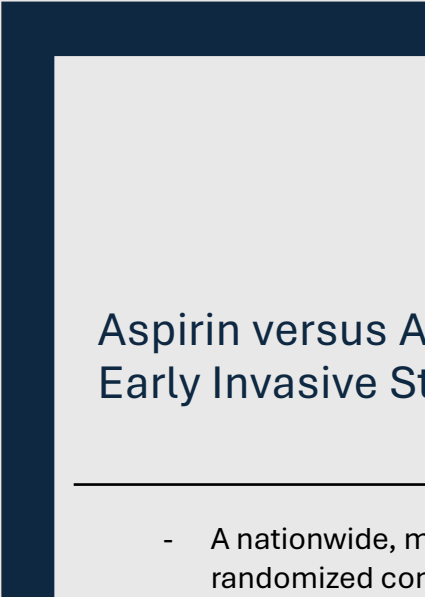




Aspirin versus Aspirin and Fondaparinux Prior to Early Invasive Strategy in Patients with NSTEMI

- A nationwide, multicenter, open-label, non-inferiority, randomized controlled trial

FOXY-TRIAL

Protocol Version 2.0.3

20.08.2026



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1. Administrative Information

Title

Aspirin versus Aspirin and Fondaparinux Prior to Early Invasive Strategy in Patients with NSTEMI
- A Nationwide, Multicenter, Open-label, Non-Inferiority, Randomized Controlled Trial.

Acronym: FOXY-trial

Trial registration

Registries:

EU Trial number: 2024-517229-18-00

ClinicalTrials.gov ID: NCT06710184

Protocol version

Current protocol is Version 2.0.3, finalized on 20.08.2026

Funding

Currently not fully funded. Has received funding of 1.076.073 DKK from Regionernes Medicin-
og Behandlingspulje together with internal funding of 2.000.000 DKK

Roles and responsibilities

Protocol Contributors:

Christian Byskov Fur, MD, Department of Cardiology, Aarhus University Hospital

Christian Juhl Terkelsen, MD, DmSC, PhD, Department of Cardiology, Aarhus University
Hospital

Jens Flensted Lassen, MD, PhD, Department of Cardiology, Odense University Hospital

Niels Thue Olsen, MD, PhD, Department of Cardiology, Rigshospitalet

Ashkan Eftekhari, MD, Department of Cardiology, Aalborg University Hospital

Carsten Stengaard, MD, PhD, Department of Cardiology, Aarhus University Hospital

Trial sponsor

Prof. Christian Juhl Terkelsen, MD, PhD, DmSc
Department of Cardiology, Aarhus University Hospital
Palle Juul-Jensens Boulevard 99

Role of study sponsor and funders

The sponsor will be responsible for the REDCap/Corolog data base, collecting data, monitoring the study, coordination of meetings for the Steering Committee, Endpoints Adjudication Committee and Safety Committees.

Funding parties to this study have no participation or authority over the designing of the study. Funding parties will not participate in the management, analysis or interpretation of the data. Funding parties will not be involved in the process of writing or publication the report.

Composition, roles and responsibilities of:

1. Coordinating Centre:

The coordinating center will be Aarhus University Hospital. The compositions will be of the following:

- Sponsor Investigator:
 - Prof. Christian Juhl Terkelsen, MD, PhD, DmSc
- Coordinating Investigator:
 - Christian Byskov Fur, MD
- Support Staff:
 - Study nurse, Statisticians, sub-investigators

Roles and Responsibilities:

The sponsor and coordinating investigators are responsible for overseeing the overall conduction of the study and to ensure protocol adherence among all the trial sites. They will facilitate the communication among the trial sites and provide support for data management and collection if necessary.

The study nurse and sub-investigators will be responsible for the recruiting and enrollment of patients together with collecting and entering of data. Statisticians will provide support in the statistical analysis and interpretation of data.

2. Clinical Trial sites:

All cardiology departments or emergency departments with admission of patients with Non-ST-Elevation Myocardial Infarction (NSTEMI). Below are the current principal investigators for each trial site.

Trial site	Principal Investigator
Aarhus University Hospital, Department of Cardiology (coordinating invasive center)	Sponsor Investigator: Proff. Christian Juhl Terkelsen, MD, Dmsc, PhD
	Coordinating Investigator: Christian Byskov Fur, MD
Aalborg University Hospital, Department of Cardiology (invasive center)	Ass. Proff. Ashkan Eftekhari, MD, PhD.

Rigshospital, Department of Cardiology (Invasive Center)	Ass. Proff. Niels Thue Olsen, MD, PhD
Odense University Hospital, Department of Cardiology (Invasive Center)	Proff. Jens Flensted Lassen, MD, PhD
Regionshospital Randers, Department of Medicine Cardiology	Bo Løfgren, MD, PhD
Gødstrup Hospital, Department of Cardiology	Morten Würtz, MD, PhD
Regionshospital Viborg, Department of Cardiology	Hanne Maare Søndergaard, MD, PhD
Sygehus Sønderjylland, Department of Cardiology	Ghassan Jadou, MD
Sygehus lillebælt, Vejle, Department of Cardiology	Dilek Hunerel Alan, MD
Esbjerg Hospital, Department of Cardiology	Christian Oliver Fallesen, MD, PhD
Sygehus lillebælt, Kolding, Department of Cardiology	Remmon R Leo Francis Washington, MD
Regionshospital Horsens, Department of Cardiology	Claus Kjær Pedersen, MD, PhD
Hospital Herlev-Gentofte, Department of Cardiology	Kristian Eskesen, MD, PhD
Bispebjerg Hospital, Department of Cardiology	Gorm Mørk, MD, PhD
Svendborg Hospital, Department of Medicine I Cardiology	Proff. Jens Lambrechtshen, MD, PhD
Hillerød Hospital, Department of Cardiology	Charlotte Kragelund, MD, PhD
Hjørring Hospital, Department of Cardiology	Peter Bisgaard Stæhr, MD, PhD
Hvidovre Hospital, Department of Cardiology	Jens Dahlgaard Hove, MD, PhD

Support Staff:

Study nurse, Sub-investigators

Roles and Responsibilities:

Each principal investigator is responsible for the conduction of trial at their respective trial site. Sub-investigators will be responsible for the recruiting and enrollment of patients together with collecting and entering of data. A study nurse assigned to each invasive center will be responsible for collecting and entering data for their respective region.

3. Steering committee

The Steering committee comprise the principal investigator, the senior investigators from the sponsoring site, and one co-investigator from each invasive center participating in the study. All non-invasive centers will be invited to join the steering committee.

Roles and Responsibilities:

The steering committee will be responsible for the overall supervision of the trial. The committee will periodically review the progress of the study and assess the safety data. The Steering Committee will convene prior to the start of the study and subsequently after the inclusion of the first 1,500 patients to assess the report on safety data from the Data Safety Monitoring Board (DSMB)

The overall responsibilities include:

- Ensuring adherence to the study protocol
- Overseeing the trial's progress and providing guidance as needed
- Evaluating safety data.

The steering committee will have the authority to prematurely terminate the trial if it is deemed necessary for safety or ethical reasons.

4. Endpoint adjudication committee

An endpoint adjudication committee (EAC) will be established with members not participating in the study conduct. The members of this committee are yet to be determined.

Roles and responsibilities:

They will adjudicate the below selected endpoints:

- Refractory ischemia resulting in acute CAG before scheduled
- Stroke
- TCI
- Myocardial infarction
- Bleeding (Bleeding Academic Research Consortium (BARC) ≥ 3)¹
- Thrombolysis In Myocardial Infarction (TIMI) flow

5. Data Safety Monitoring Board (DSMB)

An independent DSMB with no involvement of the day-to-day activities or financial interest in the conduct of the study. The DSMB comprises of two cardiologists, an epidemiologist and a statistician.

Roles and responsibilities:

The primary role of the DSMB is to ensure the safety of the patients and the validity and integrity of the data.

Time Schedule:

Patient enrollment is expected to start in March 2025. The trial is expected to run for 3.5 years. The follow-up period for primary endpoints will end 30 days after enrollment of the last patient. We expect at publication of the primary endpoints in 2029. Longtime follow-up will result in further publications later on.

¹ See table 5 in Appendix for BARC definitions.

The trial will be conducted in compliance with the protocol, with the Regulation and with the principles of good clinical practice.

