Danish trial of beta blocker treatment after myocardial infarction without reduced ejection fraction (DANBLOCK)

Protocol Identification Number: DANBLOCK

EudraCT Number: 2018-002699-42

SPONSOR: Professor Eva Prescott

Department of Cardiology, Y

Bispebjerg Frederiksberg University Hospital

Bispebjerg Bakke 23, 2400 NV, København, Denmark

Primary investigator: Professor, Eva Prescott

Email: Eva.Irene.Bossano.Prescott@regionh.dk

Tel: +45 22 57 26 14

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Generelle oplysninger til brug for lægemiddelstyrelsen:

- *Navn og titel på person/personer, som er autoriseret til at underskrive protokollen og protokolamendment(s) for Sponsor:*

Eva Prescott, Professor

Thomas Sehested, Læge

- *Navn og titel på de forsøgsansvarlige investigatorer, samt adresse og tlf.nr. på de pågældende forsøgscentre:*

Alle kardiologiske afdelinger i Danmark inviteres til at deltage i forsøget. Nedenfor er angivet oplysninger for de 5 regionalt ansvarlige:

Navn & titel	Repræsenterer	Adresse	Telefon & e-mail
Ida Gustafsson, klinikchef	Region H	Bispebjerg Frederiksberg Hospital, Bispebjerg Bakke 23, 2400 NV, København, Denmark	23113596 Ida.gustafsson@regionh.dk
Michael Hecht Olsen, professor	Region Sjælland	Kardiologisk afdeling, Holbæk Sygehus, OUH	61304904 Michael.olsen@dadlnet.dk
Kristian Korsgaard Thomsen, overlæge	Region Syd	Kardiologisk afdeling, Esbjerg Sygehus	Kristian.thomasen@svs.regionsyddanmark.dk
Michael Mæng, professor	Region Midt	Kardiologisk afdeling, Aarhus Universitetshospital	michael.maeng@clin.au.dk
Svend Eggert Jensen, lektor, overlæge	Region Nord	Kardiologisk afdeling, Aalborg Universitetshospital	svend.eggert.jensen@rn.dk

- *Forsøget udføres i overensstemmelse med protokollen og gældende myndighedskrav/lovgivning på området*
- *For tidsplan, herunder datoer for forsøgets påbegyndelse, forsøgsperiode og afslutning henvises venligst til punktet timeline i indholdsfortegnelsen*

Contact details of steering committee, DSMB and CEAC

Sponsor	Department of Cardiology, Y. Bispebjerg & Frederiksberg, University Hospital. Bispebjerg Bakke 23, 2400 NV, København, Denmark
Principal investigator, SC member	Professor Eva Prescott, MD, DMSc, Department of Cardiology, Bispebjerg Frederiksberg Hospital
Project manager, SC member	Thomas S. G. Sehested, MD, Department of Cardiology, Copenhagen, University Hospital, Herlev and Gentofte, Denmark
Project assistant	Anna Meta D. Kristensen, Stud. Med, Department of Cardiology, Bispebjerg Frederiksberg Hospital
SC member	Professor Ann Dorthe Zwisler, MD, PhD, Danish Centre for Rehabilitation and Palliative Care, Odense University Hospital and University of Southern Denmark
SC member	Professor Svend Eggert Jensen, Department of Cardiology, Aalborg University Hospital
SC member	Kristian Korsgaard Thomsen, MD, PhD, Department of Cardiology, Esbjerg Hospital
SC member	Professor Mogens Lytken Larsen, MD, DMSc, Department of Cardiology, Aalborg UniversityHospital
SC member	Ida Gustafsson, MD, PhD, Department of Cardiology, Bispebjerg Frederiksberg Hospital
SC member	Professor Michael Hecht Olsen, Department of Cardiology, Holbæk Sygehus, region Seeland
SC member	Ann Bovin, MD, PhD, Department of Cardiology, Regional Hospital West Jutland
SC member	Professor Hans Erik Bøtker, MD, DMSc, Department of Cardiology, Aarhus University Hospital
SC member	Karsten Veien, MD, PhD, Department of Cardiology, Odense University Hospital
SC member	Professor Christian Torp-Pedersen, MD, DMSc, Ålborg University Hospital, Department of Health Science and Technology
SC member	Sussie Foghmar, Hvidovre Amager Hospital, Representative of Cardiac Rehabilitation Nursing
SC member	Charlotte Cerquira, MD, PhD, Department Manager, The regional clinical quality development program
SC member	Theis Lange, biostatistician, Section of Biostatistics, University of Copenhagen
Data Safety Monitoring Board	Kristian Thygesen (cardiologist) Chris Gale (cardiologist) Biostatistician TBD

Furthermore, all primary investigators have been invited to the steering committee to ensure that all sites are represented.

Signature page

Title: Danish trial of beta blocker treatment after myocardial infarction without reduced ejection fraction (DANBLOCK)

Protocol ID no:

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I hereby declare that I will conduct the study in compliance with the Protocol, ICH-GCP and the relevant governing requirements and law:

Name	Role	Signature	Date
Eva Prescott	Principal investigator & sponsor		
Thomas S. G. Sehested	Project manager		
Ann Dorthe Zwisler	Representing the Working group on Cardiovascular Prevention and Rehabilitation		
Mogens Lytken Larsen	Representing the Working group on Cardiovascular Prevention and Rehabilitation		
Ann Bovin	Representing the Working group on Cardiovascular Prevention and Rehabilitation		
Ida Gustafsson	Regional PI, Eastern Denmark (Region H)		
Michael Hecht Olsen	Regional PI, Sealand (Region Sjælland)		
Svend Eggert Jensen	Regional PI, Northern Denmark (Region Nord)		
Kristian Korsgaard Thomsen	Representing the Danish cardiac rehabilitation database (MD part) and Regional PI Southern Denmark (Region Syd)		
Michael Mæng	Regional PI, Middle Denmark (Region Midt)		
Karsten Veien	Representing the Danish society of cardiology working group of ACS & PCI		
Christian Torp-Pedersen	Expert trialist		
Sussie Foghmar	Representing the DHRD (nursing part)		
Charlotte Cerquira	Representing RKKP & DHRD		
Theis Lange	Expert biostatistician		

Local investigators/MD responsible for conducting the trial

Please see appendix 8. This will be kept updated and any changes reported to EC and DMA/EudraCT

Protocol synopsis

Protocol title: Danish trial of betablocker treatment after myocardial infarction without reduced ejection fraction (DANBLOCK)

Primary investigator and sponsor: Professor, Eva Prescott. Bispebjerg & Frederiksberg, University Hospital, Department of Cardiology, Y, Bispebjerg Bakke 23, 2400 NV, København, Denmark

Aim: To determine whether long-term treatment with oral betablocker (BB) therapy after myocardial infarction (MI) in patient with no heart failure reduces the composite outcome of recurrent non-fatal MI, all-cause mortality, revascularization with percutaneous coronary intervention or coronary artery bypass graft, stroke, heart failure, malignant ventricular arrhythmia, or resuscitated cardiac arrest.

Intervention: BB therapy versus no therapy.

Study Design: Prospective, randomized, controlled, open-label, blinded endpoint (PROBE design) clinical trial testing the benefits of long-term oral BB therapy in patients discharged after an acute MI.

