MI is designed to be a multi-centre, stepped-wedge, cluster randomized trial with all hospitals eventually receiving the intervention. Compared to a parallel design, this design is more attractive to the participating hospitals as the adoption of a sex-specific threshold has already been recommended by both the 4th International Definition of Myocardial Infarction and the International Federation of Clinical Chemistry and Laboratory Medicine. In addition, as considerable variability in the study outcome is expected across hospitals, a stepped-wedge design will be more powerful than a parallel design.(7)

The design and rationale has previously been described in detail.(10) Briefly, CODE-MI will recruit 30 secondary and tertiary care hospitals with onsite cardiology services across Canada. The hospitals will cross over sequentially, in random order, from control to intervention phase. In the *control phase*, the overall hs-cTn threshold will be used in both sexes to diagnose MI in patients presenting to the ED with symptoms suggestive of myocardial ischemia. In the *intervention phase*, the lower female-specific threshold will be introduced. The threshold for the diagnosis of men will remain unchanged; see (10) for the rationale. Other than implementing the female-specific threshold, the participating hospitals will follow their own procedures for further investigations, including using their own rule-in and rule-out pathways for monitoring changes in troponin over time. Those investigations will be constant between the control and intervention phases, allowing us to assess the impact of the change in the 99th percentile threshold.

The *primary cohort* consists of women presenting to the ED with symptoms suggestive of myocardial ischemia and a 24-hour peak hs-cTn value within the female-specific and the overall thresholds (the threshold window) according to the assay being used,(11) as the diagnostic assessment of these patients is most likely to be affected by the lowering of the hs-cTn diagnostic threshold. The *primary outcome* is a composite of all-cause mortality, readmission for non-fatal MI, incident heart failure, or emergent/urgent coronary revascularization at one year after the initial presentation (1-year MACE). The primary efficacy analysis will compare the 1-year MACE rate before and after the introduction of the female-specific threshold in the primary cohort. Routinely collected laboratory and administrative data, and vital statistics, will be used to define the study cohort and obtain outcomes.

Rationale for Conducting the Feasibility Study

This feasibility study was undertaken to address several challenges in the design of CODE-MI. The first challenge was to obtain a reliable estimate of the number of eligible patients. The study cohort selection relies on the Canadian Emergency Department Information System (CEDIS) Presenting Complaints codes, which is a list of triage complaints developed to capture a patient's symptom, complaint, or reason for seeking emergency medical care and is universally used in Canada.(12) However, there is no existing validated algorithm using CEDIS presenting complaint codes to identify patients presenting to the ED with signs and symptoms consistent with myocardial ischemia/injury. This is especially challenging for women as they are less likely than men to exhibit typical ischemic symptoms. Instead, they are more likely to experience atypical symptoms, such as dyspnea, chest discomfort, indigestion, nausea and weakness.(13-16)

The second challenge was obtaining a reliable estimate of the outcome rate under control conditions. There are limited studies reporting an adverse event rate in women who present to the ED with suspected ACS and a peak hs-cTn test value within the threshold window. Among these studies, the reported event rates among women varied considerably, ranging from 13% to 28%.(17-19) Furthermore, due to the differences in cohort selection and outcome definition, these results could not be directly applied to the CODE-MI trial. Moreover, these studies were either limited to only one site, or if they included multiple sites, they did not publish the observed variability in event rates across sites, which is necessary to consider in the design of a cluster randomized trial.

The third challenge was to estimate the power of the study to detect a clinically important change in the primary outcome due to the intervention, as the design of CODE-MI is complex. The most commonly used method is an analytical approach by Hussey and Hughes,(8) and its variants.(20) Such methods are based on a weighted least squares analysis and do not account for secular trend. A more recent procedure proposed by Li et al (21) allows interperiod correlation and bias-corrected variance estimators for small number of clusters. However, similar to Hussy and Hughes's procedure, it is not easily adaptable to handle deviations from a standard design or variable cluster size. Therefore, we opted to use simulations tailored to the design and planned statistical analysis of CODE-MI.

Using the most recent available administrative health data from hospitals in Ontario, Canada, this feasibility

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study aimed to: (1) estimate the number of eligible patients, (2) assess the primary outcome rate, and its variability among hospitals under the control conditions, and (3) determine the power to detect a clinically important difference in the primary outcome rate.

Methods

Data Statement

The data used in this study are held at ICES in Toronto, Ontario. ICES is an independent, non-profit research institute whose legal status under Ontario's health information privacy law allows it to collect and analyze health care and demographic data, without consent, for health system evaluation and improvement. The use of data in this project was authorized under Section 45 of Ontario's Personal Health Information Protection Act, which does not require review by a Research Ethics Board. While data sharing agreements prohibit ICES from making the dataset publicly available, access may be granted to those who meet pre-specified criteria for confidential access. The full dataset creation plan, and analytic methods and code are available from the authors upon request understanding that the computer programs may rely upon coding templates or macros that are unique to ICES and are therefore either inaccessible or may require modification.. The authors have full access to all the data in the study and take responsibility for its integrity and the data analysis.

Sources of Funding

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Data Sources

The National Ambulatory Care Reporting System was used to identify patients visiting an ED with symptoms suggestive of myocardial ischemia, using specific ED presenting complaint codes (Table 1). These patients were linked to other administrative databases that included: the Ontario Laboratories Information System, used to capture hs-cTn test records; the CIHI Discharge Abstract Database, used to determine clinical outcomes using International Classification of Disease (ICD)-10-CA or Canadian Classification of Health Interventions (CCI) codes (see Supplementary Table); the Registered Persons Database (RPDB), used to capture both in and out of hospital deaths. The RPDB is a database containing demographic information on persons registered under the Ontario Health Insurance Plan and who are eligible for the Ontario Drug Program. These datasets were linked using unique encoded identifiers and analyzed at ICES.