2. Abbreviation list

Abbreviation	Full Term
ACS	Acute Coronary Syndrome
ADP	Adenosine Diphosphate
AHA	American Heart Association
APPT	Activated Partial Thromboplastin Time
BARC	Bleeding Academic Research Consortium
CABG	Coronary Artery Bypass Grafting
CAG	Coronary Angiography
CPR	Civil registration number (Det Centrale Personregister)
CT	Computed Tomography
cTN	Cardiac Troponin
DKMA	Danish Medicines Agency
DOAC	Direct Oral Anticoagulant
DMC	Data Monitoring Committee
DSC	Danish Society of Cardiology
DSMB	Data Safety Monitoring Board
EAC	Endpoint Adjudication Committee
ECG	Electrocardiogram
eGFR	Estimated Glomerular Filtration Rate
ESC	European Society of Cardiology
GDPR	General Data Protection Regulation
GCP	Good Clinical Practice
IMP	Investigational Medicinal Product
INR	International Normalized Ratio
LVEF	Left Ventricular Ejection Fraction
LMWH	Low Molecular Weight Heparin
MI	Myocardial Infarction
NSTEMI	Non-ST-Elevation Myocardial Infarction
NSTEACS	Non-ST-Elevation Acute Coronary Syndrome
OR	Odds Ratio
PCI	Percutaneous Coronary Intervention
RCT	Randomized Controlled Trial

REDCap	An electronic Case Report Form (eCRF)
Corolog	An electronic Case Report Form (eCRF)
STEMI	ST-Elevation Myocardial infarction
SUAE	Suspected Unexpected Adverse Event
TIA	Transient Ischemic Attack
TIMI	Trombolysis In Myocardial Infarction
UFH	Unfractionated Heparin
UAP	Unstable Angina Pectoris
VMK	Medical Ethics Committee (Videnskabsetisk Medicinske Komité)

3. Introduction

Background and Rationale

Background

The current guidelines from European Society of Cardiology (2023) (ESC) and American Heart Association (2014) (AHA) provide a Class-I recommendation for the administration of aspirin together with an anticoagulant in the immediate treatment of Non-ST-Elevation Myocardial Infarction (NSTEMI) (1, 2). For patients scheduled for coronary angiography (CAG) within 24 hours, the recommendation is to initiate unfractionated heparin (UFH) bolus of 70-100 U/kg followed by an adjustable infusion until an activated partial thromboplastin time (APPT) of 60-80 seconds (1). Patients not planned for CAG within 24 hours are recommended to be treated with fondaparinux 2.5 mg subcutaneous (s.c.) once a day until potential revascularization with percutaneous coronary intervention (PCI) or discharge(1). According to the clinical guidelines from Danish Society of Cardiology (DSC), fondaparinux is recommended as the first choice for all patients with NSTEMI in Denmark, and heparin is rarely used on this indication (3).

A plaque rupture in NSTEMI results not only in the activation of platelets but also in the activation of the coagulation cascade through exposure of tissue factor in the extrinsic pathway (4, 5). This cascade leads to activation of Factor VII and X, which cleave prothrombin to thrombin. Thrombin then converts fibrinogen to fibrin, leading to thrombus formation (6). Fondaparinux, a synthetic pentasaccharid, directly binds to and enhances the effect of antithrombin, specifically inhibiting activated factor X disrupting the coagulative cascade (7–12)(7). Fondaparinux has a half-life of about 17 hours, compared to just 1.5 hours for UFH (8). This makes the administration and monitoring of UFH treatment substantially more difficult and time-consuming compared to treatment with fondaparinux.

The evidence behind the Class-I recommendation for anticoagulant treatment in patients with NSTEMI is based on two meta-analyses: Oler et al. (1996) and Eikelboom et al. (2000) (9, 10). The meta-analysis from Oler et al. included six studies that investigated the effect of combination therapy with aspirin and heparin compared with aspirin alone in patients with Non-ST-elevation Acute Coronary Syndrome (NSTEMI), comprising unstable angina pectoris (UAP) and Non-ST-Elevation Myocardial Infarction (NSTEMI). The study showed no statistically significant reduction in the relative risk (RR) = 0.67 (95% CI 0.44-1.02) for new myocardial

infarction (MI) or death. However, the results indicated a trend towards a potential positive effect of the combination treatment with both heparin and aspirin (9).

The indication of a possibly positive effect of combination treatment with both aspirin and anticoagulants was further strengthened with the publication of the FRISC I study (1996), which included 1506 patients with NSTEMI. This was twice as many patients as in all the studies included in the meta-analysis by Oler et al. The patients in the FRISC I study were randomized to treatment with either aspirin and placebo or aspirin and dalteparin (low molecular weight heparin [LMWH]). The primary endpoint was the occurrence of death or new MI within 6 days. The results showed a significant reduction in the primary endpoint, with an odds ratio (OR) of 0.37 (95% CI 0.20-0.68, $p = 0.001$) (11).

Eikelboom et al. (2000) expanded the meta-analysis by Oler et al. to include the FRISC-I study. The expanded meta-analysis demonstrated a statistically significant OR of 0.53 (95% CI 0.38-0.73, $p < 0.001$) in favor of combination therapy compared to aspirin alone when considering death and new MI in patients with NSTEMI (10). The meta-analysis also compared UFH to LMWH and did not demonstrate a difference in treatment efficacy. However, treatment with LMWH was associated with an increased risk of severe bleeding when the treatment exceeded seven days (10).

It's important to note that these studies were conducted at a time when invasive evaluation with CAG was not routinely performed in patients with NSTEMI. For instance, the FRISC-I study showed that the total number of revascularizations after 6 days amounted to 0.8 % and this was due to intractable angina despite relevant medication (11).

Early invasive evaluation in patients with NSTEMI was only introduced after 1999. A cornerstone of this change was the FRISC-II study (1999), which investigated the effect of an early invasive strategy versus medical treatment in patients with NSTEMI (12). Of the patients in the invasive arm 96% had a CAG performed within 7 days with a median of 4 days (12). All patients were treated with either LMWH or UFH prior to the CAG or at least five days in the non-invasive arm. Patients treated invasively compared to noninvasively showed a risk reduction in death or new MI after six months with a risk-ratio of 0.78 (95% CI 0.62-0.98, $p = 0.031$) (12). When considered alone, the occurrence of new MI the risk reduction was also significantly reduced. The difference on mortality alone was not reduced significantly, but there was a trend towards reduction in the invasive arm. Furthermore, the occurrence of symptoms and readmissions were halved (12). Today, early invasive treatment is recommended in all patients with NSTEMI (1, 2).

In 2006, the OASIS 5 trial, a randomized controlled trial (RCT) of 20,078 patients, demonstrated that treatment with fondaparinux was non-inferior to treatment with enoxaparin (LMWH) in combination therapy with aspirin in patients with NSTEMI (13). The primary endpoint was death, new MI or refractory ischemia within 9 days and the study showed a hazard ratio of 1.01 (95% CI 0.90-1.13). Interestingly, treatment with enoxaparin was associated with a higher risk of bleeding, long-time mortality and morbidity (13). These results have been the foundation for the current guidelines by ESC, which recommend treatment with fondaparinux in patients with NSTEMI when CAG and possibly PCI are not available within 24 hours (1).

Risk of bleeding:

Intuitively, combination therapy with aspirin together with an anticoagulant will increase the bleeding risk compared with aspirin alone. In the meta-analysis from Eikelboom et al. (2000) they demonstrated an increased OR of 1.88 (CI 95% 0.60-5.87, $p=0.28$) for severe bleeding when treated with UFH and aspirin compared to aspirin alone (10). This result was not significant, however, could imply an increased risk of bleeding with combination therapy.

The meta-analysis from Eikelboom et al. did not report results about minor bleedings.

However, by reviewing the papers included in the meta-analysis from Eikelboom et al. one by one, a clear tendency towards an increased risk of minor bleedings can be observed. The occurrence of minor bleedings ranges from 6-14 % in the group with combination therapy compared to 0-3 % in the group with aspirin alone (11, 14-17). Even though no statistical analysis was performed, the difference in minor bleeding is undoubtedly significant.

Severe bleedings involved events such as intracranial bleeding, requirement of blood transfusion, and bleeding resulting in death. Minor bleedings referred to hematomas and bleeding from insertion site, although the accurate definitions of minor and severe bleedings varied from study to study.