Main Inclusion Criteria: Patient that have suffered a MI, both Non-ST elevation MI and ST elevation MI, can be randomized within 14 days of MI with no signs of heart failure and a LVEF>40%.

Main Exclusion Criteria: Any indication or contraindication for BB treatment other than secondary prevention according to the treating cardiologist

Sample Size: A total of approximately 2760 patients (the trial is event driven) will be recruited and randomized 1:1 to BB treatment (type and dosage according to treating physician) or no BB treatment. Treatment must be initiated within 14 days of MI.

Location: All departments of cardiology in Denmark are invited to participate. All patients admitted to hospital for MI will be screened for in- and exclusion criteria and contacted if eligible.

Study Period: Anticipated recruitment period: 6 years. Estimated date of first patient enrolled: December 2018. Estimated end of follow-up December 2024.

Treatment Duration: Estimated (non) treatment duration of 11 months-6 years.

Follow-up: Patients will be followed from the randomization date until end of follow-up with respect to the primary and most secondary endpoints.

Endpoints:

1. <u>Primary:</u>
    - All-cause mortality, recurrent non-fatal MI, revascularization with PCI or CABG, stroke, heart failure, malignant ventricular arrhythmia, or resuscitated cardiac arrest.
2. <u>Secondary:</u>
    - To determine whether long-term treatment with BB therapy reduces:
        - Each of the components of the primary outcome
        - CV mortality
        - Atrial fibrillation/atrial flutter and other tachyarrhythmia
        - Unstable angina
        - Angina symptoms
        - Exercise capacity
    - To determine whether long-term treatment with BB therapy increases:
        - Bradycardia, syncope or need for pacemaker

        - Asthma and COPD symptoms
        - Stroke
        - Blood pressure control
        - Diabetes (new diagnosis and dysregulation)
        - Peripheral artery disease
    - To determine whether long-term treatment with BB affects the following patient reported outcome (PRO):
        - Quality of life, depression, sexual dysfunction and sleep disorders
3. Safety endpoint:
        - A composite of recurrent MI, heart failure, all-cause mortality, malignant ventricular arrhythmia, or resuscitated cardiac arrest 30 days after randomization.

Assessment of primary study and safety end points: The primary and safety endpoints will be obtained through individual-level linkage between data obtained at inclusion and nationwide administrative registries: 1. The Danish Cause of Death Registry, 2. The Danish National Patient Register that holds information on all hospital admissions with registration in accordance with the international classification of disease 10th revision (ICD-10), 3. The Danish Register of Medical Product Statistics holds information concerning redeemed prescription medication in accordance with the anatomical therapeutic chemical (ATC) classification system and 4. The Central Person Registry (CPR-registeret) which holds information on whether the person is alive and living in Denmark. Serious adverse events (SAE) will be monitored through patient reported hospital admission by surveys every 3 months combined with local follow-up on patients that do not respond to surveys.

Assessment of secondary study end points: Secondary endpoints will be assessed through individual-level linkage between administrative registries, clinical registries on cardiac rehabilitation (DHRD), e-questionnaires for PRO and hospital admissions as described above every 3 months.

Intervention and dosage of BB treatment: The intervention will be active treatment with BB, type and dosage according to treating cardiologist choice and control will be standard care (without BB treatment). The treating cardiologist is recommended to use the highest dose deemed tolerable for the patient at the time of randomization. Dosage, adherence and cross-over will be monitored through linkage to the Danish Register of Medical Product Statistics.

Sample size considerations: Assuming a hazard ratio of 1.2 for the non-treated group compared to the treated the trial has 80% power to detect this effect with an accumulation of 950 events of the primary endpoint. As the study is event-driven linking the study data to the registries will be crucial for providing an estimate of the event rate of the new composite endpoint and thus the number of study participants and follow-up length needed.

Statistical Analysis: Intention-to-treat analysis will be carried out. Additionally, a secondary per-protocol analysis will be performed, where compliant BB-users are considered exposed during follow-up. Outcome analysis will be assessed by Cox-regressions.

Data Safety Monitoring Board (DSMB): This committee consisting of two senior cardiologists and one trial-science statistician will overview safety and will have access to unblinded data. They will formally review the accumulating data every 6 months throughout the study period to ensure there is no avoidable increased harm to patients. The DSMB may recommend trial termination due to excess risk associated with no treatment with BB.

Economic conditions: Payment of study expenses will follow patient inclusion: Each participating centre will be re-imbursed for the time spent on screening and patient inclusion, in addition to a set-up investigators fee. Costs of medication is by the patient (exempted from Paragraph 13 by DMA)

Recruitment: All patients admitted to hospital for MI will be screened for in- and exclusion criteria and contacted if eligible. Logistics of identifying and contacting the patients will be organized locally; some hospitals will randomize patients before discharge, others will contact patients after discharge. Patients will be randomized 1:1.

Publication policy: On study completion the results will be submitted for publication in an international medical journal. The results of this study will also be submitted to the Competent Authority and the Ethics Committee according to EU and Danish regulations.

List of abbreviation and definitions of terms

Abbreviations	**Explanations**
AHA/ACC	American Heart Association/American College of Cardiology
BB	Beta blockers
CABG	Coronary artery bypass graft
CEAC	Clinical Events Adjudication Committee
DCS	Danish Society of Cardiology
DHRD	Danish Cardiac Rehabilitation database
DMA	Danish Medicines Agency (Lægemiddelstyrelsen)
eCRF	Electronic case record form
ESC	European Society of Cardiology
GP	General practitioner
HF	Heart failure
LVEF	Left ventricular ejection fraction
MI	Myocardial infarction
NSTEMI	Non-ST elevation myocardial infarction
PCI	Percutaneous coronary intervention
PRO	Patient reported outcome
PROBE	Prospective, randomized, open label, blinded endpoint evaluation
QoL	quality of life
REDCap	Research electronic data capture
RKKP	The regional clinical quality development program
STEMI	ST-elevation myocardial infarction
UAP	Unstable angina pectoris

Introduction

Prognostic benefit of betablocker treatment after MI

Beta-blockade has been a cornerstone in the treatment after acute myocardial infarction (MI) for decades. Beta blockers (BBs) competitively inhibit the myocardial effects of catecholamines and reduce myocardial oxygen consumption by reducing blood pressure, heart rate and myocardial contractility. Trials have shown benefit of acute treatment with BB in hemodynamically stable patients [1,2], solid evidence of survival benefit in patients with reduced left ventricular ejection fraction (LVEF)[3–6] and a 23% reduction in mortality in early long term post-MI trials.[7]

Most BB trials were conducted before reperfusion was standard treatment and before efficient secondary prevention with statins and antiplatelet agents reduced case-fatality. In contemporary post MI patients, the ischemic substrate is small, risk of arrythmias reduced and the outlook much improved.[8,9] Additionally, in hypertension, BBs are no longer first line treatment due to their inferior effect on reduction of coronary heart disease, stroke and mortality compared to alternative treatment options.[10] Therefore, studies have called the current role of BB after MI with preserved LVEF into question.[11]

