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PROTOCOLS

DANSPOT: A Multicenter Stepped-Wedge Cluster-Randomized Trial of the Reclassification of Acute Myocardial Infarction: Rationale and Study Design

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BACKGROUND: Cardiac troponins are the preferred biomarkers for the diagnosis of acute myocardial infarction. Although sex-specific 99th percentile thresholds of troponins are recommended in international guidelines, the clinical effect of their use is poorly investigated. The DANSPOT Study (The Danish Study of Sex- and Population-Specific 99th percentile upper reference limits of Troponin) aims to evaluate the clinical effect of a prospective implementation of population- and sex-specific diagnostic thresholds of troponins into clinical practice.

METHODS: This study is a nationwide, multicenter, stepped-wedge cluster-randomized trial of the implementation of population- and sex-specific thresholds of troponins in 22 of 23 clinical centers in Denmark. We established sex-specific thresholds for 5 different troponin assays based on troponin levels in a healthy Danish reference population. Centers will sequentially cross over from current uniform manufacturer-derived thresholds to the new population- and sex-specific thresholds. The primary cohort is defined as patients with symptoms suggestive of acute coronary syndrome having at least 1 troponin measurement performed within 24 hours of arrival with a peak troponin value between the current uniform threshold and the new sex-specific female and male thresholds. The study will compare the occurrence of the primary outcome, defined as a composite of nonfatal myocardial infarction, unplanned revascularization, and all-cause mortality within 1 year, separately for men and women before and after the implementation of the new sex-specific thresholds.

CONCLUSIONS: The DANSPOT Study is expected to show the clinical effects on diagnostics, treatment, and clinical outcomes in patients with myocardial infarction of implementing sex-specific diagnostic thresholds for troponin based on a national Danish reference population.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT05336435.

Key Words: acute coronary syndrome ■ biomarkers ■ myocardial infarction ■ sex factors ■ troponin

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Nonstandard Abbreviations and Acronyms

cTnI	cardiac troponin I
cTnT	cardiac troponin T

Cardiac troponin I (cTnI) and T (cTnT) are the preferred biomarkers for the assessment of myocardial injury and the diagnosis of acute myocardial infarction (MI).[1,2] According to the Fourth Universal Definition of MI, myocardial injury is defined by any measurement of cardiac troponins (cTn) levels above the 99th percentile threshold established for a healthy reference population. The diagnosis of MI is based on the detection of a rise or fall of cTn with at least 1 value above the diagnostic threshold, in addition to clinical evidence of myocardial ischemia.[1]

Since the introduction of high-sensitivity assays of cTnI (hs-cTnI) and high-sensitivity cardiac troponin T assay, several studies have demonstrated lower thresholds of cTn among women.[3–8] This appears to be caused by sex-specific differences in cardiac muscle mass and left ventricular morphology.[9–11] On this basis, the clinical use of a uniform diagnostic threshold for cTn may lead to a systematic underdiagnosis of MI in women[12,13] and potentially an overdiagnosis of MI in men. Previous studies indicate that women with MI more often than men have unfavorable outcomes such as a higher risk of recurrent MI, subsequent disabling heart failure, and elevated short- and long-term mortality.[14–16] The poorer prognosis among women with MI may in part be related to underdiagnosis and delayed diagnosis of MI due to their lower troponin levels.

A prospective interventional study (The High-Sensitivity Troponin in the Evaluation of patients with suspected Acute Coronary Syndrome [High-STEACS] trial) investigating a single hs-cTnI assay (Abbott ARCHITECT-STAT) reported a 42% increase in women diagnosed with myocardial injury following the implementation of sex-specific diagnostic thresholds.[17] While recommended in international guidelines,[1,18,19] the clinical significance of implementing sex-specific diagnostic thresholds for cTn remains inadequately researched and lacks firm establishment. Consequently, only a limited number of nations have incorporated sex-specific thresholds,[20,21] and numerous countries, including Denmark, have hesitated to adopt these thresholds.[22] Furthermore, the most recent guidelines from the European Society of Cardiology now advocate for using uniform thresholds.[2]

Differences in the thresholds of cTn are not only sex-specific but also related to the demographic characteristics of the reference population selected.[6,23] A study of healthy participants demonstrated a significant association between cTn levels and ethnicity,[6] emphasizing the importance of a well-characterized reference population reflecting the ethnic composition in the applicable geographical area.[18] A clinical trial is needed to demonstrate whether the clinical application of population-specific thresholds of cTn alters the clinical outcomes.

Here we describe the design of DANSPOT (The Danish Study of Sex- and Population-Specific 99th percentile upper reference limits of Troponin). The study aims to determine sex-specific diagnostic thresholds of cTn based on a healthy Danish reference population and to stepwise implement these new sex-specific cTn thresholds in a nationwide cluster-randomized trial.