Table 1. Candidate Canadian Emergency Department Information System Presenting Complaints codes

Cardiovascular	Respiratory
003 - Chest pain (cardiac features)	651 - Shortness of breath
004 - Chest pain (noncardiac features)	653 - Cough/congestion
005 - Palpitations/irregular heartbeat	654 - Hyperventilation
006 - Hypertension	659 - Wheezing - no other complaints
007 - General weakness	
008 - Syncope/presyncope	
009 - Edema, generalized	
010 - Bilateral leg swelling/edema	
012 - Unilateral reddened hot limb	
011 - Cool pulseless limb	

Hospitals and Patients

This feasibility study is based on the 11 CODE-MI participating hospitals which are located in Ontario, and had data available for this analysis. All ED visits to these hospitals between October 1, 2014 and September 30, 2017 were included. Patients under 20 years of age and non-Ontario residents were excluded. While data from the National Ambulatory Care Reporting System, the Discharge Abstract Database, and the RPDB were available for all hospitals during this 3-year period, hs-cTn test results were only available for four hospitals, from October 1, 2014 to September 30, 2015.

Statistical Analyses

Estimating the number of eligible patients

The analyses were carried out iteratively in order to identify the most relevant ED presenting complaint codes. As women are more likely to exhibit atypical symptoms, in the first iteration, we explored a broad list of presenting complaint codes, including all codes from the cardiovascular category except traumatic and non-traumatic cardiac arrest (001 and 002), and codes from the respiratory category that are known to be associated with myocardial ischemia (Table 1). The following analyses were performed:

Step 1–Determination of the number of women presenting with the selected preliminary presenting com-

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plaint codes from October 2014 to September 2017 at each ED, and the rate of ACS diagnosis among these patients: ED visit records from the National Ambulatory Care Reporting System can have up to three complaint codes. When more than one complaint code from Table 1 was present at a visit, the visit was categorized by the more primary presenting complaint. For patients with multiple visits during the study period, only the first was included. From this ED cohort, we report the number of patients by presenting complaint code.

To explore the relationship between the ED presenting symptoms and being diagnosed with ACS, we report the number of ACS diagnoses for each presenting complaint code listed in Table 1. A patient is considered as having ACS if diagnosed with unstable angina (ICD-10 I20.4) or MI (ICD-10 I21, I22), either at the index ED/hospital discharge or at any subsequent ED visit or hospital admission within a year from the index ED presentation. We extended the diagnostic timeframe to one year in order to capture patients who were not appropriately diagnosed at the index care episode. The analysis was repeated for a subset of patients who had a cTn test ordered within 24 hours of ED presentation at 6 hospitals where cTn test data were available during October 2014 to September 2015. Two of these hospitals used a contemporary cTn assay whereas the rest used a hs-cTn T assay (Roche Diagnostics Elecsys).

Step 2–Evaluation of the proportion of patients selected from the first step, whose peak hs-cTn value within 24 hours of ED presentation fell within the overall and female-specific thresholds (the threshold window): This analysis was limited to patients from the four hospitals with hs-cTn results from October 2014 to September 2015. For the hs-cTn T assay used at these hospitals, the cut-off window is 9 ng/L (female) to <14 ng/L (overall), as recommended by the International Federation of Clinical Chemistry (11). We report the number and proportion of females within the threshold window (ie, primary cohort), by hospital, and by presenting complaint code.

From these initial analyses, we identified the most relevant presenting complaint codes for selecting patients with symptoms suggestive of myocardial ischemia and repeated the above steps with the selected final codes. Based on the results, we estimated the number of women, per 1,000 ED visits, who are eligible for the primary cohort. This enables us to estimate the anticipated sample size of the primary cohort based on the annual ED visits at the participating hospitals, which is routinely reported by CIHI (2017/2018).(22) When data were not available from CIHI, other sources, such as hospital annual reports were used.

Assessing the 1-year MACE rate and variability in the primary cohort

This analysis was limited to patients from the 4 hospitals with hs-cTn results during October 2014 to September 2015. Due to low event numbers from individual hospitals, the 1-year rates were either pooled from all four hospitals and reported by each presenting complaint codes as selected above, or pooled from all selected presenting complaint codes and reported by hospital.

To estimate the overall outcome rate and hospital variability, we analyzed the number of events from individual hospitals using a logistic regression model with hospital-specific random intercepts. As only four hospitals were available for this analysis, the hospital variability cannot be precisely determined. We also conducted a complementary analysis using an ACS cohort from all eleven hospitals to obtain a supplementary estimate of the hospital variability. In the ACS cohort, we included all women who, regardless of their presenting complaint codes, were hospitalized from the ED and subsequently discharged with a most responsible diagnosis of unstable angina (I20.4) or non-ST segment elevation MI (NSTEMI, I21 or I22 supplemented by R94.31), between October 2014 and September 2017. STEMI patients were excluded as they routinely bypass the ED and are referred directly to the cardiac catheterization laboratory. In addition, cTn values are not used to diagnose STEMI. The number of events in this ACS cohort was obtained by hospital and analyzed using the same logistic regression model.

Evaluating power via simulations

Simulations were conducted to evaluate the power for testing the effect of using the female-specific hs-cTn threshold on the study's primary outcome in the primary cohort. The simulation settings are outlined below.