A meta-analysis of randomized trials that compared effect of BB treatment in pre- and reperfusion era concluded that the reduction in mortality with BB treatment was only documented in the pre-reperfusion era.[12,13] In a meta-analysis of more recent trials and observational studies, including only patients with acute MI who underwent PCI, all-cause mortality was not significantly reduced in patients with preserved LVEF.[14] Long-term BB treatment has not been investigated in patients with non-ST-segment elevation MI and preserved LVEF.[15] Large registry based studies have given mixed results on the effect of long-term treatment with BBs[11,14,16–25] and are likely to be biased. A meta-analysis of randomized trials of BB in heart failure (HF) recently reported an insignificant mortality reduction in the patients with LVEF 40-49% but was based on only 575 randomized patients.[26] Thus, the beneficial effect of long-term treatment with beta-blockade after MI for patients with preserved and midrange LVEF is controversial. The lack of evidence in the reperfusion era has resulted in divergence between guideline recommendations: the AHA/ACC guidelines strongly recommend BB in patients with STEMI (Class I recommendation) and less strongly in patients with NSTEMI (IIa) while the ESC guidelines recommend treatment in STEMI (Class IIa) but have no recommendations in NSTEMI.[15,27–29] Danish guidelines recommend routine treatment for a minimum of two years following MI. Consequently, most patients in Denmark are treated with BB after MI.[30]

The patient perspective

Despite wide-spread use and tolerability, side-effects are well-known and common. They include depressive symptoms, sexual dysfunction, vivid dreams, cold hands and feet, weight gain and fatigue. Not all of these side effects are supported by evidence from randomized trials, e.g., the association between BB and depression has yet to be proven. BBs also reduce maximal heart rate and recent evidence indicates that patients treated with BBs have lower maximal exercise capacity, an indicator of daily function capacity and a strong prognostic marker. Patients participating in cardiac rehabilitation often complain of side effects and upon discontinuation many patients feel relief. The lower compliance with BB treatment compared to other cardiovascular medications is thought to be related to side effects.[30] On the other hand, BB treatment reduces angina symptoms, which has profound effects on quality of life (QoL). Thus, the benefit of BB treatment on survival outlook needs to be weighed against the impact on side-effects as well as QoL.

Study Hypothesis

Treatment with beta blockers is superior to not treating with beta blockers following myocardial infarction in patients without heart failure (LVEF of >40%) in terms of all-cause mortality, recurrent myocardial

infarction, stroke, revascularization with percutaneous coronary intervention (PCI) or coronary bypass intervention graft (CABG), heart failure, malignant ventricular arrhythmias or resuscitated cardiac arrest.

Study objectives

Primary objective and endpoints:

To determine whether long-term treatment with BB therapy after MI with no signs of HF reduces the composite outcome of:

- Death from any cause
- Recurrent acute myocardial infarction
- Stroke
- Revascularization with PCI or CABG
- Malignant ventricular arrhythmias or resuscitated cardiac arrest
- Heart failure

Secondary objective and endpoints:

To determine whether long-term treatment with BB therapy reduces:

- Each of the components of the primary outcome
- Cardiovascular mortality
- Atrial fibrillation/atrial flutter and other tachyarrhythmias
- Angina symptoms
- Exercise capacity
- Unstable angina

To determine whether long-term treatment with BB therapy increases:

- Bradycardia, syncope or need for pacemaker
- Asthma and COPD symptoms
- Blood pressure control
- Diabetes (both newly diagnosed and dysregulation of existing diabetes
- Peripheral artery disease (PAD)

To determine whether long-term treatment with BB affects the following patient reported outcome (PRO)

- Quality of life (including angina and dyspnea), depression, sexual dysfunction and sleep disorders

In case of effect of BB treatment on primary outcome to investigate the cost-effectiveness of long-term treatment with BB in relation to health-related QoL.

Study endpoints

Primary endpoint

The composite endpoint of all-cause mortality, recurrent non-fatal MI, revascularization with PCI or CABG, stroke, heart failure, malignant ventricular arrhythmia, or resuscitated cardiac arrest will be assessed through registries and adjudication. All primary and safety endpoints are monitored and adjudicated as described below and under safety while the study is ongoing. The final primary endpoint will be through a combination of adjudicated endpoints and registry linkage.

Adjudication of endpoints

Adjudication of endpoints will be through review of hospital records, a clinical endpoint adjudication committee (CEAC), local adjudication and rigorous application of endpoint-definitions following the objective criteria in the 2017 Cardiovascular and Stroke Endpoint Definition for Clinical Trials. [31] (Please see

appendix 5). Local end-point adjudication will be monitored by the GCP/sponsor. The original primary endpoints (death, unstable angina, acute myocardial infarction, heart failure and stroke) will continuously be adjudicated locally. There will an independent event adjudication committee consisting of 3 Scandinavian cardiologists. All primary endpoints will be adjudicated by the CEAC:

Secondary endpoints and their justification

- The endpoints cardiovascular mortality, atrial fibrillation/atrial flutter, other tachyarrhythmia, bradycardia, syncope, need for pacemaker, worsening of asthma/CODP and PAD will be assessed through registry linkage for hospital admission and through review of hospital admission as described under 'Safety Monitoring and Reporting'.
- Common side-effects to BB: Quality of life measures (EQ5D), depressive and anxiety symptoms (HADS), sexual dysfunction in men and women (IIEF, FSFI, short versions) and sleep disorders (Bergen insomnia scale)
- Symptom-burden after MI (NYHA, CCS, Seattle Angina questionnaire): Despite complete revascularization a significant proportion of patients still have angina symptoms. Continued angina affects QoL and is associated with anxiety and depression. BBs are first-line treatment of angina pectoris but whether this effect of BB is clinically relevant in a contemporary post-MI population is unknown.
- Benefit from cardiac rehabilitation on VO2peak: BB treatment leads to reduced maximal heart rate and increased muscle fatigue. Early trials have indicated that exercise capacity is not affected by treatment, but this has never been tested in a randomized trial of patients with no HF. We wish to determine whether VO2peak, an objective indicator of physical functioning and an important predictor of prognosis, is affected by BB treatment.
- Blood pressure control: Any beneficial effect of BB treatment in this pragmatic design, where blood pressure is not controlled as part of the study protocol, may be due to better blood pressure control. BB treatment will also increase pulse pressure which might increase the risk of stroke[32] and counteract any beneficial effect of BB treatment. We plan substudies to test the hypothesis that BB treatment is most beneficial in patients with high heart rate or diastolic hypertension and the least beneficial in patients with isolated systolic hypertension[33], prediabetes[34], diabetes[32] or new onset diabetes during follow-up. Blood pressure will be monitored during cardiac rehabilitation and use of blood pressure lowering medication will be assessed through the National Prescription Registry.
- Diabetes control: The use of BBs in patients with diabetes may reduce insulin sensitivity[35], increase plasma glucose, mask hypoglycaemic symptoms and increase the risk of new onset diabetes[36–38] but limited data is available. We will assess the metabolic control among patients with established diabetes and the incidence of new onset diabetes.

Study design

Overall study design

The trial will be a prospective, randomized, controlled, open-label, blinded endpoint (PROBE design[39]) clinical trial testing the benefits of long-term oral BB therapy in patients discharged after an acute MI. A total of approximately 2760 patients with MI, both NSTEMI and STEMI, with no signs of HF during hospital admission and with a LVEF of >40% will be recruited and randomized 1:1 to BB treatment (type and dosage according to treating cardiologist) or no BB treatment. Treatment will be initiated within 14 days of MI. Pragmatic clinical trials are performed under normal conditions with the intention of providing results that are more applicable to clinical practice and decision making. Outcomes will be from hospital records, clinical registry data and e-questionnaires keeping costs at a minimum. Bias will be reduced through 1) Randomization, 2) Since the design is open label, rigorous endpoint adjudication is essential and hard, clinical meaningful endpoints have been selected as primary endpoints, 3) To address multiplicity concerns the primary endpoint is a composite endpoint, and 4) The pragmatic design of this trial increases the generalizability of its conclusions to real daily clinical practice.