STUDY OBJECTIVES

The objective of the study is to evaluate the clinical effect on diagnosis, treatment, and outcomes of implementing sex-specific diagnostic thresholds of cTn based on a Danish reference population for the diagnosis of MI. Specifically, the study investigates whether:

1. Reclassification of patient diagnosis by implementing sex-specific diagnostic thresholds of cTn leads to a significantly larger proportion of women, and a correspondingly reduced proportion of men, being offered additional work-up, diagnosed with MI, or treated for MI. Additional work-up is defined as invasive coronary angiography or coronary computed tomography. Treatment for MI is defined as coronary revascularization and/or treatment with acetylsalicylic acid, other platelet inhibitors, and statins.
2. The introduction of sex-specific thresholds of cTn leads to an improved prognosis for women with MI (defined as a reduction of primary outcome events in the group of reclassified patients) defined as the incidence of MI, unplanned revascularization, or all-cause mortality within 1 year from index admission.
3. The introduction of sex-specific thresholds of cTn reduces the frequency of unnecessary invasive coronary angiographies (no significant stenosis) for men without increasing the risk of adverse outcomes.

METHODS

This is a nationwide multicenter investigator-initiated, cluster-randomized clinical trial. The authors declare that all supporting data are available within the article (and its online supplementary files).

Trial Design and Randomization

The study is performed as a cluster-randomized trial using a stepped-wedge design, with participation of 22 out of the 23 Danish medical centers managing patients with acute coronary syndrome (ACS). The study is performed as a nationwide collaboration between hospital laboratories and associated cardiology or internal medicine departments, and the study is endorsed by the Danish Society of Cardiology and the Danish Society of Clinical Biochemistry.

The units of randomization include 22 departments of clinical biochemistry throughout Denmark using high-sensitivity assays for the analysis of cTn. These departments and their associated 30 cardiology and internal medicine departments are organized as 22 administrative clusters (referred to as centers). All centers have agreed on participation before being randomized to a step-by-step sequential crossover, with a monthly start time interval. Each center is randomized to a shift from the current uniform manufacturer-derived diagnostic threshold of cTn to the new population- and sex-specific diagnostic thresholds of cTn (Figure 1). The control phase involves the months using uniform thresholds in clinical practice, while the intervention phase involves the months using the new sex-specific thresholds in clinical practice. All patients are followed in the following Danish registries for 12 months after discharge from their index admission: the Danish National Patient Register, the Danish Heart Register, and the Danish Register of Medicinal Product Statistics.

Given the design of our study, which spans a 12-month follow-up period, limited preliminary results are available before the conclusion of the inclusion period. Consequently, establishing a safety monitoring board has not been deemed relevant, because it would have minimal data to analyze until most trial centers are included, and the inclusion period approaches its conclusion.

Implementation

Ahead of the implementation of the new diagnostic thresholds of cTn, contact persons representing all included departments of cardiology and clinical biochemistry have been informed of the rationale and plan for the implementation. An implementation meeting between cardiologists and clinical biochemists from each center is held with a DANSPOT study investigator 1 month before the implementation of the new sex-specific thresholds. Centers are provided with a standardized newsletter and presentation