Hospitals: In total, there are 30 participating hospitals in CODE-MI trial, however, some hospitals, within a specific region, share ED, laboratory and cardiology service resources and need to transition as a group to the new threshold. We refer these grouped hospitals as a cluster. As a result, there are 22 clusters to be randomized with one cluster consisting of 3 hospitals, 6 clusters consisting of 2 hospitals, and the remaining 16 clusters consisting of a single hospital.

Study duration and intervention implementation schedule: The CODE-MI trial will consist of five steps at 5-month intervals. As some hospitals will not yet have started using hs-cTn assay at the first step, or will not have sufficient experience (at least 2 months) with using a hs-cTn assay, clusters containing these hospitals will not be ready for randomization at the first step. As such, in the feasibility study we considered 2 strata of randomization: the 15 clusters currently using hs-cTn assay will be allocated equally across the 5 steps; the remaining 7 clusters, with delayed introduction of hs-cTn assay, will be allocated at Steps 2 to 5, with 2 clusters each at Steps 2 to 4, and 1 cluster at Step 5. To increase power, the control phase can begin up to 20 months prior to the first step in the 13 clusters with established experience running hs-cTn assay. See Figure 1 for a diagram of the study schedule.

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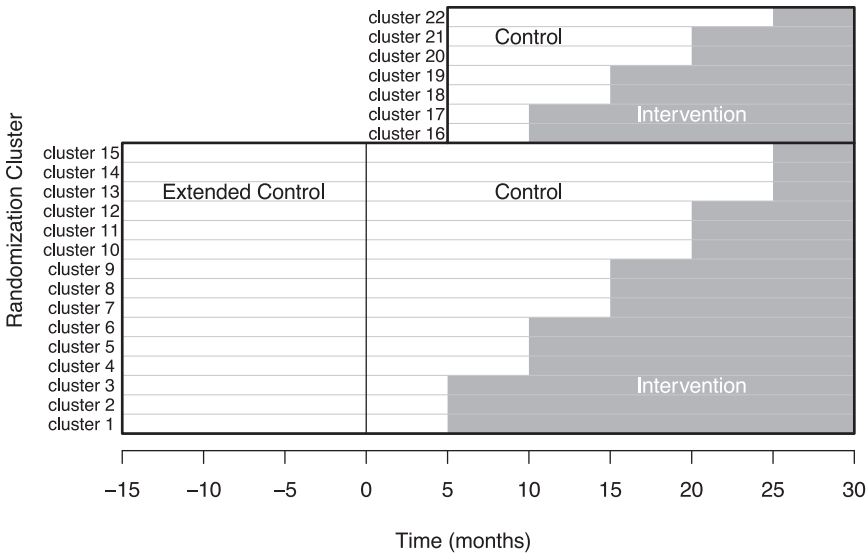
Figure 1



Study duration and intervention implementation schedule. Clusters 1 – 15 are the clusters currently using hs-cTn assay and will be allocated equally across the 5 steps. Thirteen of these clusters with extensive experience with hs-cTn will have an extended control period of 15 months. Two clusters will not have an extended control period. However, since their actual allocation will depend on the study randomization, they are not distinguished from those with an extended control period in this figure. Clusters 16 – 22 are clusters with delayed introduction of hs-cTn assay and will be allocated at Steps 2 – 5.

Cluster volume: For each cluster, the mean number of eligible patients per study period was estimated based on the total annual ED visits and estimated eligible female patients per 1,000 ED visits. Based on the mean number of eligible patients in each cluster, the number of eligible patients at each 5-month period was then generated using a Poisson distribution in the simulations.

Data generation and power estimation: A logistic regression model was used to generate patient outcomes. Time period and intervention indicator were included as fixed effects and clusters were included as random effects, following a normal distribution. Hospitals within a cluster share the same random effect (see Supplementary Materials for more details).

In the main simulation scenario, we assumed no secular trend and the median event rate during the control phase and variability across clusters were based on the estimates from the logistic regression fitted to the 4 hospitals with hs-cTn data. We varied the odds ratio of the intervention from 0.82 to 0.78.

For each generated dataset, we estimated the intervention effect using a mixed-effects logistic regression with the time variable specified in 2 ways: (a) as a categorical variable with 2 levels, and (b) as a continuous variable. This allowed us to assess the robustness of our power calculation and potential bias in the estimate of the intervention effect with imperfect specification of the secular trend. For comparison purposes, we also fitted a model without adjusting for secular trend. The null hypothesis was tested using the log likelihood ratio test at a significance level of 0.05. To verify the robustness of our power estimation, we also considered several additional scenarios: (i) a lower event rate, (ii) a smaller and greater cluster variability, (iii) a linearly decreasing secular trend, and, (iv) a lower number of eligible patients (see Supplementary Materials for more details).

In the above scenarios, only data from women were simulated and analyzed. As men from the study sites will not undergo the intervention, the value of including them as controls in the analysis to increase the study power was explored. An equal number of men and women from each cluster was generated. We assumed that the men have a different event rate, but share the same cluster-specific random effect and secular trend with the women. The intervention effect was estimated using a mixed-effects logistic regression with three fixed effects: intervention, time period, and sex.

The simulations were run 2000 times for each scenario, keeping standard errors of the estimated powers at less than 1%. All computations were conducted using RStudio (v1.1.383).(23) The logistic regression was fit using *glmer* from package *lme4* (v1.1-15).(24) The simulation code can be found in Supplementary Materials.