Treatment responsibility during the trial

After the patient has been included in the trial, randomized and BB has been prescribed in the active treatment group, further follow-up and treatment responsibility for the patient is not with the investigator, but is according to the local cardiology clinical practice: This can be cardiologist out-patient care in the department of cardiology, in the cardiac rehabilitation or by the patient's GP. The patient receives a card with information on participation in the trial, website with description of the trial (hosted by OPEN), contact information on local MD responsible for the DANBLOCK trial and a reminder to report any hospital-admission in the e-questionnaire every 3 months.

Recruitment plan and time frame

Patients can potentially be recruited from all 36 departments of Cardiology in Denmark. All patients admitted to hospital for MI will be screened for in- and exclusion criteria and contacted if eligible. Logistics of identifying and contacting the patients will be organized locally; some hospitals will randomize patients before discharge, others will contact patients after discharge.

- Study period: From December 2018 to December 2024
- Recruitment period: Between December 2018 and January 2024
- Treatment duration: Minimum 6 months from randomization
- Follow-up: Patients will be followed until December 2024
- Anticipated publication of results will be June 2025

Study population

Selection of Study population

Patients that have suffered a first-time or recurrent MI (both non-ST elevation MI and ST elevation MI are eligible). Patients will be screened for in- and exclusion criteria and contacted (if eligible) before discharge or during cardiac rehabilitation. Randomization must be no later than two weeks after myocardial infarction.

Inclusion Criteria

To be eligible for this study the following inclusion criteria must be meet:

- 18 years or older
- LVEF > 40%
- Myocardial infarction (MI) within previous two weeks

The diagnosis of acute MI must meet the Universal ESC definition of MI[40]: Detection of a rise and/or fall of cardiac biomarker values with at least one value above the 99th percentile upper reference limit and with at least one of the followings:

  - Symptoms of ischaemia.
  - New or presumed new significant ST-segment–T wave (ST–T) changes or new left bundle branch block (LBBB).
  - Development of pathological Q waves in the ECG.
  - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

Exclusion Criteria

Patient will be excluded if they meet any of the following criteria:

- Clinical evidence of heart failure at the time of discharge
- Pregnancy or of childbearing age not using safe anticonception throughout the study period**
- Lack of signed informed consent and expected cooperation during follow-up

** The BB used in the trial have not documented safety during pregnancy. The following is considered safe anticonception: Hormonal anticonception, encompassing (p-piller, implantat, transdermal depotplastre, vaginalring eller depotinjection)

Any medical condition where BB treatment is indicated according to the treating physician, which may include:

- BB treated arrhythmias
- BB treated hypertension
- Reduced left ventricular ejection fraction
- Cardiomyopathies

Any contraindication to BB treatment according to the treating physician, which may include:

- Hypotension
- Brady-arrhythmias
- Severe peripheral artery disease
- History of not able to tolerate BB-therapy
- Severe COPD or asthma
- Severe valvular heart disease
- Any condition (i.e. dementia) that could lead to increased risk for the patient when treated with BB-therapy

The exclusion is not limited to this list and the responsible treating physician will need to consider if any other contraindication might exist for the patient. Both patients treated with a BB before their MI and patients in whom BB was initiated during the hospital admission are eligible for the trial. Patients are allowed to participate in other contemporary studies.

Original sample size and power calculation

In Denmark annually 9100 patients suffer a first-time or recurrent MI with a NSTEMI-STEMI ratio of approx. 3:1.[41,42]

Pilot work on Danish data

We used the Danish nationwide registry (2010-2015) to identify a population of patients with MI, but without a previous diagnosis of HF. The monthly risk of the primary endpoint (the composite of all-cause mortality, recurrent MI, stroke, heart failure and unstable angina pectoris) was 1.62 % and the monthly risk of all-cause mortality was 0.06 %. These values formed the basis for the presented power analysis.

Sample size

Some patients need BB therapy for other indications such as HF, atrial fibrillation or continued angina pectoris and will be excluded after the judgment of the attending cardiologist. A conservative estimate is that 65% of MI patients will be eligible for the study and the number of eligible MI patients per year approximately 5950.[43] We conservatively estimate 30% will be included in the trial, equivalent of 3570 patients over the 2-year inclusion period (2*5950*0.3). We thus plan to screen approximately 10000 patients and include 3570 subjects and we expect that 2500 patients will provide data from participation in a full cardiac rehabilitation program.

Power calculation

Analysis will be intention to treat (ITT) i.e. patients will be analysed in the group to which they were randomized. We expect some cross-over between groups but aim to keep this at a minimum primarily by informing the participating investigators of medical alternatives to change in BB treatment (e.g. alternative medical treatment for blood pressure control and alternative medication for angina). Cross over will be

monitored through patient-report (every 3 months) and if excessive may lead to decisions regarding futility of the trial.

From the arguments in the previous section we deduce that a monthly event rate of the primary outcome for the care as usual group of 1.6 % can be presumed and that around 150 patients can be included per month. These patients will be randomized 1:1 to the two groups.

We will analyze the power of an ordinary superiority trial. The trial will be designed to achieve a pre-specified number of events. Assuming a hazard ratio of 1.2 for the non-treated group compared to the treated the DANBLOCK trial alone has 80% power to detect this effect with an accumulation of 900 events of the primary endpoint. However, for logistic reasons inclusion will be stopped substantially before this number of events is achieved. This is because events will keep accumulating for 2 years after last-patient-randomized. We estimate that we will reach that number of events in around 30 months after including the first patient. With two years inclusion and further two years follow-up the trial would have 90% power. However, the true event rate of this study might be lower than what is found in the registers because of difficulty with including and obtaining informed consent from the sickest patients. This will lower power in an unpredictable way. In summary we feel confident that the planned study has at least 80% power.

After one year of patient inclusion, we will assess the actual event-rate and re-assess whether the goal of 900 events can be achieved with the planned inclusion period. Based on this information the Steering Committee will decide on whether patient inclusion should be extended or stopped early due to efficacy. This does not change the sample size planned for, which remains at 900. It is merely a logistic consideration.

The study data from DANBLOCK will be pooled with results from BETAMI and will be initially published together. Furthermore, a meta-analysis will be carried out in collaboration with REDUCE. The combined power of the meta-analysis will be calculated.

For the secondary outcomes (except hospital admissions) the DANBLOCK trial has ample power, e.g. with V02peak assessed on 2000 patients we will have 80% power to detect a difference in improvement in VO2peak between the two groups of 0.5 ml/kg/min conservatively assuming a mean improvement of 2.4 and a SD of 4.3 (from existing registry data).