A substantial part of the minor bleeding complications was associated with catheterization.

This was also observed in the FRISC-II study, where an increased occurrence of bleeding was observed in the invasive arm compared to the non-invasive arm, despite the shorter treatment period with LMWH in the invasive arm(12).

Rationale:

All the above-mentioned studies were conducted in a period where early invasive treatment by no means were standard practice in the treatment of patients with NSTEMI. In the FRISC-I study, which must be seen as one of the main pillars in the introduction of anticoagulative treatment in the acute setting of NSTEMI, only 0.8% of all the patients were revascularized after 6 days (11). This stands in substantial contrast in today's practice, where the year rapport from the Danish Heart Registry from 2022 showed that 96% of patients with either NSTEMI or UAP were invasively assessed and potentially revascularized within 72 hours (18). This must in any case raise questions about the validity of the studies as a basis for the current guidelines in the treatment of NSTEMI.

A reconsideration of the current treatment strategy is further supported by the potential increased risk of bleeding associated with combination therapy compared to aspirin alone. It is therefore natural to question whether we are currently subjecting patients to unnecessary risk with the current treatment regime.

Additionally, reducing the extent of medical treatment for patients with NSTEMI would lead to decreased cost. Furthermore, you would expect a reduced workload at the cardiology departments, especially them using UFH as their first choice for anticoagulant treatment, as it requires close monitoring of the APPT.

Choice of comparators

This study will only compare fondaparinux and aspirin versus aspirin alone as this is the standard practice in Denmark. According to AHA guidelines, options for anticoagulation include Enoxaparin, UFH, fondaparinux or bivalirudin (2). Similarly, ESC recommends using UFH if CAG is performed within 24 hours, and fondaparinux if the procedure is delayed beyond 24 hours (1, 2). The evidence from prior studies (Eikelboom et al. and Yusuf et al.) showed that the efficacy of UFH is equivalent to LMWH and that fondaparinux is equivalent to LMWH(10,

13). Based on this, we believe that the results from this study can be applicable to the other options of anticoagulative options prior to CAG in NSTEMI patients and not exclusively to fondaparinux.

Objectives:

Primary objective:

To compare efficacy in patients treated with aspirin alone compared to combination therapy with fondaparinux and aspirin prior to early invasive strategy in patients with NSTEMI.

Secondary objective:

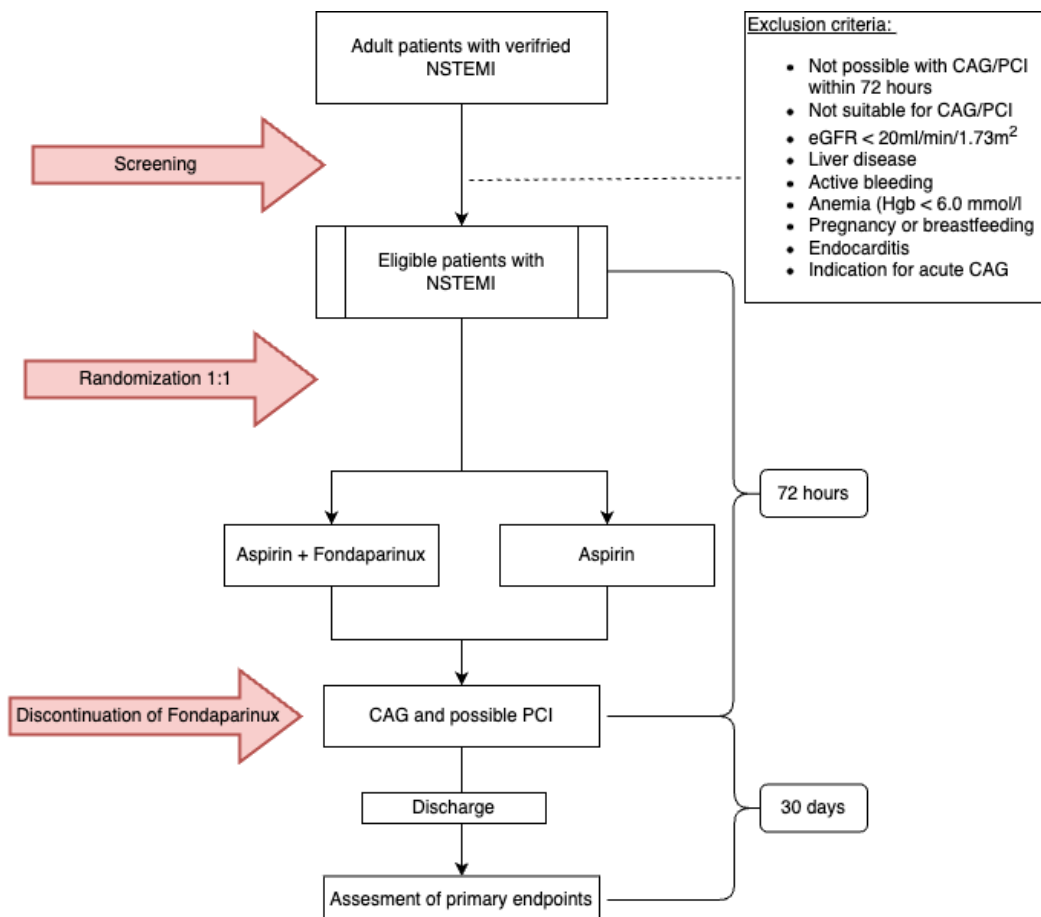
To evaluate and compare the relative bleeding risk associated with the use of aspirin alone and in combination with fondaparinux prior to an invasive strategy in patients with NSTEMI

Hypothesis's:

- Treatment with aspirin alone is non-inferior in prevention of death, new MI and refractory ischemia within 30 days compared to combination treatment with aspirin and fondaparinux in patients with NSTEMI prior to early invasive strategy
- Treatment with aspirin alone is superior to combination treatment with aspirin and fondaparinux regarding the risk of bleeding defined as BARC ≥ 3 criteria (19)) in patients with NSTEMI prior to early invasive strategy

Trial Design:

The trial is designed as a nationwide, multicenter, open label, non-inferiority, randomized controlled trial.



4. Participants

Recruitment strategy

To ensure comprehensive inclusion and meet the required sample size all cardiology and emergency departments with admission and management of NSTEMI patient will be invited to participate in the study. This approach will ensure enrollment from all regions in Denmark. The current trial sites available to enroll and conduct trial related procedures are listed under section 2. “Clinical trial sites”. The participating trial sites will be updated in the protocol and in CTIS accordingly. Each participating clinical site will receive a fee for each patient they enroll in the study encouraging enrolment and involvement in the study.

Additionally, one of the investigators will visit the clinical sites to promote the study, provide detailed information and encourage active participation and patient inclusion.

Screening, Recruitment of patients and informed consent:

All patients with verified NSTEMI will be screened for inclusion in this trial. Eligible patients, who meets all the inclusion criteria and non-exclusions criteria will be invited to participate in the study. The eligible patients will be identified by the treating medical doctor (sub-investigator) to avoid delay in time for randomization and treatment. The treating medical doctors will be trained by the local principal investigator to ensure they have the competences

to provide detailed information about the study, obtaining free and informed consent, familiarity with the randomization process and software to ensure Good Clinical Practice (GCP). Obtainment of informed consent, enrollment and randomization will happen proximately after the diagnosis of NSTEMI, before any trial related procedures or administration of fondaparinux are initiated. The participant will be given a reduced time of one hour to decide whether to participate in the study. This reduced timeframe is necessary due to the emergent nature of NSTEMI and recommendations to initiate treatment as soon as the diagnosis of NSTEMI is established.

The medical doctor responsible for obtaining consent will ensure the participants understands the information provided. This will include:

- Encourage the participant to ask questions and address any concern or possible misconceptions.
- Adjust the explanation of the study to meet the participants (or legal representatives) level of understanding. Such as ensuring complex medical terms are simplified when necessary.
- Encourage the patient (or legal representative) to include a family member or friend in the process of receiving study information and give consent.
- If the participant has any specific needs, such as language barrier, appropriate measures will be taken, such as use of interpreters (Including family/friends), to ensure they can make an informed decision.
- Consent will only be obtained once the participant (or legal representative) has demonstrated a sufficient understanding of the study.