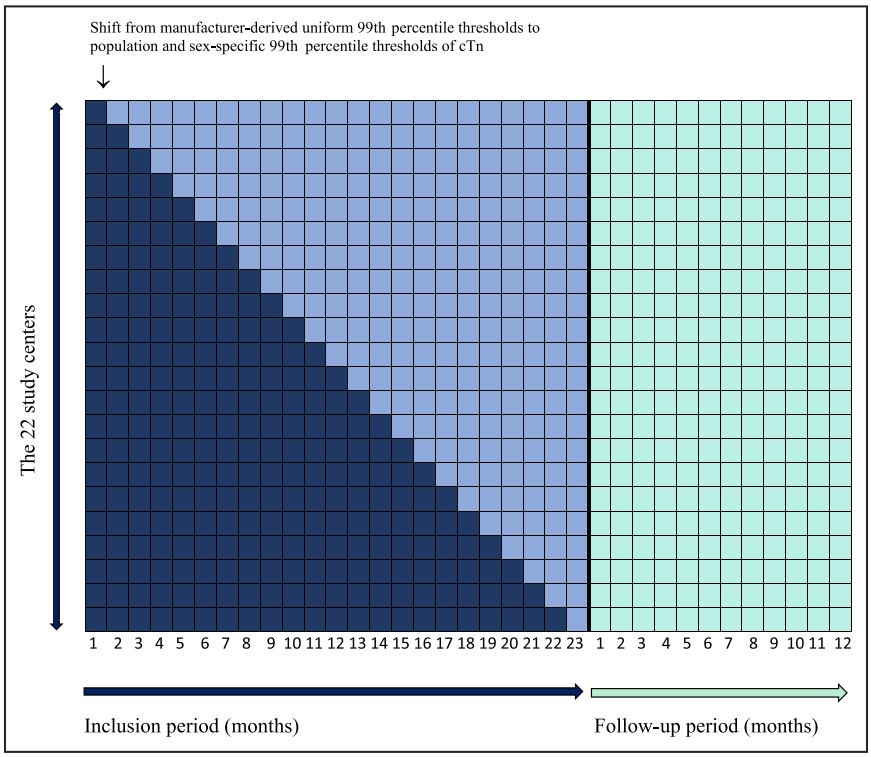


Figure 1. Study design of the DANSPOT trial, a nationwide implementation of population- and sex-specific diagnostic thresholds of cardiac troponin using a stepped-wedge design.
With a monthly start interval, each center implements the new population- and sex-specific diagnostic thresholds. After discharge from index admission, patients are followed individually for 12 months. cTn indicates cardiac troponin.

slides on the study to further inform relevant clinical departments locally. Study investigators oversee the project management and ensure laboratories change to the new diagnostic thresholds of cTn in the laboratory system at the time of implementation, and that all relevant departments are informed by the cardiologists and clinical biochemists. In all cases, the population- and sex-specific diagnostic thresholds are ensured to be stated in the clinically applied laboratory reporting system, visible, and accessible to all clinical personnel.

Timeline

The implementation of the new sex-specific diagnostic thresholds started at the first center on April 1, 2022. The estimated duration of the project is 3 years, encompassing 23 months of inclusion of centers and 12 months of follow-up of patients (Figure 2). The data covering the initial month following the implementation of the new thresholds will be excluded from the study, because it will be seen as an adjustment period for each center. Consequently, the inclusion period will be extended by 1 month. Thus, the inclusion period will finish by February 29, 2024. The first results from the study are expected by mid-2025.

Inclusion Criteria for Patients

Although the new sex-specific diagnostic thresholds apply to all patients admitted at the included centers, only a selected cohort of patients are of interest for the study. During the inclusion period, all patients (≥18 years of age) presenting to an emergency or coronary department will be eligible for inclusion in a screening database if they have had a minimum of 1 measurement of cTn. In cases of multiple admissions of the same patient during the inclusion period, only the first study-eligible (index) admission will be included, while subsequent admissions are only evaluated in follow-up analyses. Patients are only included if they are residents in Denmark, defined by a permanent Civil Personal Registration number. From this screening database, the primary cohort for analysis will be identified (Figure 3).

Primary Cohort

The primary cohort will include the women and men who are expected to be most significantly impacted by the intervention, and these patients are specifically defined by (1) presenting complaints or emergency department (ED) diagnosis suggestive of ACS, (2) at least 1 cTn measurement within 24 hours of admission, and (3) a peak cTn value between the assay-specific current uniform diagnostic threshold and the new sex-and population-specific diagnostic thresholds for women and men separately (Figure 3). Presenting complaints or emergency department diagnosis codes suggestive of ACS will be identified in patients' records by the following *International Classification of Diseases, Tenth Revision*. codes; "chest pain" (R074), "angina pectoris" (I20), "observation due to suspicion of myocardial infarction" (Z034), "myocardial infarction" (I21), "abdominal and pelvic pain" (R10), "pain in the throat and chest" (R07), "dyspnea" (R060), "reflux" (K21) and "observation due to suspicion of another cardiovascular disorder" (Z035). We included a wide range of presenting complaints/emergency department diagnoses to increase the possibility of detecting type 2 infarction, and women with myocardial ischemia, accounting for the possibility of these women experiencing a range of symptoms beyond chest pain, which increases the likelihood of misdiagnosis.

Patients will be excluded from the primary cohort if they are discharged from their index admission with any of the following diagnoses: pericarditis, myocarditis, endocarditis, cardiomyopathy, valve disease, arrhythmia, heart failure, pulmonary embolism, digestive system diseases excluding reflux, diseases of the urinary and reproductive organs, and diseases of bones, muscles, and connective tissue, and do not have a discharge diagnosis of MI or angina pectoris.

The primary cohort is further divided into a group of women potentially reclassified from no-MI to MI and a group of men reclassified from MI to no-MI. These will be analyzed separately to assess (1) the superiority of the new female diagnostic threshold, and (2) the safety of the new male diagnostic threshold in a noninferiority analysis.