Amendment 2022

The inclusion- and event rate in DANBLOCK have been continuously assessed since the first patient was randomized in December 2018. The inclusion- and event rate have been lower than expected, in part due to COVID-19. In July 2022, 3.5 years since the first patient was randomized, approximately 2000 patients have been randomized and the steering committee has been compelled to apply for changes in addition to the already approved prolongation to ensure the completion of the study. The composite primary endpoint has been expanded from all-cause mortality, heart failure, recurrent MI, stroke and unstable angina to all-cause mortality, heart failure, recurrent MI, stroke, revascularization with PCI or CABG, malignant ventricular arrhythmia or resuscitated cardiac arrest. Furthermore, the follow up period for the last patient randomized has been changed from 2 years to a minimum of 6 months and the study will be event driven. The decision to change the primary endpoint was done prior to registry linkage and with no knowledge of the distribution of endpoints. As stated above, at study end results from DANBLOCK will be pooled with results from BETAMI and will be initially published together. A new power calculation has therefore been made. The analysis is based on a time-to-event outcome. We aim to have sufficient power to detect a true treatment effect with a hazard ratio of 1.2. It is observed that 80 % power is obtained with approximately 950 events in total. Completion of DANBLOCK and BETAMI is therefore based on the total number of events (approximately 950) in the two trials. Study inclusion will be terminated when the observed number of events and the observed event rate indicate that a total number of events will be accumulated within 6 months, to fulfil the criteria of a minimum follow-up of 6 months for all subjects randomized in the trial.

Linking the study data to the registries will be crucial for providing an estimate of the event rate of the new composite endpoint and thus the number of study participants and/or follow-up length needed. A statistical analysis plan describing all the statistical methods will be produced prior to database lock in close collaboration with the BETAMI study group including statisticians. The SAP will also describe the analyses set and all endpoints in detail.

Treatment

Patients will be randomized 1:1. The intervention will be active treatment with BB, type and dosage according to treating cardiologist choice and control will be standard care without BB treatment. The study is open label. The treating cardiologist is recommended to use the highest dose deemed tolerable for the patient. The patient will be randomized within 14 days during admission or after discharge but no more than 14 days after myocardial infarction. All other standard of care therapy will be prescribed according to guidelines. Concomitant medication will be ascertained through linkage to the Danish Prescription Registry.

Type, dosage and administration of drug

If the patient is randomized to BB therapy the treatment will be given orally. Dosage used will reflect contemporary management and will be according to the treating cardiologist. The highest tolerated dose is recommended. The following list is on the generic BB drugs and common dosage

- Bisoprolol up to a total dose of 10 mg daily
- Carvedilol up to a total dose of 50 mg daily
- Metoprolol succinate up to a total dose of 200 mg daily
- Nebivolol up to a total dose of 10 mg daily

Duration of treatment

Treatment is planned from enrolment to study end, i.e. a minimum of 6 months from randomization. After study end continued BB treatment, discontinuation or uptake of BB treatment is according to the treating cardiologist/GP.

Costs of medication

The costs of medication for patients randomized to BB treatment will be covered by the patients. The study has been exempted from paragraph 13 in 'Bekendtgørelse om god klinisk praksis I forbindelse med kliniske forsøg med lægemidler på mennesker' by the Danish Medicines Agency.

Drug accountability and labelling

BB use will be ascertained through the prescription registry and through information in e-questionnaires every 3 months throughout the study period. There will be no labelling and batch registration of the prescribed medication following an exemption from the DMA because a) The IMPs have marketing authorization. b) The IMPs have been in extensive clinical use for decades, hence the safety profile of these drugs is very well established and new information in this regard is unlikely to emerge, c) The patients who are randomized to receive the IMP would have received the IMP regardless of the inclusion in the trial, at the same doses and duration as in the trial, i.e. the treatment will be in accordance with current clinical practice, d) The safety of the patients who are randomized to receive the IMP will not be altered because of inclusion in the trial and e) The suggested exemption will not alter the safety of the subjects.

Patient compliance and concomitant medication

Information on compliance, dosage and crossover during follow-up and concomitant medication will be monitored through linkage to the Danish Prescription Registry and through the e-questionnaire as described above.

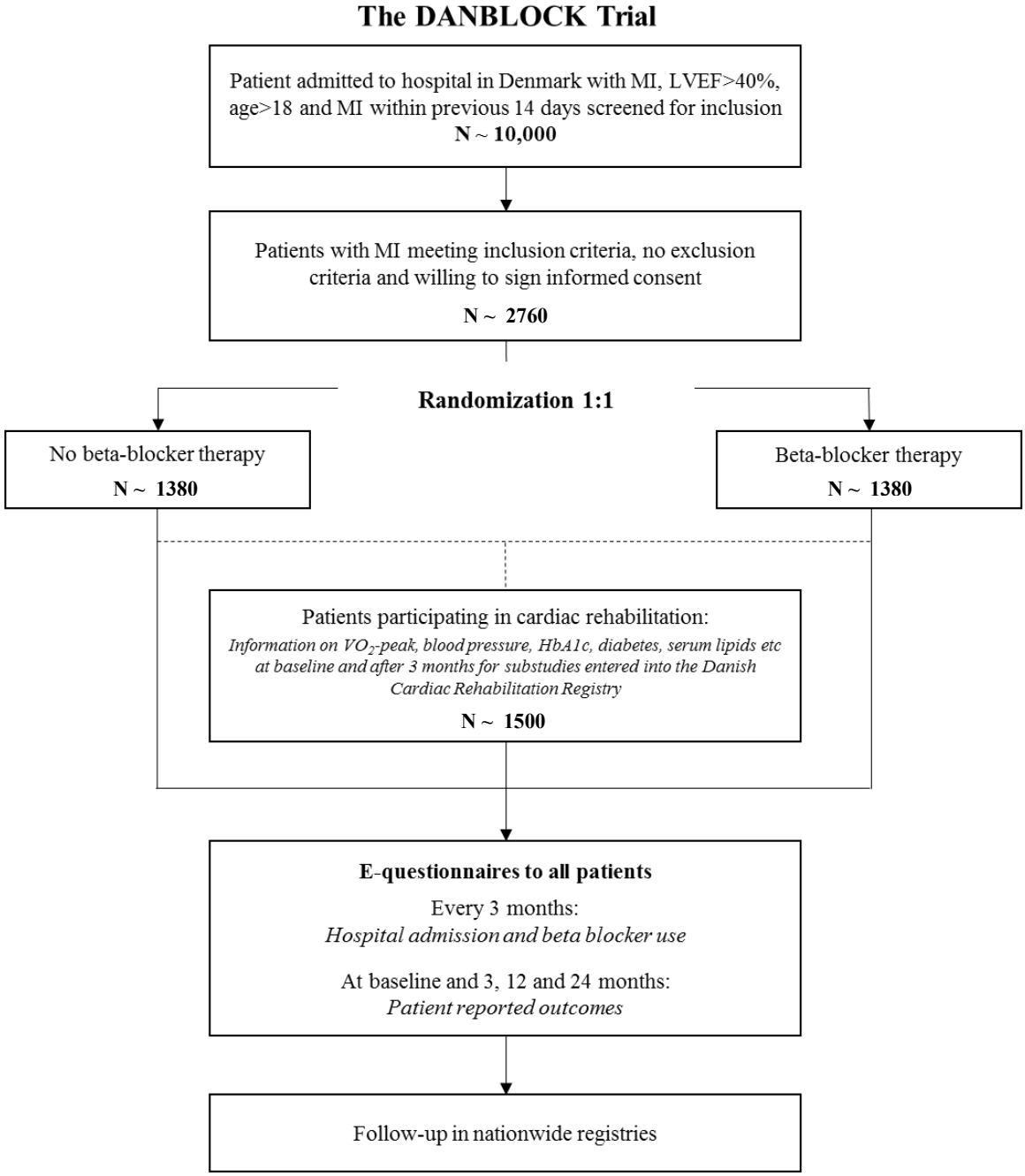
Criteria for interruption of study medication

BB can be stopped in the intervention arm and taken up in the control arm at the discretion of the attending cardiologist or GP. Criteria for stopping medication include but are not limited to:

- Pregnancy or wish to become pregnant
- Safety issues as judged by the investigator
- Withdrawal of consent
- Adverse events and adverse reactions related to BB treatment

Study procedures

Study Flowchart



Screening

Patients admitted to hospital for MI will be screened for in- and exclusion criteria in the participating sites. Patients fulfilling the inclusion criteria will be registered in the eCRF with information on reasons for not being included in the trial.