The information of the study and signing of the informed consent will occur in a private setting, most often in the patient's room. If there is a fellow patient in the same room, the participant will be offered the option to move to a private room within the department to receive the information.

The participants will be clearly informed during the consent process that they have the right to withdraw their consent at any time and without providing a reason for the withdrawal.

The participants will be assured that their decision to withdraw will not affect their future medical care or relationship with their healthcare providers. In case of withdrawal the participant will be excluded from the study. Their data collected up to that point will still be used in the study. The informed consent will involve approval to access the subject's electronic medical record.

Potential participants who do not speak Danish will not be able to participate in the trial. This limitation is due to the reduced timeframe available for participants to decide on their participation in the study, during which it is not feasible to provide a certified interpreter.

Eligibility criteria:

Patients must meet all the below mentioned criteria to be eligible for the trial:

Inclusion criteria:

- Diagnosis of NSTEMI verified by:
 - Rise or/and fall in cardiac troponin (cTN) and
 - Symptoms of acute ischemia or ECG-changes compatible with acute ischemia.
- Age ≥ 18 years old
- Expected remaining lifespan ≥ 1 year

- Independent capacity to act and provide informed written and oral consent.

Patients meeting any of the below mentioned criteria cannot be enrolled in the trial:

Exclusion criteria:

- Treatment with any anticoagulants before enrollment and randomization
 - Including any direct anticoagulant (DOAC), LMWH, UFH or warfarin.
- Not possible with CAG and PCI within 72 hours
- Unsuitable for CAG and possible PCI due to poor condition
- Estimated glomerular filtration rate (eGFR) < 20 ml/min/1.73m²
- Known liver disease
- Active bleeding or high risk of bleeding where treatment with Fondaparinux is contraindicated.
- Anemia (B-Hemoglobin < 6.0 mmol/l)
- Pregnancy² or breastfeeding
- Endocarditis
- Indication for acute CAG before enrollment and randomization:
 - ST-elevation Myocardial Infarction (STEMI)
 - Patients classified as “Very High Risk” according to ESC guidelines, defined as(1):
 - Hemodynamic instability (in need of inotropic support) or cardiogenic shock (DANGER-SHOCK criteria (20)) at time of admission.
 - Acute heart failure because of presumed acute ischemia
 - Life-threatening arrhythmias or cardiac arrest
 - Mechanical complications (such as papillary muscle rupture with acute mitral regurgitation, free wall rupture and interventricular rupture)

5. Assignment of interventions

Allocation

Sequence generation:

A specialized password-protected web-based randomization software will be used to generate the allocation sequence. This will ensure that the sequence is generated in a random and unpredictable manner.

The randomization will be stratified by gender and site. Participants will be randomized 1:1 to treatment with either aspirin alone or aspirin with fondaparinux.

Allocation concealment mechanism:

The randomization will occur locally at each clinical site. Access to the randomization webpage will require a hyperlink and login, which will be available exclusively to investigators.

² Female under the age of 55 must have performed a plasma-HCG before inclusion.

For randomization, the investigator will enter the subject's social security number (CPR-number) and verify that the subject meets all inclusions criteria and none of the exclusion criteria.

The allocation sequence will be generated in real-time ensuring that the sequence is concealed from investigators until the moment of assignment. The assignment will immediately be shown to the investigator through the web-based system, without revealing the future sequence.

The system will maintain an audit trail of all randomization activities.

Implementation:

Medical doctors responsible for the treatment and admission of the patients with NSTEMI will enroll, randomize and assign participants to the intervention groups. These medical doctors will be locally instructed in the procedures and assigned as sub-investigators. They will be provided with a precise and comprehensive written guide on the randomization process by the principal investigator.

Blinding:

The study is open label. Neither the patients, care providers, interventional cardiologists or investigators will be blinded in this study.

6. Interventions:

Low-intervention study

Fondaparinux and aspirin are designated as IMPs for this trial. Fondaparinux as test medicinal product and aspirin as auxiliary medicinal product. These products are marketed, approved products that are not blinded or modified from their marketed forms. The use will strictly comply with the current guidelines and the used doses are identical to the drug-labels. The medicinal products have been used for decades in the treatment of NSTEMI both nationally and globally. For this reason we do not expect any new adverse events and categorize the study as a low-intervention study.

Investigational Medicinal Products

The used investigational products are listed below. Known side effects of the IMP's are listed in table 4 in the appendix.

Fondaparinux:

Fondaparinux be the medicinal test product. Patients randomized to treatment with fondaparinux together with aspirin will receive 2.5 mg subcutaneously (s.c.) as soon as possible after enrollment. This treatment will continue with 2.5 mg s.c. daily until CAG and possible PCI which are scheduled to be performed within 72 hours. The treatment with fondaparinux will be discontinued after PCI or if the CAG shows no need for PCI.

Aspirin:

Aspirin will be a medicinal auxiliary product. It will be administered in adherence to the current guidelines on treatment of NSTEMI. All patients will receive an initial bolus of 300 mg aspirin given orally regardless of current antithrombotic treatment. Most patients will have already received this treatment in the ambulance on suspicion of ACS. If the bolus of aspirin has not been administered before enrollment, it will be administered as soon as possible.

Patients already treated with antithrombotic medication will continue with their original treatment until CAG and possibly PCI.

Patients not treated with antithrombotic medication will be prescribed with aspirin 75 mg a day until CAG and possibly PCI.

Table 1 Investigational medicinal products and dosages

Generic drug labels	Dosage
Fondaparinux	2.5 mg s.c.
Acetylsalicylic acid	300 mg bolus followed by 75 mg daily

Content labeling and accountability of Investigational Medicinal Products (IMPs):

Content labeling: Both aspirin and Fondaparinux are standard components in the treatment of NSTEMI. They are already part of routine care and are being sourced from existing hospital stock. These medications are not provided specifically for the trial by pharmaceutical companies, and no additional supplies will be purchased for this study. This means that no special labeling is required, as the medications are identical to those normally administered to patients.

Accountability: The administration of these IMP will be strictly controlled by attending nurses while the patient is admitted. This oversight ensures that the standard protocol for medication administration is followed and compliance of the patient will not be an issue.

Both the prescribing and administering these IMPs is recorded separately in the electronic medication charts as part of standard clinical care. As the IMPs are only prescribed and administered during admission this record serves as a robust system to keep accountability.

Criteria for discontinuing or modifying allocated treatments for a given trial participant

Discontinued treatment

In case of severe bleeding defined as BARC criteria ≥ 3 , treatment with fondaparinux and aspirin must discontinue until the bleeding has resolved. Further antithrombotic and anticoagulative treatment will be decided by a specialist and may vary from individual to individual. This event within 30 days will be considered as a safety endpoint.

In case of thrombotic event such as transient ischemic attack (TIA) or ischemic cerebrovascular accident (CVA), the anticoagulative and antithrombotic treatment may be changed in consultation with a neurologist. This event within 30 days will be considered a safety endpoint.

Furthermore, any given treatment may be discontinued if the treating medical doctor believes it will be life-threatening or significantly harmful to continue. The reason for discontinuation must be clearly documented in the subjects' electronic medical record.

Relevant concomitant care and interventions

Permitted:

- Standard care for the patients with NSTEMI such as:
 - Glyceryl nitrate either sublingually or as infusion
 - Initiation of treatment for hypertension or hypercholesterolemia
 - Medication for pain relief, including opioid agonist or paracetamol.
- Computed Tomography (CT)-CAG as an initial assessment of the coronaries instead of a diagnostic CAG before a possible PCI.
- All patients will follow the routine procedures and tests for NSTEMI patients which will include ECG, echocardiography, standard blood sample, including repeated measurements of cTN.
- CT scan to exclude differential diagnosis or possible complications
 - Preferably, the CT-scan for differential diagnostic purpose should be performed before randomization and enrollment.

Prohibited:

- Anticoagulant medication not specified in the study protocol.
- Experimental treatments outside of the study protocol.

Procedures during the intervention period:

Early invasive strategy:

Early invasive strategy in patients with NSTEMI involves CAG/CT-CAG and possibly PCI within 24 hours. The current guideline from ESC recommends an inpatient invasive strategy of all patients with NSTEMI and consideration of early invasive strategy(1). As mentioned in the Danish Heart Registry, 96% of patients with NSTEMI are evaluated by CAG within 72 hours. The study strives towards an early invasive strategy in most subjects; however, patients are eligible to participate if the CAG/CT-CAG and PCI are expected within 72 hours and this timespan will be considered as early invasive strategy.