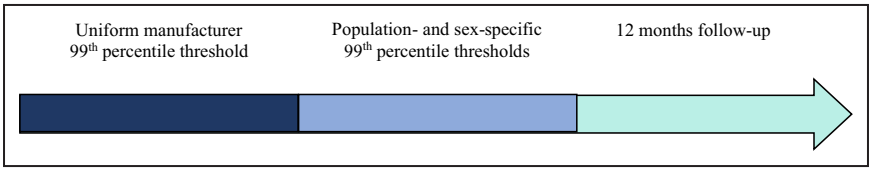


Figure 2. Implementation of population- and sex-specific diagnostic thresholds.
Each center uses the uniform manufacturer-derived threshold and is randomized to implement the new population- and sex-specific thresholds during the inclusion period. Patients will individually be followed for 12 months after discharge from index admission.

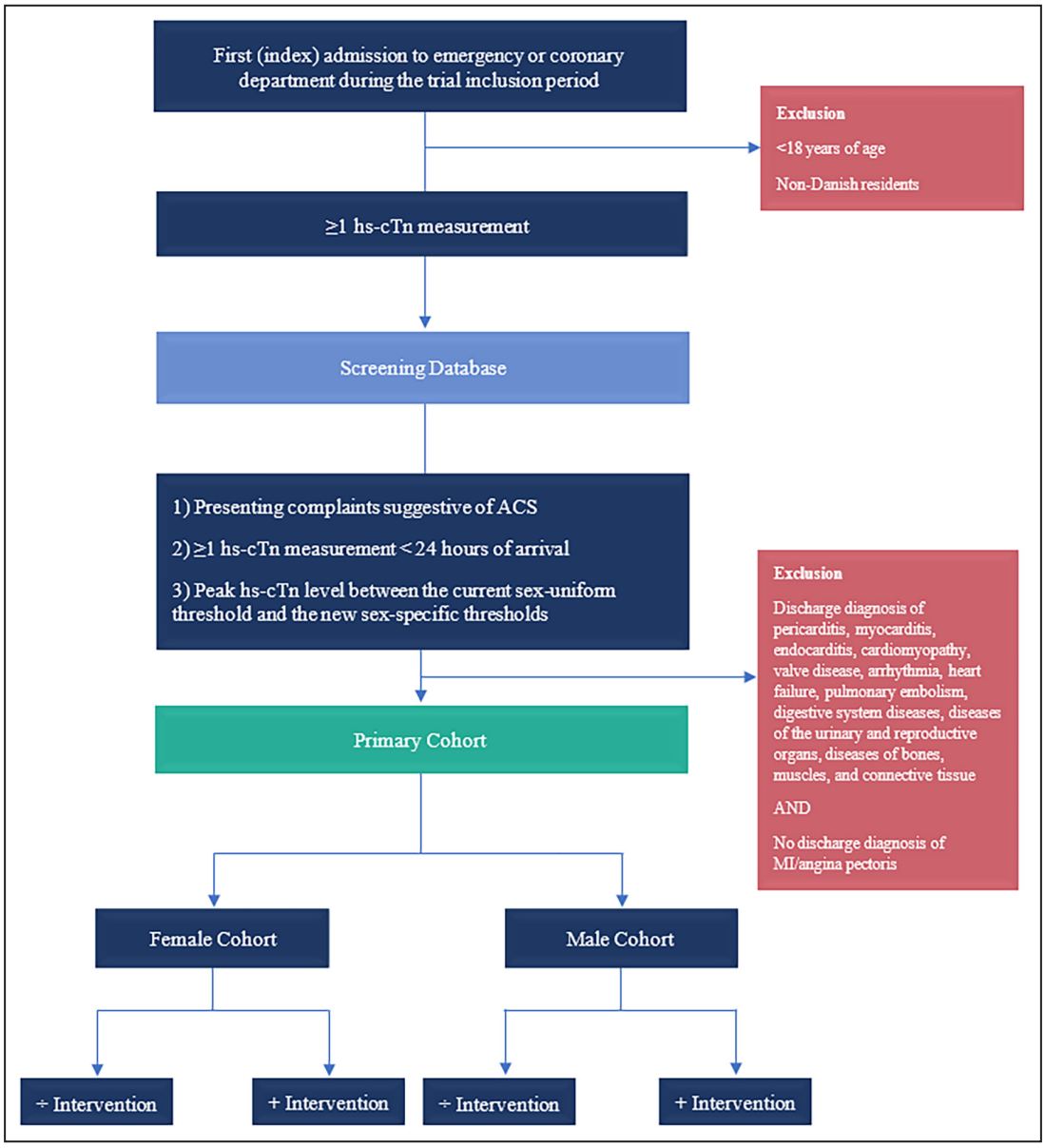


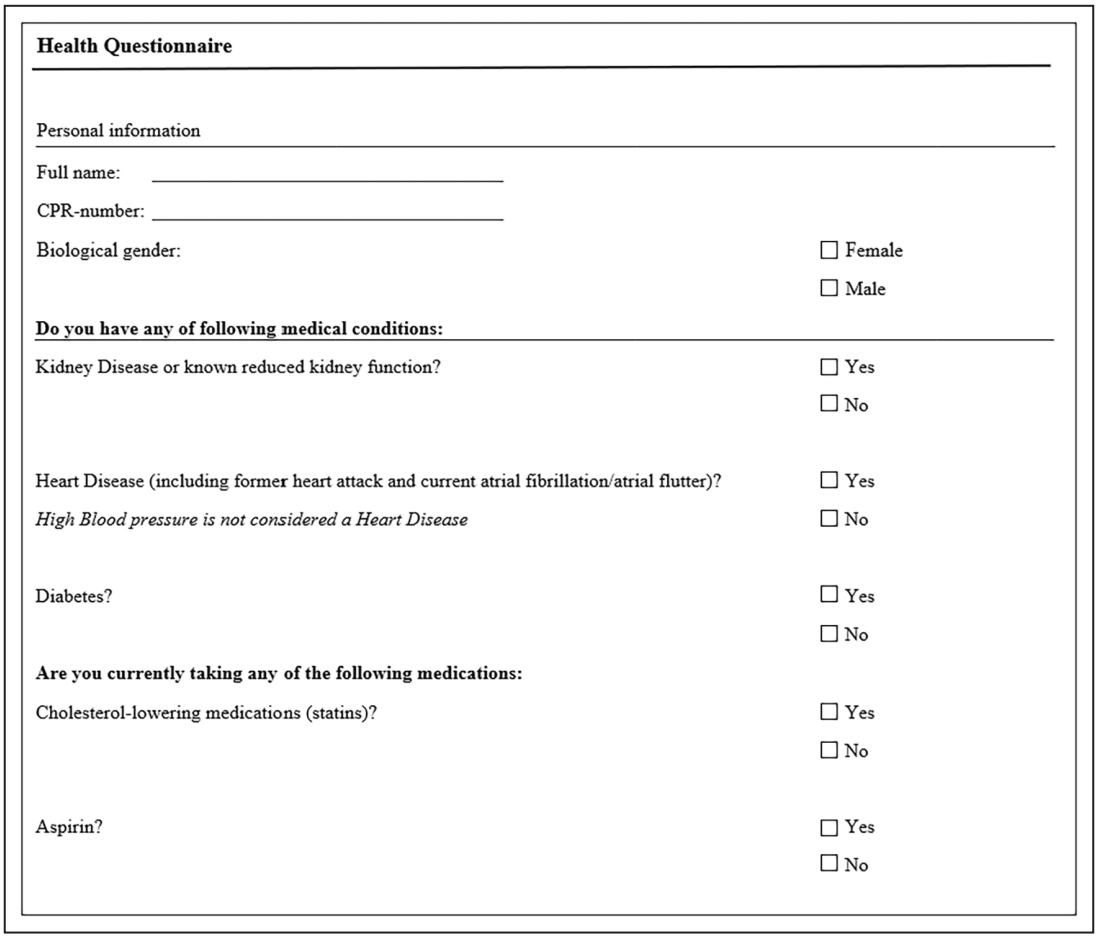
Figure 3. Flowchart for the selection of the primary cohort for analysis. Current uniform threshold and new sex-specific thresholds are assay-specific for each center.
ACS indicates acute coronary syndrome; Hs-cTn, high-sensitivity cardiac troponin assay; and MI, myocardial infarction.

Biobank

For the determination of sex-specific diagnostic thresholds of cTn based on a healthy Danish reference population, a central biobank of blood samples was established. For this purpose, blood samples were collected in the latter part of 2021 from healthy Danish active and former blood donors, stratified by age and sex.

An invitation letter was sent to potential participants by a secure nationwide digital postbox (e-Boks). Upon registration, participants were screened with a simple health questionnaire (Figure 4), in concordance with the recommendation of the use of a questionnaire to exclude cardiovascular comorbidities and medications.[24] Exclusion criteria were any history of heart disease, kidney disease, or diabetes as well as use of statins or acetylsalicylic acid. The recruitment of participants for the establishment of the biobank was initiated in collaboration with The Danish Blood Donor Study.[25] Participants were recruited from the Capital Region of Denmark and Region Zealand.