Randomization and datahandling

Randomization and eCRF (electronic case record forms) will be by the REDCap (Research Electronic Data Capture) system through OPEN. This is an open-label trial and both patient and the local investigator will be aware of treatment allocation. Data will be stored in a secure server and will be kept confidential according to legal regulations for data protection. After randomization, each patient will receive a card identifying the

clinical trial that will contain a brief explanation of the aims of the trial. In the trial card, the arm in which the patient was included (BB yes or no) will be stated, together with address of the website with information on the trial, a reminder to report hospital admissions in the e-questionnaire every 3 months and contact information to the MD responsible for the trial locally ('local investigator') and study nurse. The patient will be encouraged to contact him/her for any question related to the trial either from the patient or from any physician seeing the patient. The patients' GP will be informed of the trial in the discharge letter. No other incentives will be established for participating in the study.

Subject identification

Once patients have signed the informed consent form, the REDCap system will assign an electronically identification number that can be linked to the nationwide administrative personal identification number (CPR).

Data Sources

Data sources are patient records, e-questionnaires and administrative and clinical registries. All outcome is registry based or from e-questionnaires. We anticipate that >80% of the patients will have a least one consultation by a nurse/cardiologist as part of introduction to cardiac rehabilitation. This will enable us to monitor a number of outcomes that are routinely collected and entered into the nationwide Danish Cardiac Rehabilitation database (DHRD).

Patient records

Patient records will be consulted for baseline information, information in relation to SAE and for adjudication of outcomes.

Registries

The following registries will be used (please see below and Table 1 for description of the data extracted):

- The Danish National Patient Register (Landspatientregistret) that holds information on all hospital admissions with registration in accordance with the international classification of disease 10th revision (ICD-10)
- The National Death Registry (Dødsårsagsregisteret), which holds information on cause of death
- The Central Person Registry (CPR-registeret) which holds information on whether the person is alive and living in Denmark
- The National Prescription Register (Lægemiddelstatistikregisteret), which holds information on medication deemed by the patient
- The National Register of Laboratory Results (Laboratoriedatabasen), which holds information on laboratory results
- The clinical registries on cardiac rehabilitation (DHRD) that holds information on type of MI, left ventricular ejection fraction (LVEF), clinical data, risk factor controls, laboratory data as well as results from functional testing at baseline and after completion of cardiac rehabilitation.

Electronic-questionnaires

E-questionnaires are used for monitoring of safety/outcomes and for monitoring of patient reported outcomes on quality of life, symptoms, etc. E-questionnaires on safety are dispatched every 3 months and described further below. For the expected 10-20% non-responders safety/outcome data is ascertained through electronic health records.

Patient reported outcome (PRO) will be collected regularly (see table 1) by e-questionnaires from the REDCap system (OPEN), which fulfils all requirements for data security and is recommended for research data-management (data-entry and storage) of research data in the Danish Regions. All questionnaires used are validated and commonly used. The e-questionnaire will be administered by e-mail. For patients who do

not have an e-mail the questionnaire will be sent by ordinary mail. Instructions on how to fill in the questionnaire will be forwarded as part of the e-questionnaires.

Data collected

(see table 1 for details)

All data will be entered into an eCRF using the REDCap system and monitored through OPEN.

Screening data

- Patient identity (CPR)
- Age, gender
- Inclusion criteria including type and date of index event (STEMI/NSTEMI) and LVEF-value
- Exclusion criteria
- Reasons for not being included in trial

Baseline data

- Demographics
- Cardiovascular risk factors
- Major comorbidities
- Procedures performed during index event (CAG, PCI, CABG)
- Laboratory data, including eGFR, Hba1c and lipids
- Exercise capacity measured by VO2peak (only in patients attending cardiac rehabilitation)
- Patient reported outcomes (PRO) on symptoms and quality of life measures (as described under secondary outcomes)

    a. **Measures for quality of life**: EQ5D (a measure of health-related quality of life that can be used in a wide range of health conditions and treatments)

    b. **Measures of depression and anxiety**: HADS (Hospital Anxiety and Depression Scale)

    c. **Measures of sexual dysfunction one year after MI**: IIEF (The International Index of Erectile Function), FSFI (Female Sexual Function Index) (short versions)

    d. **Measures of sleeping disorder**: Bergen insomnia Scale

    e. **Angina burden following MI**: NYHA (New York Heart Association); CCS (Canadian Cardiovascular Society grading of angina pectoris); Seattle Angina questionnaire (SAQ) (for those who report angina symptoms).

Data Collected during follow-up: Primary, most secondary and safety endpoints are monitored through e-questionnaires, registry linkage and electronic health records throughout the trial. Follow-up also includes DHRD data and PRO from e-questionnaires described above. Patient reported SAE will be administered every 3 months. PRO through e-questionnaires will be administered at 3, 12 and 24 months.

Registry data

The primary endpoints and all secondary endpoints will be ascertained through registry linkage, e-questionnaires and patient records. Adherence to BB and other medication is ascertained through The Danish Register of Medical Product Statistics, which holds information concerning redeemed prescription medication in accordance with the anatomical therapeutic chemical (ATC) classification system. From this register we will be able to determine compliance, discontinuation, type and estimate dose of BB therapy.

Table 1. Overview of activities

	Screening population	Patients included in the trial						
	Screening	**Baseline**	**Treatment period following randomization**					**Study end**
Time and assessment	0-14 days following MI	At randomization	3 mo	6 mo	1 year	24 months	Every 3 mo thereafter	
In/exclusion criteria, basic information and reasons for not entering the trial [1]	x							
Informed consent, randomization and collection of baseline data[2]		x						
Self-reported e-questionnaires on QOL and symptomburden[3]		x	x		x	x		
Risk factor control and benefit from cardiac rehabilitation[4]								x
Adherence to medication[5]								x
Adherence to medication – selfreported[6]			x	x	x	x	X Every 3 months until study end	x
Patient reported of SAE in e-questionnaire every 3 months[8]			x	X + at 9 mo	X + at 15, 18 and 21 mo	X	X Every 3 months until study end	x
Endpoints from registry data[7]								During follow up

1 All patients with MI who fulfil inclusion criteria should be screened and entered in the eCRF. Data is collected during hospital admission.

[2] Data collected during hospital admission from patient and hospital records

[3] The following e-questionnaires on symptoms and quality of life will be administered: EQ5D, HADS, IIEF/FSFI (short versions), Bergen Insomnia Scale, NYHA, CCS, SAQ (for those reporting symptoms of angina). Adherence to medication will also be assessed.