Percutaneous Coronary Intervention:

The indication for PCI is determined by the treating cardiologist performing the invasive evaluation. CAG and PCI is performed equally across all patients regardless of prior medical treatment with or without fondaparinux. In case of PCI, the patients will be administered with an intravenous bolus of UFH on 70-100 U/kg.

Cardiology departments only performing diagnostic CAG/CT-CAG and not PCI will follow the assigned treatment protocol. In need of PCI the subjects will continue with their assigned treatment until the PCI has been performed.

Post-interventional treatment

Treatment post CAG and PCI

Treatment with Fondaparinux will be discontinued after possible PCI or if PCI is not indicated. Medically treatment after the invasive evaluation and potential PCI will follow the national and regional guidelines and will be independent of the assigned intervention group.

The subsequent antithrombotic treatment will be decided by the treating interventional cardiologist. In general, the subjects undergoing PCI will be prescribed with lifelong aspirin, 75 mg a day, together with an adenosine disphosphate (ADP) receptor inhibitor. First choice in Denmark is prasugrel, 60 mg loading dose followed by 10 mg a day for 12 months. There can be several reasons why another drug, dose or length of treatment may be more suitable, such as high age or low body weight. In these cases, this will be decided by the treating interventional cardiologist.

Besides antithrombotic medication, the subject will be prescribed with a high-dose statin. First choice in Denmark is atorvastatin, 80 mg a day.

In case of reduced LVEF ($LVEF \leq 40\%$) due to acute MI the patient will be initiated on decongestive treatment and referred to the heart failure clinic for further up-titration and follow-up.

All patients will receive an offer for integrated rehabilitation regardless of revascularization or not.

7. Follow-up:

No clinical visits are scheduled after discharge. Since Fondaparinux will only be administered during hospitalization and until coronary angiography (CAG) or possible percutaneous coronary intervention (PCI) is performed, any side effects are expected to occur within this period. The defined primary endpoints will be collected directly from the patient's electronic medical records 30 days after enrollment. A registry-based follow-up will be used to assess mortality and long-term endpoints.

Participant timeline

Table 2 Participant Timeline

	STUDY PERIOD									
	Enrolment	Allocation	Post-allocation and primary endpoint			Register based follow-up				Close-out
TIMEPOINT	-t1	0	0-72 hours	From CAG to discharge	30 days	180 days	1 year	3 years	5 years	10 years
ENROLMENT:										
Eligibility screen:	X									
Informed consent	X									
Allocation		X								

INTERVENTIONS:										
Aspirin			(x)							
Aspirin and Fondaparinux			(x)							
CAG/CT-CAG + (PCI)			x							
ASSESSMENTSⁱ:										
Mortality			x	x	x	x	x	x	x	x
Refractory ischemia			x							
New MI				x	x	x	x	x	x	x
Echocardiography			x	x						
Severe bleeding			x	x	x					
Severe thrombotic event			x	x	x					
Blood samples ⁱⁱ			x							

ⁱAll assessments up to 30 days except mortality will be obtained directly from the patient's electronic medical record. Information regarding mortality will be obtained from registry.

ⁱⁱStandard blood panel used for all patients with NSTEMI

8. Outcomes:

Primary efficacy endpoint:

Consists of a composite endpoint of:

- 30-day mortality
- 30-day recurrent MI
- Clinical deterioration resulting in acute CAG before the scheduled

Clinical deterioration resulting in acute CAG is defined as conversion to “Very High Risk”, followed by an acute CAG before scheduled and possible PCI. The definition of “Very High Risk” is according to the ESC guideline (2023).

Secondary endpoints:

- Composite of occurrence of death or new MI within 180 days, 1 year, 3 years, 5 years and 10 years.
- Incidence cerebrovascular accident (CVA) within 30 days including:
 - Ischemic Stroke
 - Transient ischemic attack (TIA)
- Length of hospital stay
- Left ventricular ejection fraction (LVEF) at discharge.

- TIMI-flow

Safety endpoints:

- Incidence of severe bleeding defined as BARC criteria ≥ 3 within 30 days.
- Incidence of severe thrombotic events within 30 days including:
 - Acute MI
 - CVA

Clinically relevance of the chosen efficacy and safety endpoints:

- Primary efficacy endpoint:
 - *30-day mortality and new MI:*

These are critical measurement of the short-term effectiveness of the two treatment groups. Reducing mortality and new MI in patients with myocardial infarction including NSTEMI is the primary goal of any treatment or intervention.

- *Clinical deterioration resulting in acute CAG:*

Clinical deterioration in patients admitted with AMI represents persistent or intermittent symptoms of acute ischemia that are unresponsive to initial medical treatment. This indicates a very high-risk subgroup that may benefit from acute intervention. This outcome is clinically relevant to see whether the acute management with anticoagulative treatment may or may not influence this outcome.

- Secondary endpoints:
 - *Composite of occurrence of death or new MI within 30 days, 180 days, 1 year, 3 years, 5 years and 10 years:*

Long term mortality and recurrent MI are essential to evaluate the sustained benefits or risk of a treatment. This helps us to understand the potential prolonged effects of a treatment beyond the immediate phase.

- *Incidence of CVA within 30 days:*

CVA is a significant thrombotic event with increased mortality and morbidity that may occur, though rarely, in relation to PCI (21). Monitoring this outcome is clinically relevant especially when the study protocol includes treatment with an anticoagulant or not.

- *Length of hospital stay:*

The duration of hospital stay is a practical measure of a treatments impact on healthcare resource. Furthermore, it can be influenced by thrombotic and bleeding complication, including minor bleeds that may delay discharge.

- *Left ventricular ejection fraction:*

LVEF is a key measurement of cardiac function. It is an important measurement to determine one of the direct effects of NSTEMI on cardiac function.

- Safety outcomes:
 - *Incidence of severe bleeding and thrombotic events:*

Incidence of severe bleeding or thrombotic event are two critical safety concerns with or without treatment with anticoagulant. Monitoring these events are essential to balance the benefits of preventing thrombotic events with the risks of bleeding complication.

9. Data collection

Plans for assessment and collection primary outcome

The data for assessment of primary endpoints and safety endpoints will mainly be obtained directly from the patient's electronic medical journal. The data will be obtained by study nurses or principal investigators and recorded in a predefined eCRF in REDCap/Corolog. This will include conversion to acute CAG, 30-day mortality, new MI within 30 days, CVA, Severe thrombotic event and severe bleedings as listed under outcomes. These endpoints will be obtained after 30 days. The primary endpoint of 30-day mortality will also be verified through the Danish Civil Registration System to cross-check for any delays or discrepancies in the reporting of deaths in the patients' electronic medical records.

Plans for assessment and collection of secondary outcome, baseline, and other trial data.

Secondary outcomes together with baselines characteristic will be obtained solely from Danish registries.

The Danish Heart Registry:

This registry contains data regarding CAG and PCI. It will provide information regarding the exact time of catheterization together with information about a potential revascularization. Furthermore, it contains baseline characteristics such as hypertension, hypercholesterolemia, smoking, familiar disposition to heart disease, LVEF, prior MI and prior PCI or CABG. This data will be used for the baseline table.

The National Patient Registry:

This registry contain information about the patients diagnoses, examinations and treatments together with time for admission and discharge. This will provide information about specific outcomes such as length of stay at hospital, re-admission, re-infarction, severe bleeding and cerebrovascular accidents.

The Danish Civil Registration System:

Provides information about the subjects' vital status and will be used to assess long term mortality in the study.

The laboratory database:

Will provide information from the blood samples at admission. Measurements involves first measured value from below:

- B-hemoglobin, mmol/l
- B-cTn
- B-thrombocytes, $\times 10^9/l$
- B-leukocytes, $\times 10^9/l$

- P-C-reactive protein (CRP), mg/l
- P-creatinine, $\mu\text{mol/l}$
- P-cholesterol, mmol/l
- P-cholesterol LDL, mmol/l
- P-cholesterol HDL, mmol/l
- P-coagulations factor II + VII+V [INR]
- P-alanine transaminase, U/l

Highest measured:

- B-cTn

Lowest measured:

- B-hemoglobin, mmol/l

The cTn measured may vary from hospital to hospital and can include both Troponin I and Troponin T, analyzed as either high-sensitive or standard. The type of cTN included will depend on the standard practice for each individual site and will be compared accordingly.