We aimed to include a total of 2000 participants (1000 women and 1000 men) for the establishment of the biobank, equally distributed within 4 predefined



Health Questionnaire

Personal information

Full name: _____

CPR-number: _____

Biological gender: ☐ Female ☐ Male

Do you have any of following medical conditions:

Kidney Disease or known reduced kidney function? ☐ Yes ☐ No

Heart Disease (including former heart attack and current atrial fibrillation/atrial flutter)? ☐ Yes ☐ No

High Blood pressure is not considered a Heart Disease

Diabetes? ☐ Yes ☐ No

Are you currently taking any of the following medications:

Cholesterol-lowering medications (statins)? ☐ Yes ☐ No

Aspirin? ☐ Yes ☐ No

Figure 4. A health questionnaire was filled out electronically for each participant at registration by a study employee in cooperation with the participant.
Data were stored in the secured web database Research Electronic Data Capture (REDcap).

age groups: 18 to 50, 50 to 59, 60 to 69, and ≥70 years of age, to cover a reference population representative of the general Danish population. Guidelines by the The International Federation of Clinical Chemistry Committee (IFCC)/Academy of the American Association for Clinical Chemistry (AACC) Academy recommend the use of at least 400 healthy men and 400 healthy women to appropriately define a threshold of cTn for each sex. Also, the use of a reference population including a distribution of individuals ≥18 years of age is recommended,[18,24,26,27] because the exclusion of younger individuals, who constitute a smaller proportion of patients with MI, may introduce bias, potentially leading to an upward shift in the 99th percentile threshold.[6,8,23,28]

Blood samples were immediately screened for indications of undiagnosed heart disease, diabetes, and renal disease using guideline-recommended surrogate biomarkers N-terminal pro-B natriuretic peptide, hemoglobin A1c, and estimated glomerular filtration rate. N-terminal pro-B natriuretic peptide was analyzed on Siemens Atellica IM, while hemoglobin A1c and creatinine for the calculation of estimated glomerular filtration rate were analyzed on Siemens Atellica CH 930. Only participants who met the following criteria for these biomarkers were included in the reference population: N-terminal pro-B natriuretic peptide for age <75 years <125 ng/L, for age ≥75 years <450 ng/L, hemoglobin A1c <6.5%, and estimated glomerular filtration rate ≥90 mL/min per 1.73 m^2.

Using standard hospital procedure, blood (48 mL in total) was sampled from a cubital vein and collected in 3 different tubes containing either an anticoagulant (lithium-heparin or K-EDTA) or a serum separator gel and clot activator. One sample was sent for immediate testing of cTn using the Siemens Atellica hs-cTnI assay, as well as testing for the previously mentioned surrogate biomarkers. All other samples were centrifuged at 3000 relative centrifugal force for 10 minutes at 20 °C, aliquoted into cryotubes, and then stored at −80 °C until analysis. A set of frozen lithium-heparin

plasma samples was subsequently sent to representative clinical biochemistry laboratories for local analyses of cTn using the remaining cTn assays.

Troponin Assays

At present, 6 different hs-cTn assays are being used in Denmark of which 5 assays cover all but 1 hospital, which was not included in the trial. The population- and sex-specific thresholds were determined using local analysis by each of the following assays: Siemens Atellica hs-cTnI assay, Siemens Dimension Vista hs-cTnI assay (Siemens Healthineers, Tarrytown, USA), Roche Diagnostics Elecsys 2010 cTnT assay (Roche Diagnostics, Rotkreuz, Switzerland), Abbott Alinity ARCHITECT STAT hs-cTnI assay (Abbott, Chicago, USA), and Ortho Clinical Diagnostics VITROS hs-cTnI. A comprehensive presentation of both manufacturer-derived thresholds and the newly established population- and sex-specific thresholds can be found in Table S1. Additionally, coefficients of variation for each assay are provided in Table S2 for reference.

Ethics

The study is in accordance with the ethical standards of the Declaration of Helsinki. The biobank was approved by the Danish Ethics Committee (Number: SJ-740) and all participants gave written informed consent to participate.

Because the implementation of sex-specific thresholds of cTn, based on a healthy Danish reference population, was within former clinical recommendations[29] at study start, the local ethics committee waived the need for formal approval and patient consent (FSP 20067240).

Outcomes

The primary outcome is a composite of (1) readmission for nonfatal MI, (2) unplanned coronary revascularization, and (3) all-cause mortality within 12 months following discharge from the index admission. We will compare the occurrence of the primary outcome separately for men and women in the primary cohort before and after the implementation of the new population- and sex-specific diagnostic thresholds.

Individuals included in the primary cohort will have any readmission within their 12 months follow-up period adjudicated by an end point committee to detect any diagnosis of type 1 or type 4b MI, and type 2 MI, except for those who have already received a diagnosis of type 1 MI and have undergone coronary revascularization, as confirmed by *ICD* codes. For the diagnosis of type 2 infarctions, we will utilize the criteria established by Saaby et al.[30] The end point committee will comprise 2 cardiologists in each of the 5 regions in Denmark. Two cardiologists will review the patient records independently, and a third cardiologist will be consulted if there are any uncertainties or disagreements. Unplanned coronary revascularization and all-cause mortality will be identified in either the patient records or the Danish registries. Unplanned coronary revascularization is defined as any percutaneous coronary intervention or coronary artery bypass grafting performed after discharge from the index admission, without the patient having undergone a coronary angiography during index admission.