[4] Data on blood pressure, serum lipids, diabetes, hba1c and VO2peak before and after rehabilitation will be through registry linkage to DHRD at study end. This data is only available for patients participating in cardiac rehabilitation.

[5] Adherence to treatment group as well as other medication will be from the National Prescription Register at study end. All primary analysis will be by the intention-to treat principle.

[6] Self-reported continued adherences to treatment group will be gathered every 3 months

[7] Hospital admission or death from a primary or secondary outcome be ascertained from the Danish National Registers, e-questionnaires and patient records.

[8] An e-questionnaire on SAE will be sent to patients every 3 months throughout the study period with a reminder after 5 and 10 days to non-responders. The patient will be given a trial card describing the trial name, website for description of the trial, contact information on investigator and a reminder to report hospital admissions in the e-questionnaires every 3 months. All patient-reported hospital admissions

(SAEs) will be evaluated by the sponsor/investigator for relationship with BB treatment or lack of BB treatment. This will be the data for biannual safety evaluation by the DSMB

Biological material

No separate blood samples or other biological material will be specifically collected for this trial and no biobank will be constructed. All blood sample assessed and used in the analysis will be from routine blood samples collected.

Procedures for discontinuation

Patient discontinuation or withdrawal

Patients will not be discontinued from the trial if they cross over from the allocated treatment arm. Patient consent withdrawals can be done at any time during follow-up with no consequence on other treatment options. Cross-over will be registered through prescription registry and through the e-questionnaires administered at baseline, after 3 months, and every 3 months thereafter. The primary statistical analysis will be intention to treat, i.e. without taking cross-over into account.

Trial discontinuation

It is important to ensure that there is no avoidable increased harm to patients in both the active and inactive group. The Data Safety Monitoring Board (DSMB) consisting of two senior cardiologists and one experienced trial-statistician will overview safety and will have access to unblinded data. The DSMB members will be independent and will not be involved otherwise in the trial. The DSMB will formally review the accumulating data to ensure there is no avoidable increased harm to patients. The data will include incidence of ventricular arrhythmias, heart failure, stroke, recurrent MI and all-cause mortality. The first data safety analysis will be made 3 months after inclusion of the first patient and biannually thereafter. The DSMB will recommend to the executive steering committee that the trial is stopped if one of the treatment arms has 50% more events than the other. A 95% Koopman confidence interval for the ratio of probabilities, defined such that the ratio is above 1.0, will be estimated. If the lower confidence limit exceeds 1.5, the stopping criteria will be deemed to have been met. All final decisions regarding trial modifications rest with the Steering Committee and is not subject to a pre-defined stopping criterion. The recommendation to either continue or stop the trial because of an unbalance in event rates between the treatment arms will be at the discretion of the DSMB.

The DSMB may also recommend that the trial is stopped if the committee at any time is of the conviction that the risk to current and future trial patients outweighs the potential impact of premature termination on future clinical practice and should be based on emergent data on patient safety or trial conduct inconsistent with pre-trial assumptions available at ethics committee approval.

In the event of a decision to terminate the study, the principle investigator will inform all investigators, relevant authorities and ethics committees of the termination within two weeks.

The trial may be discontinued for futility if the inclusion rate is such that the study cannot reach the desired number of patients within a reasonable time frame. This decision lies with the Steering Committee

End of patient inclusion and end of study

The steering Committee is responsible for decision of modification of patient inclusion based on interim analyses as described in the section ‘Sample size and power calculation’.

The Steering committee is responsible for decision to end the study either due to safety reasons or futility, as described above or due to achievement of the desired number of primary endpoints.

The sponsor and principal investigator will inform all investigators, the relevant competent authorities and the Ethics Committees in the event of an early termination of the trial along with the reasons for such action. If the study is terminated early on grounds of safety, the competent authorities and the Ethics Committees will be informed within 15 days.

All patients will be informed of study end. Continued treatment/discontinuation or uptake of BB will be at the discretion of the treating physician. The study group will provide written guidance for the patient and the treating physician.

Patient involvement

Because of the central role of patient reported outcomes, user involvement is an important part of the DANBLOCK trial, and will be organised in collaboration with REHPA, knowledge-centre of rehabilitation and palliative care. Patient expert groups that reflect the patients eligible for inclusion in the study will be set up containing 4-8 members ideally representing patients recruited from hospital and cardiac rehabilitation. The patient expert groups will meet to share their experiences with BB treatment, development of patient material, e-questionnaires and how to best set up the patient recruitment seen from a patient perspective. Further meetings of the patient expert group will be undertaken during the project to ensure patient involvement in the process of interpretation and dissemination of results and ensure patient recruitment.

We strive to recruit patients from different backgrounds. All participants in the expert patient group will be provided with travel expenses and food and beverage during meetings. There will be a closing event at the end of the project where all stakeholders, study participants, and carers will be invited to hear the results of the project and give their input into the next steps for use of BB following acute coronary syndrome.

We will ensure all patient experts; trial participants; research collaborators and stakeholders involved in the project are kept informed at all stages via the DANBLOCK project website and a newsletter by post.

Safety monitoring and reporting

Adverse events

BBs have been widely used for more than 40 years and treatment with BB is currently standard of care after MI. Any safety concerns are therefore primarily related to lack of treatment with BB after MI. The potential **serious** consequences of NOT being treated with a BB after MI are the following: *Increased risk of MI, ventricular arrhythmia, development of heart failure and cardiac death*. The possible **non-serious** consequences of NOT being treated with a BB after MI are: *poorer angina control and risk of supraventricular arrhythmia.*

The main objective of the trial is to assess whether treatment with BB in the selected patients (i.e. who have received todays standard of care and who do not have heart failure) reduces the risk of death, heart failure and new MI compared to no such treatment. Non-serious consequences (supraventricular arrhythmia) and side-effects are mainly relevant in terms of impact on quality of life, health care utilization and employment and are part of the secondary endpoints of the trial.

Monitoring of safety

In each case safety is ensured by

1) The original primary endpoints recurrent MI, unstable angina, stroke, heart failure, and death will be monitored through repeated assessment of hospital admission. Participants receive E-questionnaires asking about hospital admission every 3 months. Orignial endpoints will be adjudicated locally in the eCRF and summarized by group assignment after 3 months and every 6 months thereafter. This ensures that any difference between groups in rates of the primary endpoints are repeatedly assessed.

2) In the E-questionnaire to the patient every 3 months the patient will report on continued use of BB and any hospital admission (i.e. SAE). After 5 and 10 days a reminder will be sent for patients that have not responded. Data on any non-endpoint SAE thus reported will be reviewed for possible causal relation to the treatment/non-treatment with betablocker (SAE/SAR/SUSAR) by the MD responsible for the trial locally after acquiring additional information from hospital records. Any hospital admission/SAE considered related to treatment/no-treatment with BB that is not included on the list of SARs will be reported to the sponsor, who will consider whether the hospital admission is a SUSAR. Any SUSAR will be reported to the DMA.
3) Patients who do not respond to the e-questionnaire will be assessed through electronic health records for hospital admission/death in the latest 3-month period.[1] Any hospital admission will be assessed for SAE locally as described above.
4) The patients GP will be informed that the patient has been included in the trial in the discharge letter. This information will include the title of the trial, EudraCT identification and web-address for more information (hosted by OPEN).
5) Each participating patient receives a trial card with the following information: Trial-name, website describing the trial (hosted by OPEN), contact information on the MD responsible for the trial locally and information on reporting of hospital-admissions via e-questionnaires every 3 months. This ensures that all professionals in contact with the patient know how SAEs/SARs will be reported.