Data management:

Data will be stored in accordance with the to the General Data Protection Regulation (GDPR). Data collected from the above-mentioned Danish registries will be stored on a digital platform called MidtX, which is specifically designed and approved for storage of sensitive personal data. This platform is created by Region Midtjylland, Denmark.

Data obtained directly from the electronic medical records will be entered and stored in predefined eCRF's, either REDCap or Corolog. Both are secure web applications for building and managing databases and are widely used in research and are compliant with regulatory standards.

10. Statistical methods:

Sample Size

According to the annual report from Danish Heart Registry (2022), patient with NSTEMI who underwent PCI had a 30-day mortality rate of 2.1 % (18). However, this data also includes patients with UAP and patients who was not treated with PCI. We expect the 30-day mortality and 30-day new MI in a cohort with only NSTEMI patients to be slightly higher, around 3 %. A local review of the data on patients with NSTEMI in Region Midtjylland showed that about 9% these patients were scheduled for an acute CAG after admission. Approximately half of these were assessed as possible subjects to this study.

Based on this, we expect about 5 % of the subjects scheduled for a subacute CAG to convert to acute CAG. In total, this gives us an expected composite event rate of 8%.

We will require a power of 80% and set a one-sided 97.5 % confidence interval (equivalently to a 95% two-sided confidence interval). Our absolute non-inferiority margin with an expected event rate of 8 % will be 2.2 %. This corresponds to a relative non-inferiority margin of **1.275**.

Assuming that the composite event rate is the same in both groups and there truly is no difference between the two interventions, a total of **4822** (2411 in each group) patients are required. This sample size will ensure that we are 80% sure that the upper limit of a one-sided 97.5%-confidence interval will exclude a difference of more than 2.2 % in favor of the aspirin group.

Adjustment sample size for loss

By adjusting for an expected loss of 5 %, our new sample size is 5076.

Adjustment of Sample Size

After inclusion of the first 1.500 patients, a pooled sample size recalculation will be performed. Based on this analysis the steering committee will decide whether the sample size should be adjusted accordingly.

See below for possible adjustments.

Table 3 Sample size calculations

Event rate, %	Relative non-inferiority margin	Absolute non-inferiority margin, %	Sample Size, n	Loss adjusted sample size, n
6	1.275	1.650	6574	6920
7	1.275	1.925	5572	5866
8	1.275	2.200	4822	5076
9	1.275	2.475	4238	4462
10	1.275	2.750	3770	3969
11	1.275	3.025	3388	3567

Feasibility

Every year, around 5900 patients in Denmark are evaluated with CAG on the indication of NSTEMI (18). We expect 5 % of these to be evaluated with an acute CAG before enrolment and randomization is possible. Around 10 % is expected to be on anticoagulant treatment at admission and therefore not eligible to participate in the study. Furthermore, we expect 5 % to be excluded based on other exclusion criteria. This results in a total of 4720 patients eligible to participate. Based on a willingness to participate of around 50%, we estimate a possible enrollment of 2360 patients a year. It seems feasible to expect the inclusion of around 2.000-2.500 patients per year, which gives us an enrollment period of maximum 2.5 years.

Statistical Analysis

Analysis for primary and secondary outcomes:

Primary Efficacy endpoint:

- Composite of 30-day mortality, 30-day new MI and refractory ischemia prior to CAG
 - The risk difference (RD) between treatment groups will be calculated. A one-sided 97.5% CI is presented for the primary composite endpoint. A one-sided Farrington-Manning test will be used to assess non-inferiority. Non-inferiority is established if the upper limit of the one-sided 97.5% CI of the risk difference do not cross the prespecified noninferiority margin.

Secondary Outcomes:

- Composite of death and MI at various time points (e.g. 30 day, 180 days, 1 year, 3 years, 5 years and 10 years)
 - Cumulative risk will be compared using Cox proportional hazards model.
 - Time-to-event data will be visualized with Kaplan-Meier curves
 - Time-to-event data of death and MI may also be presented separately. In this case, mortality will be visualized using Kaplan-Meier curves, while MI will be analyzed using Aalen-Johansen estimates to account for death as a competing risk.
- Cumulative risk of cerebrovascular Accidents (CVA) after 30 days:
 - Cumulative risk will be compared using Cox proportional hazards model.
 - Time-to-event data will be visualized using Aalen-Johansen estimates
- Length of hospital stay
 - The duration for hospital stay will be calculated from randomization to discharge. Since the distribution is expected to be skewed, the data will be presented as median and analyzed using a non-parametric test (e.g., Mann Whitney test).
- Left ventricular ejection fraction (LVEF) at discharge

LVEF will be analyzed using an independent samples t-test, provided the assumption of normality is met. If the data are not normally distributed, a non-parametric Mann-Whitney U test will be used instead.

Safety Outcomes:

- Cumulative risk of severe Bleeding (BARC Criteria ≥ 3) through day 30
 - Cumulative risk will be compared using Cox proportional hazards model.
 - Time-to-event data will be visualized using Aalen-Johansen estimates

Subgroup analyses

The following sub-group analyses will be performed:

1. Gender
2. Age (<75 or ≥ 75 years)
3. Time from randomization to CAG (<24 hour, 24-72 hours and >72 hours)
4. Place of randomization (peripheral hospital or invasive center)
5. CAG vs CCTA
6. LAD vs Non-LAD culprit
7. DM vs non-DM

Analyses for baseline characteristics:

Continuous data will be presented as mean with standard deviation or median with interquartile range, depending on the fulfillment of normality assumptions. They will be compared across the two intervention arms using either a two-sample t-test or nonparametric Wilcoxon rank test, as appropriate. Categorical data will be presented as count and percentages and compared using either Chi-square test or Fischer's exact test, as appropriate.

Methods for additional analyses:

Subgroup analysis may be conducted across various age groups along with gender. A forest plot could be generated to visually compare the treatment effects across subgroups.

If non-inferiority is demonstrated for aspirin versus aspirin and fondaparinux, a post-hoc superiority analysis may also be conducted without worrying about impacting type one error (22). Furthermore, a superiority analysis may be conducted on the secondary outcomes.

Analysis population and missing data:

The two interventions groups will be analyzed as both intention-to-treat and per-protocol approach as recommended for non-inferiority trials(23, 24).

Intention-to-treat:

This approach analyzes subjects in the groups to which they were originally assigned, regardless of which treatment they end up with.

Per-Protocol:

This approach only analyzes whose subjects fully adherent to the assigned intervention and study protocol.

Missing data:

Primary, secondary and safety outcomes will be available through various registries and the subject's electronic medical journal, which should prevent missing data. However, if a patient migrates to another country and is lost to follow-up, the time-to-event data for that subject will be included until the time of migration and then treated as right censoring.

11. Safety and Monitoring

Data Safety Monitoring Board (DSMB)

Composition of the DSMB; Its role and reporting structure:

The DSMB will be composed of the following members:

- Two cardiologists not involved in the conduct of the trial
- Statistician
- Epidemiologist

Role and reporting structure:

The primary role of DSMB is to monitor the safety and efficacy of the trial. The members of DSMB will be independent and will not be involved in the otherwise conduction of the trial or have any financial interests in the outcome of the study.

The DSMB will report directly to the study sponsor, principal investigator and steering committee.

Stopping guidelines

Stopping guidelines:

The trial may be terminated early based on the following criteria:

- **Safety:** The trial may be terminated early if there is evidence of significant harm to the participants in either of the two intervention groups.

Any potential decision to stop the trial will be discussed and decided by the steering committee based on the recommendations from a report from DSMB.

Harms

When administering any anticoagulant or antithrombotic medication, the primary goal is to prevent a severe thrombotic event all while balancing the potential risk of bleeding. This also accounts for the anticoagulative treatment in NSTEMI patients where both those risks must be considered thoroughly.

Not administering fondaparinux may increase the risk of a thrombotic such as new MI and stroke, which are among the most severe thrombotic complications. Conversely, administering fondaparinux may elevate the risk of bleeding, including serious events like intracranial bleeding, tamponade or bleeding requiring transfusion. Both the thrombotic and bleeding complications can ultimately be fatal.