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Table 2. Number of women with diagnosis of acute coronary syndrome (ACS) at the index presentation, or at a subsequent emergency department visit or hospital admission within 1 year by Canadian Emergency Department Information System Presenting Complaint code

Presenting Complaint Code	N	ACS (%)
003 - Chest pain (cardiac features)	**32,858**	**2,836 (8.6%)**
004 - Chest pain (noncardiac features)	**15,929**	**343 (2.2%)**
005 - Palpitations/irregular heartbeat	9,631	147 (1.5%)
006 - Hypertension	4,811	79 (1.6%)
007 - General weakness	18,822	445 (2.4%)
008 - Syncope/presyncope	11,904	156 (1.3%)
010 - Bilateral leg swelling/edema	2,414	37 (1.5%)
651 - Shortness of breath	**25,895**	**888 (3.4%)**
653 - Cough/congestion	10,449	79 (0.8%)
Total*	134,373	5,047 (3.8%)

Codes in bold were selected as part of the final inclusion criteria.
* Total also included the presenting complaint codes with small counts (1,000 cases or <6 cases diagnosed with ACS): 009, 011, 012, 654, 659. cTn, cardiac troponin.

Results

Number of Eligible Patients

During the study period, there were 2,073,849 ED visits at the 11 hospitals, varying from 116,116 to 290,518 visits per hospital. Of those, we identified 134,372 unique adult female patients who presented with the complaint codes listed in Table 1. The number of unique patients by each presenting complaint code and proportion diagnosed with ACS are reported in Table 2.

The initial analysis confirmed that cardiac chest pain (003) is the most common presenting symptom among women who later are diagnosed with ACS, however, noncardiac chest pain (004) and shortness of breath (651) also account for a noteworthy proportion of ACS patients. These three codes captured 80.6% of the total ACS patients in the cohort of the initial analysis. The proportions of women with an ACS diagnosis were 8.6% among those with cardiac chest pain, 2.2% among those with non-cardiac chest pain and 3.4% among those presenting with shortness of breath. The proportions of women with an ACS diagnosis were higher when a cTn test was ordered at 9.4%, 4.2%, and 3.7%, respectively. Among women presenting with general weakness (007), the proportion with ACS was also relatively high (2.4%). However, when limited to those with cTn ordered, the ACS proportion was lower (3.0%) than the other three codes. Since general weakness could be due to many conditions other than ACS, it was not selected to be part of our inclusion criteria.

When re-deriving our ED cohort using these three presenting complaint codes, 82,142 unique female patients were identified (Figure 2a). Of those, 35,474 (43.2%), 17,034 (20.7%), and 29,634 (36.1%) had cardiac chest pain, noncardiac chest pain and shortness of breath, respectively. With all hospitals combined, the rate of unique females presenting to ED with any of these three codes, over the total ED visits, was 39.6 per 1,000 ED visits. This rate varied from 29.5 to 55.2 from hospital to hospital.

When limited to the four hospitals with hs-cTn data, there were 10,957 women in the ED cohort, of which 7,946 (72.5%) had at least one hs-cTn ordered within 24 hours (Table 3 and Figure 2b). The hs-cTn testing rate among women with cardiac chest pain was 91.6%, followed by 61.3% and 60.2% for noncardiac chest pain and shortness of breath, respectively. Among those with hs-cTn tests, 843 (10.6%) had a peak hs-cTn value within the threshold window (median age [interquartile range]: 76 [65-83]; peak hs-cTn: 11 [10-12]). The proportion in the threshold window was highest for women with shortness of breath (13.2%), and similar for women with cardiac and noncardiac chest pain (9.76% and 8.66%, respectively).

The above results provided a basis to estimate the sample size. Using the cohort formed by presenting complaint codes 003, 004 and 651, on average, 39.6 women per 1,000 ED visits (82,142/2,073,849, Figure 2a) were eligible for inclusion in the ED cohort. Among these, 7.7% of patients had peak hs-cTn values within the threshold window. Hence, we expect approximately 3 women (39.6 × 7.7%) per 1,000 ED visits, will be eligible for inclusion in the primary cohort.

Based on the total ED volume of each hospital, we estimated that the number of eligible women per 5-month period may vary between 50 and 300 across the 22 clusters with a mean of 127 women. See Figure 3 for the distribution of the estimated cluster volume. The enrolment duration will vary from five to nine 5-month periods with a total of 164 site-periods. Under the schedule shown in Figure 1, the total expected number of women is approximately 11,600 during the control phase and 8,000 during the intervention phase.

1-year MACE rate and variability in the primary cohort

In total, 105 of the 843 women in the primary cohort had the MACE outcome; 72 deaths, 29 readmissions for incident heart failure, 7 readmissions for MI, and 7 emergent/urgent revascularizations. The Chi-squared test