Secondary outcomes will also be investigated for the primary cohort and will be identified from adjudication (diagnosis of MI) and from the Danish registries. They include the number of men and women diagnosed with myocardial injury and MI, the number of coronary angiographies or coronary computed tomographies without revascularization, the number of coronary revascularizations (percutaneous coronary intervention and coronary artery bypass grafting), the number of unplanned revascularizations separately, treatment with acetylsalicylic acid, other platelet inhibitors and statins, readmission within 12 months, admission length, and all-cause mortality separately.

STATISTICAL ANALYSIS

Calculation of the New Thresholds

The new population- and sex-specific diagnostic thresholds of cTn were calculated at the outset of 2022 using nonparametric methods as endorsed by the International Federation of Clinical Chemistry and Laboratory Medicine Task Force on Clinical Applications of Bio-Markers.[18,26] Outliers were excluded based on 2 methods: (1) participants with 1 cTn assay value at least 1.5 times the manufacturer-derived threshold but all other assay values below the threshold provided by their manufacturer will be excluded as an analytical outlier, and (2) the criteria of Reed-Dixon.[31,32] To minimize the risk of outliers stemming from undetected cardiac issues and analytical interference, we rigorously selected participants in our healthy reference population. This involved using questionnaires, screening with surrogate biomarkers, and excluding individuals suspected of analytical interference. To ensure a conservative approach, we opted for the Reed-Dixon method, as recommended in recent guidelines.[18]

The details of the method and results of calculating the population- and sex-specific diagnostic thresholds used for this trial will be described separately in another publication.

Power Calculation

The process of calculating statistical power was conducted while accounting for clustering effects. We have

conducted the power calculations through simulations, which included small differences in risk between sites, which effectively corresponds to introducing a non-zero intracluster correlation coefficient. Note, however, that the sample calculation is not done simply by an inflation factor relative to a 1:1 randomized study. The simulation-based approach provides a more detailed power calculation because it does not depend on any mathematical approximations.

Based on data from the Danish Heart Foundation, ≈2500 women and 5000 men are diagnosed yearly with MI in Denmark.[33] With an estimated 20% of patients with suspected ACS having an MI, this would correspond to ≈12 500 ACS admissions for women and 25 000 for men a year across the 22 clusters. Based on registry data,[22] we expect ≈8% of these will fulfill the criteria for inclusion in the primary cohort. This results in a primary cohort of ≈1000 women a year and a full cohort of ≈1900 women during the inclusion period of 23 months ((2500*5*0.08/12)*23=1916). With a cohort this size and an estimated rate of the primary outcome of 15% (High-STEACS), we will have a power of 81% to find a difference between 15% and 8.1%. About 3800 men are expected to be included in the primary cohort. With a cohort this size and an expected event rate of the primary outcome of 15%, we will have a power of 81% to detect a noninferiority margin of 0.45 for the men, giving a risk difference between 15% and 21.7%.

Data Analyses

The data will be analyzed with logistic regression with additive effects (ie, main effects) of clusters, time period, and treatment status. This follows standard practice for step-wedge designs and will yield an estimate of effect similar in interpretation to what would have been achieved in a regular 1:1 randomized trial. Accordingly, the estimate and its corresponding confidence interval can be used to assess noninferiority as in a regular trial.

DISCUSSION

Cardiac troponins are considered the criterion standard biomarkers for the diagnosis of MI. Although recommended in international clinical guidelines, the use of sex-specific thresholds of cTn has not been implemented in many countries, including Denmark.[22] Previous studies have demonstrated significantly lower cTn levels in healthy women as compared with healthy men,[3,5–7] but clinical outcomes related to the use of sex-specific thresholds of cTn have not been fully investigated. With this study, we aim to determine the clinical significance of implementing sex-specific diagnostic thresholds of cTn based on a national reference population of healthy Danish blood donors, systematically determined according to the IFCC/AACC Academy Guidelines.

The design of the study has several strengths. First, 22 out of 23 hospitals in Denmark eligible for participation (ie, managing patients suspected of ACS) are enrolled in the study. Only 1 hospital is not participating, due to economic and practical reasons (catchment area of 39 545 citizens[34]). Using the Danish registries, we can identify patients admitted with suspected ACS to this hospital during the study period, allowing for more transparency. Thus, we include almost the entire Danish population (N=5.8 million) and avoid selection bias. Also, the use of a stepped-wedge design with enrollment during 23 months allows for a controlled sequential implementation limiting potential seasonal variation biases.[35]

As previously described, the thresholds of cTn depend on the reference population selected. The variation seen in several studies reporting thresholds of cTn is believed to be related to the differences in population characteristics (ie sex, age, and ethnicity) due to the sensitivity given by the 99th percentile threshold.[5,6,23] In this study the determination of the new sex-specific thresholds of cTn are based on 1 well-characterized and representative Danish reference population. Also, a previous study demonstrated variation in sex-specific thresholds of cTn across 9 hs-cTnI and 3 high-sensitivity cardiac troponin T assays using a universal sample bank.[3] This variation may, in part, be attributed to assay-specific analytical variation and/or interference. In our study, we had the advantage of analyzing all samples using 4 different cTn assays initially, enabling us to compare cTn levels across assays and to exclude participants displaying the presence of evident analytical interference.