However, as outlined in the introduction, given the current practice of early invasive treatment in patients with NSTEMI, we believe that there is insufficient evidence to support the notion that not administering fondaparinux or any other anticoagulant increases the risk of thrombotic events. The contemporary approach with early invasive assessment and intervention significantly reduces the risk of thrombotic complications as demonstrated in the FRISC-II study(12), potentially rendering the anticoagulation unnecessary thus avoiding the associated risks of bleeding.

Monitoring and reporting of safety:

Given the 17-hour half-life of fondaparinux, we find it reasonable to believe that any potential adverse event would occur in close relation to the administering or non-administration of fondaparinux, as well as the early invasive assessment. Based on this, safety events will be monitored through a 30-day period, focusing on events of severe bleeding and thrombotic events.

Severe adverse events of bleeding and thrombotic events will be collected by the associated study nurse or PhD-student directly from the subject electronic medical record after day 30. The safety data will be entered in a predefined database in REDCap/Corolog. Annually, the accumulated safety data will be made available to the DSMB. The first safety data will be available to the DSMB one year after the enrolment of the first patient. The DSMB will report on the safety data annually, and these reports will be sent to the Competent authority, The Danish Medicines Agency (DKMA). The annual safety report will be submitted to CTIS.

The trial is a low-intervention study. Fondaparinux currently holds a class 1 recommendation for the treatment of NSTEMI, has been widely used for years, and has a well-established safety profile. Additionally, the aim of the study is to evaluate the removal of this treatment, meaning that the “intervention group” will not receive fondaparinux. Based on this, serious adverse events (SAE) will be in relation to not receiving fondaparinux. SAEs and SUSARs will be registered after day 30 or upon the first awareness of the event. SUSARs and SAE will be reported by the PI directly to the sponsor within 24 hours. The PI at each trial site is responsible

for evaluation of causality. Definitions of adverse events and reactions are provided in table 4. All registrations will take place in RedCap. We believe this approach is fully in accordance with Regulation (EU) no. 536/2014 and aligns with the Danish Medicines Agency's guidance on risk-based recording and reporting of adverse events in clinical trials.

Suspected Unexpected Serious Adverse Reaction:

Fondaparinux has been used in the treatment of NSTEMI for several decades, so we do not expect any SUSARs with the treatment. Potential SUSAR's will only be reported in the first 30 days after enrollment. This is due to the discontinuation of fondaparinux after the invasive assessment. Any SUSAR in the intervention group without fondaparinux will be related to the NSTEMI. In the event of an SUSAR, sponsor will report immediately and directly to the GCP-unit according to national guideline in Denmark. The GCP-unit will be responsible for reporting SUSAR's to the national authority and the EudraVigilance database. Fatal or life-threatening SUSAR is reported as soon as possible, and no later than 7 days after the sponsor becoming aware of it. All other SUSARs (not fatal or life-threatening) will be reported within 15 days of the sponsor becoming aware of them.

Table 4 Definition of adverse events and reactions

Adverse events and reactions	Definition
Adverse Events (AE)	Any untoward medical occurrence in the subjects associated with the use of fondaparinux, whether or not considered drug related*. Will not be reported in this study.
Serious adverse events (SAE)	Any untoward medical occurrence that at any dose requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, results in a congenital anomaly or birth defect, is life-threatening, or results in death*. The following SAE will be registered: • Death • Severe thrombotic events including: ○ Myocardial Infarction ○ ischemic stroke ○ Transient ischemic attack.
Serious adverse reactions (SAR)	Severe Bleedings defined as BARC ≥ 3 (See table 6 in Appendix)
Supected unexpected serious adverse reactions (SUSARs)	A suspected serious adverse reaction to fondaparinux that it is not consistent with the safety profile of fondaparinux as described in its Summary of Product Characteristics (SmPC)

*Definition from the US Food and Drug administration.

12. Ethics and dissemination

Research ethics and approval

The trial will be approved through the Clinical Trial Information System (CTIS) by the Medical Ethics Committee (VMK) and the DKMA before initiation.

This trial will challenge the current practice and guidelines for the use of with anticoagulants in the immediate treatment of patients with NSTEMI prior to invasive assessment. The existing guidelines are based on evidence from a time when early invasive treatment was not a standard practice. We have thoroughly weighed the risks and benefits of combination therapy with fondaparinux and aspirin versus aspirin alone, and we believe that the current practice potentially place our patients at unnecessary risk. We are confident that the conduct and rationale behind this trial will fully comply with the legislation from both VMK and DKMA.

We commit to maintaining an open dialogue with VMK and DKMA to ensure that this trial consistently adheres to ethical standards and GCP regarding clinical trials.

Protocol amendments

All significant protocol amendments will be submitted to the VMK and DKMA for review and approval before implementation. This will involve detailed documentation of the changes, including the rationale and potential impact on the trial. Additionally, any protocol modification will be updated in ClinicalTrials.gov and CTIS.

In case the trial protocol has been published, any protocol modification that may affect the outcomes will be communicated directly to the publishing journal.

Confidentiality

Personal information about enrolled patients will only be collected by authorized study personnel. All personal data will be stored in secure, password protected databases and digital platforms such as REDCap/Corolog and MidtX, which are approved and adhere to GDPR for the storage of personal data. Only de-identified data will be shared with any third-party data analysts or statisticians.

Provision and Compensation

Subjects will not receive any compensation for participating in the study. In case of harm related to any of the two interventions, patients may seek compensation through “Patienterstatningen”, the Danish official authority responsible for handling compensation claims related to medical treatment.

Dissemination policy

Communication of the trial results

Publication:

The study expects to result in a publication in at least one recognized international peer-reviewed journal. The paper will be drafted irrespective of whether the results are neutral, positive, negative or inconclusive.

Participants:

If desired, participants may receive a summary of the trial results after the end of the trial. Participants will be informed about this possibility at the enrolment.

Healthcare professionals:

Results will be communicated to healthcare professionals through presentation at relevant medical conferences and meeting.

Registries:

The results will be reported and made available at ClinicalTrials.gov and CTIS. This will be provided as soon as possible and no later than one year after the trial has ended.

Authorship and acknowledgement

Authorship eligibility for the potential papers resulting from this trial will follow the Vancouver Recommendations (also known as the ICMJE guidelines). Individuals who contributed significantly to the study but do not fulfill the requirements for co-authorship will be acknowledged.

13. References

1. Byrne RA, Rossello X, Coughlan JJ, et al. 2023 ESC Guidelines for the management of acute coronary syndromes. Eur Heart J. 2023;44(38):3720-826. doi: 10.1093/eurheartj/ehad191. PubMed PMID: 37622654.
2. Amsterdam EA, Wenger NK, Brindis RG, et al. 2014 AHA/ACC Guideline for the Management of Patients with Non-ST-Elevation Acute Coronary Syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2014;64(24):e139-e228. Epub 20140923. doi: 10.1016/j.jacc.2014.09.017. PubMed PMID: 25260718.
3. Ashkan E, Pedersen CK, Høfsten DE, et al. Behandlingsvejledning I Akut Koronart Syndrom Dansk Cardiologisk Selskab.
4. Bhatt DL, Hulot JS, Moliterno DJ, et al. Antiplatelet and anticoagulation therapy for acute coronary syndromes. Circ Res. 2014;114(12):1929-43. doi: 10.1161/circresaha.114.302737. PubMed PMID: 24902976.
5. Zaman AG, Helft G, Worthley SG, et al. The role of plaque rupture and thrombosis in coronary artery disease. Atherosclerosis. 2000;149(2):251-66. doi: 10.1016/s0021-9150(99)00479-7. PubMed PMID: 10729375.
6. Palta S, Saroa R, Palta A. Overview of the coagulation system. Indian J Anaesth. 2014;58(5):515-23. doi: 10.4103/0019-5049.144643. PubMed PMID: 25535411; PubMed Central PMCID: PMC4260295.