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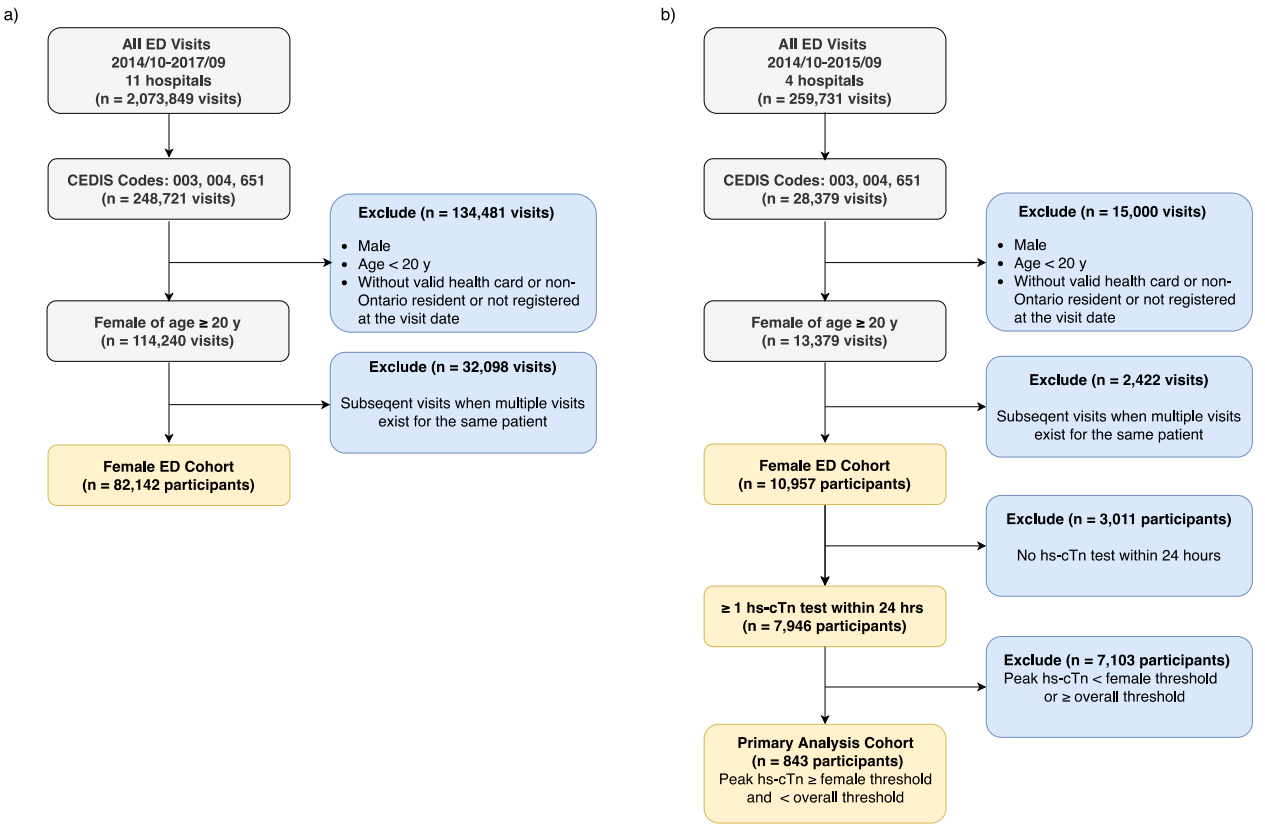
Figure 2



Flow chart of patient selection. (**a**) Emergency cohort. (**b**) Primary cohort.

Table 3. Characteristics of emergency department (ED) visits for hospitals with hs-cTn data (October 2014 to September 2015)

	Total	Hospital 1	Hospital 2	Hospital 3	Hospital 4
Total ED visits	259,731	46,606	93,720	61,154	58,251
ED cohort: women	10,957	2,555	3,096	2,299	3,007
presented with CEDIS code 003, 004, or 651	(4.2%)	(5.5%)	(3.3%)	(3.8%)	(5.2%)
(% among total ED visits)					
hs-cTn cohort: hs-cTn ordered within 24 hours	7,946	1,827	1,802	1,657	2,660
(% among ED cohort)	(72.5%)	(71.5%)	(58.2%)	(72.1%)	(88.5%)
Primary cohort: women with peak hs-cTn between the	843	220	180	161	282
threshold window	(7.7%)	(8.6%)	(5.8%)	(7.0%)	(9.4%)
(% among ED cohort)	(10.6%)	(12.0%)	(10.0%)	(9.7%)	(10.6%)
(% among hs-cTn cohort)					
1-year primary outcome	105	20	35	15	35
(% among primary cohort)	(12.5%)	(9.09%)	(19.4%)	(9.3%)	(12.4%)

CEDIS code, Canadian Emergency Department Information System Presenting Complaint code; hs-cTn, high-sensitivity cardiac troponin.

indicated that the proportions of women with MACE outcome were significantly different across hospitals (P= .008). The logistic regression with hospital-specific random intercepts yielded a median event rate of 12.2% (95% CI: 7.9%-17.7%). The standard deviation of the hospital random effect was estimated at 0.288, corresponding to an interquartile range of (10.3%, 14.4%) for the hospital-specific event rates. These results were used to simulate outcome events in the main scenario of our power evaluation.

In the complementary analysis using an ACS cohort, 3,593 female ED patients were hospitalized with their most responsible diagnosis being unstable angina or NSTEMI, of whom 1,006 (28.0%) experienced a pri-

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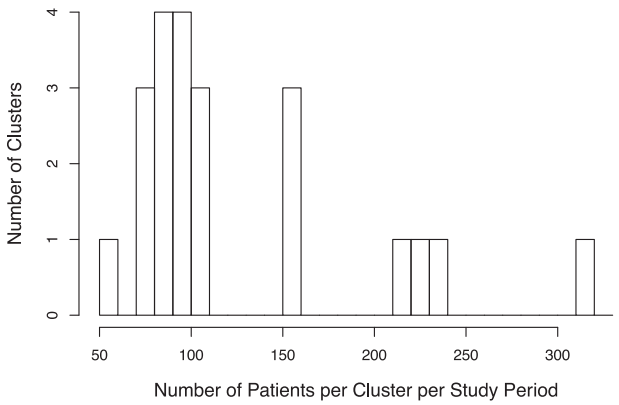
Table 4. Estimated power across a range of intervention effect and analytic approach

Intervention effect		Estimated power by analytic approach		
Odds ratio	Change in outcome rate	No trend	Categorical trend*	Linear trend
0.82	12.24% to 10.25%	98.2	77.9	75.4
0.81	**12.24% to 10.16%**	**98.2**	**82.2**	**81.6**
0.80	**12.24% to 10.07%**	**99.2**	**85.6**	**82.2**
0.78	12.24% to 9.80%	99.9	93.3	92.6

Codes in bold were selected as part of the final inclusion criteria.
*Time period was included as a categorical variable with two levels.