The study also has limitations. We acknowledge that volunteering blood donors included in the healthy reference population may represent a healthier group of individuals than the general population and may not directly reflect the entire Danish population. To counter this, we chose to increase the size of our biobank beyond the size of the recommended reference material. Additionally, we screened participants for recommended surrogate biomarkers and self-reported health with the use of a simple health questionnaire. No further clinical examinations such as ECGs or imaging modalities were performed. The use of such clinical examinations could potentially lead to lower thresholds of cTn.[12] However, using such screening modalities for participant selection could potentially lead to the selection of a reference population unrepresentative of the general population.

An additional limitation could stem from the recent European Society of Cardiology (ESC) recommendations regarding the adoption of 0/1h and 0/2h algorithms.[2] Presently, most Danish centers adhere

to the ESC 0/3 h algorithm. Among the 30 hospitals included (organized into 22 clusters/centers), 3 hospitals use the ESC 0/2h algorithm. One center has further tailored the 0/2h algorithm by incorporating a sex-specific approach, adjusting the rule-in threshold to align with the updated sex-specific thresholds of cTn. The remaining 2 centers adhere to the ESC-recommended assay-specific rule-in and rule-out thresholds. The Danish Society of Cardiology is presently evaluating the 2023 ESC guideline recommendations concerning the adoption of 0/1h and 0/2h algorithms. However, the endorsement will not be concluded within the inclusion period of this trial. How these algorithms will be integrated into Danish centers remains uncertain. The choice lies between implementing the uniform ESC-recommended rule-in and rule-out thresholds or using a sex-specific adjusted rule-in threshold. This decision may significantly impact the study results. Utilizing uniform thresholds in the algorithms could potentially result in the oversight of nonfatal MI cases among women during the follow-up period and consequently underestimate the primary outcome.

Furthermore, the adjudication of the MI diagnosis cannot be fully blinded for the end point committee members. The implementation of the new sex-specific diagnostic thresholds of cTn is apparent in the laboratory system, visible to all health care professionals at the medical center. Additionally, health care professionals are informed of this transition through a newsletter notification. To accommodate this, members of the end point committee in 1 region of Denmark will adjudicate patient records in another region without direct knowledge of the implementation dates of centers in that specific region.

Moreover, we recognize that the incorporation of the Beckman Coulter assay would have added robustness to our study by encompassing all major troponin platforms. Regrettably, the trial site in Denmark, which exclusively uses the Beckman Coulter assay, was unable to participate in the study. Even if inclusion had been feasible, the limited catchment area of this site might not have yielded enough data to comprehensively assess the clinical impact. The High-STEACS trial (N=48 282) evaluated the clinical effect of introducing sex-specific thresholds for a hs-cTnI assay on the primary outcome of MI and cardiovascular death within 1 year in patients with ACS and found no improvement in clinical outcomes.[36] However, the trial was designed to evaluate both the implementation of a high-sensitivity assay over a contemporary sensitivity assay and the effect of sex-specific thresholds. Notably, women remained less likely to receive treatment for MI than men, which may have contributed to the null finding for improvement in clinical outcomes among women. Furthermore, the trial only evaluated a single hs-cTnI assay (Abbott ARCHITECT STAT hs-cTnI), and the sex-specific thresholds were based on those recommended by the manufacturers and not on a local reference population.

Studies have found that women experiencing MI are less likely to receive examination, treatment, and intervention and have worse outcomes than men.[15,16] Proper diagnostic accuracy is crucial to allow for further assessment and appropriate treatment. The use of a uniform diagnostic threshold has been suggested as a potential factor contributing to the underdiagnosis and undertreatment of women with MI.[37] The implementation of sex-specific thresholds is expected to reclassify and increase the number of MI diagnoses in women. Likely, this sex-differentiated approach will result in more women receiving the necessary examinations (ie, coronary angiography or coronary computed tomography) and the appropriate treatment in the form of either revascularization and/or life-long prophylactic treatment.

In conclusion, we expect that the introduction of sex-specific diagnostic thresholds can improve diagnostic accuracy and thereby improve clinical outcomes among women with MI. At the same time, we expect to reduce the proportion of overdiagnosed men, likely reducing the number of unnecessary examinations and treatments. The choice of outcomes for the study will enable us to evaluate such clinical effects.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Tables S1–S2.
Reference [39].

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