7. Schiele F. Fondaparinux and acute coronary syndromes: update on the OASIS 5-6 studies. *Vasc Health Risk Manag.* 2010;6:179-87. Epub 20100415. doi: 10.2147/vhrm.s6099. PubMed PMID: 20407625; PubMed Central PMCID: PMC2856573.
8. Cook BW. Anticoagulation management. *Semin Intervent Radiol.* 2010;27(4):360-7. doi: 10.1055/s-0030-1267849. PubMed PMID: 22550377; PubMed Central PMCID: PMC3324206.
9. Oler A, Whooley MA, Oler J, et al. Adding heparin to aspirin reduces the incidence of myocardial infarction and death in patients with unstable angina. A meta-analysis. *Jama.* 1996;276(10):811-5. PubMed PMID: 8769591.
10. Eikelboom JW, Anand SS, Malmberg K, et al. Unfractionated heparin and low-molecular-weight heparin in acute coronary syndrome without ST elevation: a meta-analysis. *Lancet.* 2000;355(9219):1936-42. doi: 10.1016/s0140-6736(00)02324-2. PubMed PMID: 10859038.
11. Low-molecular-weight heparin during instability in coronary artery disease, Fragmin during Instability in Coronary Artery Disease (FRISC) study group. *Lancet.* 1996;347(9001):561-8. PubMed PMID: 8596317.
12. Invasive compared with non-invasive treatment in unstable coronary-artery disease: FRISC II prospective randomised multicentre study. FRagmin and Fast Revascularisation during InStability in Coronary artery disease Investigators. *Lancet.* 1999;354(9180):708-15. PubMed PMID: 10475181.
13. Yusuf S, Mehta SR, Chrolavicius S, et al. Comparison of fondaparinux and enoxaparin in acute coronary syndromes. *N Engl J Med.* 2006;354(14):1464-76. Epub 20060314. doi: 10.1056/NEJMoa055443. PubMed PMID: 16537663.
14. Cohen M, Adams PC, Hawkins L, et al. Usefulness of antithrombotic therapy in resting angina pectoris or non-Q-wave myocardial infarction in preventing death and myocardial infarction (a pilot study from the Antithrombotic Therapy in Acute Coronary Syndromes Study Group). *Am J Cardiol.* 1990;66(19):1287-92. doi: 10.1016/0002-9149(90)91155-y. PubMed PMID: 2244556.
15. Théroux P, Ouimet H, McCans J, et al. Aspirin, heparin, or both to treat acute unstable angina. *N Engl J Med.* 1988;319(17):1105-11. doi: 10.1056/nejm198810273191701. PubMed PMID: 3050522.
16. Gurfinkel EP, Manos EJ, Mejail RI, et al. Low molecular weight heparin versus regular heparin or aspirin in the treatment of unstable angina and silent ischemia. *J Am Coll Cardiol.* 1995;26(2):313-8. doi: 10.1016/0735-1097(95)80001-w. PubMed PMID: 7608429.
17. Cohen M, Adams PC, Parry G, et al. Combination antithrombotic therapy in unstable rest angina and non-Q-wave infarction in nonprior aspirin users. Primary end points analysis from the ATACS trial. Antithrombotic Therapy in Acute Coronary Syndromes Research Group. *Circulation.* 1994;89(1):81-8. doi: 10.1161/01.cir.89.1.81. PubMed PMID: 8281698.
18. Kvalitetsudviklingsprogram RK. Dansk Hjerteregister - Årsrapport 2022. 2022.
19. Mehran R, Rao SV, Bhatt DL, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. *Circulation.* 2011;123(23):2736-47. doi: 10.1161/circulationaha.110.009449. PubMed PMID: 21670242.
20. Møller JE, Engstrøm T, Jensen LO, et al. Microaxial Flow Pump or Standard Care in Infarct-Related Cardiogenic Shock. *New England Journal of Medicine.* 2024;390(15):1382-93. doi: doi:10.1056/NEJMoa2312572.
21. Dukkipati S, O'Neill WW, Harjai KJ, et al. Characteristics of cerebrovascular accidents after percutaneous coronary interventions. *Journal of the American College of Cardiology.* 2004;43(7):1161-7. doi: <https://doi.org/10.1016/j.jacc.2003.11.033>.

22. FDA, CDER, CBER. Non-inferiority Clinical Trials to Establish Effectiveness. U.S. Department of Health and Human Services Food and Drug Administration, 2016.
23. Hahn S. Understanding noninferiority trials. Korean J Pediatr. 2012;55(11):403-7. Epub 20121123. doi: 10.3345/kjp.2012.55.11.403. PubMed PMID: 23227058; PubMed Central PMCID: PMC3510268.
24. Snapinn SM. Noninferiority trials. Curr Control Trials Cardiovasc Med. 2000;1(1):19-21. doi: 10.1186/cvm-1-1-019. PubMed PMID: 11714400; PubMed Central PMCID: PMC59590.

14. Appendices

Tables:

Table 5 know side effect of the investigational medicinal products

Drugs	Incidence	Side effects
Fondaparinux	Common (1-10%)	Anemia, bleeding
	Uncommon (0.1-1%)	Coagulation disorders, thrombocytopenia, nausea, vomiting, pain, fever, local reactions and discomfort at injection site, elevated liver transaminases, headache, chest pain, dyspnea, itching, rash, edema.
	Rare (0.01-0.1%)	Gastrointestinal discomfort, tiredness, restlessness, allergic reactions, elevated bilirubin, hypokalemia, dizziness, confusion, drowsiness, cerebral hemorrhage, hypotension, syncope, hot flushes.
	Very Rare (<0.01%)	Anaphylactic reaction, angioedema.
Acetylsalicylic Acid	Very common (>10%)	Bleeding, abdominal pain, gastroesophageal reflux, pyrosis.

	Common (1-10%)	Gastrointestinal bleeding, melaena, diarrhea, flatulence, nausea, vomiting, angioedema, urticaria, headache, insomnia, bronchospasm.
	Uncommon (0.1-1%)	Tinnitus, hematemesis, dizziness, allergic reactions, anaphylactic reaction, dyspnea, sweating.
	Rare (0.01-0.1%)	Anemia, hearing loss, gastrointestinal perforation, hypoglycemia, cerebral hemorrhage, vasculitis.
	Very Rare (<0.01%)	Agranulocytosis, aplastic anemia, eosinophilia, neutropenia, thrombocytopenia, stomatitis, hepatitis (dose related, mild, reversible toxic hepatitis), Stevens-Johnson syndrome, renal impairment, erythema multiforme, purpura, toxic epidermal necrolysis (TEN)
	Unknown	Heart insufficiency, gingival bleeding, epistaxis, hypertension, edema

Table 6 Bleeding Academic Research Consortium (BARC) definition for bleeding^{19}

Type 0		No bleeding
Type 1		Bleeding that is not actionable and does not cause the patient to seek an unscheduled performance of studies, hospitalization, or treatment by a health care professional; it may include episodes leading to self-discontinuation of medical therapy by the patient without consulting a health care professional.
Type 2		Any overt, actionable sign of hemorrhage (e.g., more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for type 3, type 4, or type 5 but does meet at least one of the following criteria: requiring nonsurgical, medical intervention by a health care professional; leading to hospitalization or increased level of care; or prompting evaluation.
Type 3	A	Overt bleeding plus a hemoglobin drop of 3 to 5 g/dL ⁱ (provided the hemoglobin drop is related to bleed); any transfusion with overt bleeding.
	B	Overt bleeding plus a hemoglobin drop of 5 g/dL (provided the hemoglobin drop is related to bleed); cardiac tamponade; bleeding requiring surgical intervention for control (excluding dental, nasal, skin, and hemorrhoid); bleeding requiring intravenous vasoactive agents.
	C	Intracranial hemorrhage (does not include microbleeds or hemorrhagic transformation, does include intraspinal); subcategories confirmed by

		autopsy or imaging, or lumbar puncture; intraocular bleed compromising vision.
Type 4		Coronary artery bypass grafting-related bleeding; perioperative intracranial bleeding within 48 hours; reoperation after closure of sternotomy for the purpose of controlling bleeding; transfusion of 5 U of whole blood or packed red blood cells within a 48-hour period; chest tube output 2 L within a 24-hour period.
Type 5	A	Probable fatal bleeding; no autopsy or imaging confirmation but clinically suspicious.
	B	Definite fatal bleeding; overt bleeding or autopsy, or imaging confirmation.

¹Corrected for transfusion (1 U packed red blood cells or 1 U whole blood = 1 g/dl hemoglobin)