Figure 3



Distribution of expected number of patients by hospital cluster.

mary outcome event within one year. Variabilities were observed across hospitals, with the rates ranging from 20.7% to 35.7% (data not shown). Based on the fitted random effect model, the standard deviation of the hospital random effect was estimated at 0.173; smaller than the estimate from the primary cohort. This result was used to guide us to specify additional scenarios in our simulation studies.

Power

We first verified the nominal alpha level under the null hypothesis, that is, no intervention effect. When simulating data with no secular trend, the observed alpha level was 0.047, 0.056, and 0.050 when the analysis included either no trend, categorical or linear trend, respectively. When, in truth, there is a linear secular trend, the observed alpha level was 0.087 and 0.058 for the 2 approaches that allow for a secular trend. Not surprisingly the alpha level was severely inflated (0.332) when trend was not considered in the analysis.

The estimated power under the main scenario of an overall event rate of 12.2% and varying intervention effect is reported in Table 4. We will have at least 82% power to detect a 20% decrease in the odds (absolute decrease 2.2%) of our primary outcome at a 0.05 significance level.

Results from additional scenarios, summarized below, confirmed the robustness of our power evaluation:

- Lowering the event rate to 10.4%, dropped the power only slightly to 78.8% under a linear trend, and 80.8% under the categorical trend.
- Altering the event rate variability across clusters (standard deviation of 0.2 and 0.4) had relatively small impact on the power. The power was above 80% in all cases.
- When simulating data with a decreasing secular trend (from 12.2% in the first period to 11.2% in the last period of the study), the analysis included a linear secular trend yielded an unbiased estimate of intervention effect with an observed power of 81%. The observed power was 91% when the analysis included a categorical trend, however, the intervention effect estimate was overestimated.
- Lowering the number of eligible patients (from 127 to 107 patients per cluster per period), decreased the power to 77.4% under a linear trend and 79.0% under the categorical trend. However, ED volume is expected to increase over time, therefore, this is an unlikely scenario.

Including a male control group improved the precision of the intervention effect estimate - the standard error of the odds ratio estimate decreased by 24%, and thus, markedly improved power to 96.7% for detecting an odds ratio of 0.80 under the main scenario.

Discussion

In this feasibility study, we utilized routinely collected administrative data to guide the design of CODE-MI, a pragmatic multicentre stepped-wedge cluster randomized clinical trial. Based on the findings of this feasibility analysis, we refined the inclusion/exclusion criteria, estimated the number of eligible patients, and determined the expected outcome event rate for the control phase. Using simulations constructed from the estimated sample size and event rate, we were also able to confirm suf-

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ficient power to detect an odds ratio of 0.80 with at least 80% power.

Troponin testing is widely used in the ED as a rule-out test; many tested patients do not have conditions related to cardiac ischemia, and therefore are unlikely to benefit from using the female-specific thresholds. Including all tested female patients is likely to diminish the ability to detect the intervention effect. Therefore, it is important to balance the sensitivity and specificity when identifying suspected ACS patients to be included in our study cohort. We found that women presenting with chest pain, with or without cardiac features, or shortness of breath were most likely to have an immediate or delayed ACS diagnosis, and therefore, these would be the most relevant symptom presentations suggestive of ischemia to include in CODE-MI. This is consistent with the literature.(14,25) It is possible that we will miss some women with suspected ACS. For example, we were not able to include complaints such as diaphoresis or radiation of pain as there are no specific presenting complaint codes for these symptoms in the Canadian ambulatory care reporting system. We did not include abdominal pain, vomiting and nausea, which are classified under the gastrointerstinal category, and will likely yield only a very small number of true ACS cases, therefore, making the cohort less specific. In addition, a combination of symptoms was not considered because only 1 complaint code was reported in the majority of ED visits (around 96% in Ontario during October 2014-September 2017) despite that up to 3 complaint codes can be entered into the reporting system. Information from an electrocardiogram is also crucial in identifying suspected ACS patients. However, this information is not readily available in the current administrative data sources. How to best identify suspected ACS patients using records from the National Ambulatory Care Reporting System remains an open question and warrants future investigations.

We observed a 12.2% event rate in the primary cohort, which is comparable to the 13.4% outcome rate observed in the High-STEACS cohort of which 901 women were within the threshold window, although differences in study population and outcome definition exist between High-STEACS (19) and CODE-MI. Shah et al (17) and Cullen et al (18) reported higher event rates, 25% and 28%, respectively. However, the numbers of patients within the threshold window from these studies were small (n = 56 and 25, respectively). Moreover, the rate reported by Cullen et al included events occurring during the index presentation.

In the stepped-wedge design, appropriate adjustment for secular trend is necessary as time and intervention assignments are inevitably correlated, but it comes at the cost of statistical power, as shown in Table 4. Incorporating a parallel control cohort in the analysis can be an effective way to adjust for secular trend. Our simulation demonstrated that the trial's power can be improved dramatically when including male patients from the study sites as controls (ie, they will not undergo the intervention and will continue to be assessed using the overall hs-cTn threshold even during the intervention phase). Another possibility is to carefully construct a parallel female control group from nonparticipating hospitals. These approaches are attractive as there is little additional cost when patient selection and outcome determination both rely on routinely collected administrative data. However, we remain cautious with these approaches as each requires the assumption that the patients in the parallel control group share the same secular trend with the female patients in our primary cohort during the study period. Alternatively, if a Bayesian approach(26) is considered, time trends estimated from the male cohort or female patients from nonparticipating hospitals can be incorporated as an informative prior.

This feasibility study also provided valuable insight into the potential magnitude of impact of adopting the female-specific hs-cTn diagnostic threshold. We estimated that, out of every 1,000 ED visits at a tertiary care Canadian hospital, with onsite cardiology services, 3 women are expected to have suspected ACS and yet have their hs-cTn test results falling within the threshold window. Canada-wide, this could amount to over 50,000 women each year, given that CIHI estimated 17.7 million ED visits occurred in Canada in 2017/2018.(27) Around 12% of these women are expected to experience an adverse cardiac event within 12 months. If adopting the female-specific hs-cTn diagnostic threshold in combination with better MI detection and care could lead to a 20% reduction in the odds of an adverse event, 1,000 adverse events can be prevented each year. We acknowledge that our estimates were based on tertiary care hospitals and, therefore, might not apply to other types of hospitals. Nevertheless, tertiary care hospitals account for a large proportion of ED visits in Canada.

Our planned analysis is based on a mixed effects logistic regression model. The generalized estimating equations (GEE) is another common approach to account for clustering of data, but it is less frequently used in cluster randomized trials.(28) Simulation studies have shown that the GEE without bias correction of the variance estimator is prone to underestimate standard errors and have reduced statistical power over random effects model when the number of clusters is within 20 to 30 clusters.(29) In addition, multilevel clustering is easy to account for in a mixed-effects model.

This feasibility study has several limitations. All hospitals in this feasibility study were from one province and all hospitals used the same hs-cTn T assay. We were not able to include hospitals using hs-cTn I assays due to data availability. We found 7.7% of the female ED cohort had their peak hs-cTn value within the threshold window. Based on the currently available evidence, other studies have reported variable proportions of women within

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the threshold window (2.5%-17.5%).(17-19,30,31) To address this limitation, we have run a simulation scenario with a sample size 10% smaller than the main scenario; reassuringly, the power is close to 80%.

The estimate of event rate variability across clusters is not very precise; however, we used a conservative estimate in our simulations as the complementary analysis of patients with NSTEMI and unstable angina suggested that the hospital variability could be lower. We also considered scenarios with smaller and greater event rate variability, across clusters, and found that the power was not sensitive to such changes.

Our simulation studies were conducted under two assumptions related to time. Firstly, we assumed that there is no interaction between intervention and time, therefore CODE-MI is not powered to detect such an interaction. Nevertheless, the interaction between female threshold and time will be investigated as a secondary analysis. We acknowledge that the overlap of CODE-MI trial with the COVID-19 pandemic may have unexpected impact over the course of the study. We will be continuously assessing this impact and will take it into account at the analysis stage, if needed. Secondly, we included secular trend as a fixed effect as we do not expect large variation in secular trend across hospitals. This assumption will be examined in the analysis. If there is clear evidence of variable secular trend, a cluster-specific random secular trend will be included in the model.

There has been an increasing number of pragmatic trials in cardiovascular research in recent years which, in contrast to traditional randomized control trials, are less costly and less subject to attrition and missing results. Routinely collected administrative health data and cardiac registries can serve as a rich and essential resource for conducting pragmatic trials assessing process change, such as CODE-MI. Moreover, conducting trials within established health care data environments increases the generalizability of findings and offers protection against selection bias,(32) as well as the opportunity for long-term follow-up.(33) We demonstrated that a careful analysis of existing administrative health data can yield information to aid the design of such pragmatic trials and to ensure adequate power. It enabled us to simulate study populations that truly reflect our design features and, therefore, allowed accurate evaluation of the study power to detect a clinically important difference. In addition, this feasibility study proved to be very helpful in developing data assembly and analysis strategies, as well as in identifying potential challenges.

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Supplementary materials

Supplementary materials associated with this article can be found, in the online version, at doi:10.1016/j.ahj.2021.01.008.

References

1. Apple FS, Ler R, Murakami MM. Determination of 19 cardiac troponin I and T assay 99th percentile values from a common presumably healthy population. Clin Chem 2012;58:1574–81.
2. Kimenai DM, Janssen EBNJ, Eggers KM, et al. Sex-specific versus overall clinical decision limits for cardiac troponin I and T for the diagnosis of acute myocardial infarction: a systematic review. Clin Chem 2018;64:1034–43.
3. Anand A, Shah ASV, Beshiri A, et al. Global adoption of high-sensitivity cardiac troponins and the universal definition of myocardial infarction. Clin. Chem. 2019;65:484–9.
4. Dey S, Flather MD, Devlin G, et al. Sex-related differences in the presentation, treatment and outcomes among patients with acute coronary syndromes: the Global Registry of Acute Coronary Events. Heart 2009;95:20–6.
5. Mehta LS, Beckie TM, DeVon HA, et al. Acute myocardial infarction in women: a scientific statement from the American Heart Association. Circulation 2016;133:916–47.
6. Humphries KH, Izadnegahdar M, Sedlak T, et al. Sex differences in cardiovascular disease – impact on care and outcomes. Front Neuroendocrinol 2017;46:46–70.
7. Hemming K, Haines TP, Chilton PJ, et al. The stepped wedge cluster randomised trial: rationale, design, analysis, and reporting. BMJ 2015;350:h391.
8. Hussey MA, Hughes JP. Design and analysis of stepped wedge cluster randomized trials. Contempor Clin Trials 2007;28:182–91.
9. Hargreaves JR, Copas AJ, Beard E, et al. Five questions to consider before conducting a stepped wedge trial. Trials 2015;16:350. doi:10.1186/s13063-015-0841-8.
10. Zhao Y, Izadnegahdar M, Lee M, et al. High-sensitivity cardiac troponin - optimizing the diagnosis of acute myocardial infarction/injury in women (CODE-MI): rationale and design for a multi-centre stepped-wedge cluster randomized trial. Am Heart J 2020;229:18–28.
11. Collinson PO, Saenger AK, Apple FS, on behalf of the IFCC C-CB. High sensitivity, contemporary and point-of-care cardiac troponin assays: educational aids developed by the IFCC Committee on Clinical Application of Cardiac Bio-Markers. Clin Chem Lab Med 2019;57:623–32.
12. Grafstein E, Bullard MJ, Warren D, Unger B. CTAS National Working Group. Revision of the Canadian Emergency

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Department Information System (CEDIS) presenting complaint list version 1.1. CJEM 2008;10:151–73.
13. Milner KA, Funk M, Richards S, et al. Gender differences in symptom presentation associated with coronary heart disease. Am J Cardiol 1999;84:396–9.
14. O'Donnell S, McKee G, O'Brien F, et al. Gendered symptom presentation in acute coronary syndrome: a cross sectional analysis. Int J Nurs Stud 2012;49:1325–32.
15. Shin JY, Martin R, Suls J. Meta-analytic evaluation of gender differences and symptom measurement strategies in acute coronary syndromes. Heart Lung 2010;39:283–95.
16. Brush JE, Krumholz HM, Greene EJ, Dreyer RP. Sex differences in symptom phenotypes among patients with acute myocardial infarction. Circ Cardiovasc Qual Outcomes 2020;13:e005948. doi: 10.1161/CIRCOUTCOMES.119.005948.
17. Shah AS, Griffiths M, Lee KK, et al. High sensitivity cardiac troponin and the under-diagnosis of myocardial infarction in women: prospective cohort study. BMJ 2015;350:g7873.
18. Cullen L, Greenslade JH, Carlton EW, et al. Sex-specific versus overall cut points for a high sensitivity troponin I assay in predicting 1-year outcomes in emergency patients presenting with chest pain. Heart 2016;102:120–6.
19. Lee KK, Ferry AV, Anand A, et al. Sex-specific thresholds of high-sensitivity troponin in patients with suspected acute coronary syndrome. J Am Coll Cardiol 2019;74:2032–43.
20. Hemming K, Lilford R, Girling AJ. Stepped-wedge cluster randomised controlled trials: a generic framework including parallel and multiple-level designs. Statist Med 2015;34:181–96.
21. Li F, Turner EL, Preisser JS. Sample size determination for GEE analyses of stepped wedge cluster randomized trials. Biom. 2018;74:1450–8.
22. Canadian Institute for Health Information. Explore your health system [Internet]. [cited 2019 Jun 10]. Available from: https://yourhealthsystem.cihi.ca/hsp/indepth#.
23. RStudio Team. RStudio: Integrated Development for R. RStudio. Inc. Boston; 2016. http://www.rstudio.com/.
24. Bates D, Mächler M, Bolker B, Walker S. Fitting linear mixed-effects models using lme4. J Stat Soft 2015;67:1–48. doi:10.18637/jss.v067.i01.
25. Shah ASV, Anand A, Strachan FE, et al. High-sensitivity troponin in the evaluation of patients with suspected acute coronary syndrome: a stepped-wedge, cluster-randomised controlled trial. Lancet 2018;392:919–28.
26. Cunanan KM, Carlin BP, Peterson KA. A practical Bayesian stepped wedge design for community-based cluster-randomized clinical trials: The British Columbia Telehealth Trial. Clin Trials 2016;13:641–50.
27. Canadian Institute Health Information. NACRS Emergency Department Visits and Length of Stay, 2017–2018 [Internet]. [cited 2020 Jul 4]. Available from: https://www.cihi.ca/en/nacrs-emergency-department-visits-and-length-of-stay-2017-2018.
28. Fiero MH, Huang S, Oren E, Bell ML. Statistical analysis and handling of missing data in cluster randomized trials: a systematic review. Trials 2016;17:72.
29. McNeish DM, Harring JR. Clustered data with small sample sizes: comparing the performance of model-based and design-based approaches. Commun Stat - Simul Comput 2017;46:855–69.
30. Mueller-Hennessen M, Lindahl B, Giannitsis E, et al. Diagnostic and prognostic implications using age- and gender-specific cut-offs for high-sensitivity cardiac troponin T - sub-analysis from the TRAPID-AMI study. Int J Cardiol 2016;209:26–33.
31. Rubini Gimenez M, Twerenbold R, Boeddinghaus J, et al. Clinical effect of sex-specific cutoff values of high-sensitivity cardiac troponin T in suspected myocardial infarction. JAMA Cardiol 2016;1:912–20.
32. Udell JA, Wang TY, Li S, et al. Clinical trial participation after myocardial infarction in a national cardiovascular data registry. JAMA 2014;312:841–3.
33. Nyström L, Andersson I, Bjurstam N, et al. Long-term effects of mammography screening: updated overview of the Swedish randomised trials. Lancet 2002;359:909–19.

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