It is the opinion of the steering committee of the trial that this monitoring ensures the safety of each participant included in the trial.

Serious Adverse Events (SAE) and Serious Adverse Reactions (SAR)

A Serious Adverse Event (SAE) is defined as any untoward medical occurrence that results in death or requires in-patient hospitalization or prolongation of existing hospitalization or results in persistent or significant disability or incapacity or is a congenital anomaly or birth defect. BB treatment is standard of care and has been widely prescribed for decades. The treatment with BB after MI has the aim of reducing cardiovascular mortality, recurrent MI and serious heart rhythm disturbances. For the BB treated group any SAE judged to be related to drug therapy is a serious adverse reaction (SAR). For the non-BB treated group focus is on SAE that may be related to NOT being treated with BB.

In both groups, safety reporting will be based on rates of all hospital admission reported by the patients and ascertained through electronic health records. Additionally, each patient will report all hospital admissions, and these will be assessed by the sponsor/investigator through review of hospital records for relation to treatment/no treatment with betablocker and reported in the eCRF. Secondary endpoints leading to hospital admission (*i.e. ventricular arrhythmia, atrial fibrillation, angina symptoms, bradycardia, syncope or need for a pacemaker, asthma, stroke and hypertension*) will be included in the SAE/SAR reporting. Patients that do not respond to the e-questionnaire will be checked through electronic health records for hospital admissions in the intermittent 3-month period. Any hospital admissions will be assessed for whether this is an original primary endpoint, secondary endpoint or SAR as described above. Monitoring will be based on rates of hospital admission derived from patient reports and other sources of entry into the eCRF and will be assessed and reported 3 months after the first patient is randomized and biannually thereafter throughout the trial period.

[1] Lovhjemmel: **LOV nr 620 af 08/06/2016, paragraf 21, stk 1: '** Et samtykke afgivet efter kapitel V i forordningen giver sponsor og sponsors repræt samtykke a investigator direkte adgang til at indhente oplysninger i patientjournaler m.v., herunder i elektroniske journaler, med henblik på at se oplysninger om forsøgspersonens helbredsforhold, som er nødvendige som led i egenkontrol med forskningsprojektet, herunder kvalitetskontrol og monitorering, som disse er forpligtet til at udføre.'

Suspected Unexpected Adverse Events (SUSARs)

Since BB's have been standard of care in MI patients for several decades, we expect no SUSARs in patients treated with BB. Any SUSAR in patients not treated with BB will be related to the indication for treatment, i.e. MI.

The SAEs MI, heart failure, hospital admission for unstable angina, stroke and death will be monitored repeatedly as described. SAEs will be monitored as described above through e-questionnaires to study participants every 3 months and through electronic health records in patients who do not respond to the e-questionnaire. Any report of an SAE by a patient will be assessed by sponsor/investigator to determine whether this is an original primary endpoint, secondary endpoint, SAE and whether this is a possible SAR. In the event of death the MD responsible for the trial locally will investigate the cause of death and report it in the eCRF as soon as possible and no more than 24 hours following the knowledge of such an event. The sponsors Medical Officer will review all SAEs reported as related to the trial drug (or lack of trial drug) and evaluate whether the event is expected according to the Reference Safety Information (RSI) for patients under treatment or related to lack of BB treatment post MI in the untreated group. The following are regarded as possibly related to treatment or lack of BB treatment and will not be reviewed independently by the sponsors Medical Officer: *Ventricular arrhythmia, supraventricular arrhythmia (including atrial fibrillation and atrial flutter), any tachycardia leading to hospital admission and angina pectoris leading to hospital admission, brady-arrhythmias, syncope, pacemaker implantation, hypertension, hypotension, dysregulated or incident case of diabetes, PAD and constipation.* These events will be reported to the DSMB biannually and to the DMA annually. The product information for the IMPs is used as RSI in this trial.

SUSARs will be reported to the Competent Authority according to national regulation. The following timelines should be followed: The sponsor will ensure that all relevant information about suspected serious unexpected adverse reactions (SUSAR) that are fatal or life-threatening is recorded and reported as soon as possible to the Competent Authorities in any case no later than 7 days after knowledge by the sponsor and that relevant follow-up information is subsequently communicated within and additional 8 days.

Safety and reporting

Accumulated data on the primary outcomes as well as SAE and SAR based on patient reports and hospital records every 3 months for both patients on BB treatment and not on treatment will be made available to the Data Safety Monitoring Board (DSMB). This process ensures that accumulated events/SAE/SAR in both the treatment group and the non-treatment group are evaluated and will form the basis of safety assessment. The DSMB will first assess the outcomes 3 months after the first patients is included and thereafter biannually throughout the study period. The Competent Authority will receive annual reports from the DSMB.

Study Organization

Sponsor

The study sponsor is Eva Prescott, Department of Cardiology, Bispebjerg Frederiksberg Hospital

The initiative to the present study was taken by members of the Working Group on Cardiac Prevention and Rehabilitation under the Danish Society of Cardiology

Steering Committee:

The steering committee (SC) is responsible for conducting the trial. The role of the SC is to define the study, write the protocol, ensure funding, oversee the scientific content and integrity of the study and monitor the study economy. The SC is also responsible for reporting of the trial results. The study will be managed by a senior researcher and a project coordinator (study nurse). Payment of study expenses will follow patient inclusion: Each participating centre will be re-imbursed for the time spent on screening and patient inclusion, in addition to a set-up investigators fee. All members of the steering committee are voting

members. The steering committee (SC) will convene when necessary (in person or video conference) to monitor study progress.

Project management: Project leader, project manager and assisting project managers

Eva Prescott is project leader (PL) and responsible for the coordinating center at the department of Cardiology at Bispebjerg Frederiksberg Hospital. The PL has the overall responsibility of conducting the trial according to good clinical practice. The PL will refer directly to the SC.

A project manager (PM) Thomas S G Sehested has been appointed. The primary task of the project manager is to promote the study, give advice to the participating centres, monitor safety in the study and follow-up on decisions made by the steering committee and serve as datamanager in collaboration with OPEN and assistant project manager. The PM will refer directly to the PL.

A PhD student will act as assistant project manager. He/she will handle safety issues, communication with authorities, GCP, eCRF, economy, etc, promote the study and give advice to participating centres and assist the project manager/project leader in their responsibilities.

PL, PM and assisting PM's will work closely together and be situated at Bispebjerg Frederiksberg Hospital

Participating Centres/investigators

The study is open to all departments of Cardiology in Denmark, most of which have already agreed to participate. A representative of each of the five Danish regions is a member of the Steering Committee. Each center will appoint an investigator who will be responsible for the conduct of the study at the department and for communication with the project management. One representative from each participating center is invited to participate in a writing group.

Data Safety Monitoring Board (DSMB)

This independent committee consisting of three international specialists, two senior cardiologists and one experienced trial-statistician, will overview safety and will have access to unblinded data. The DSMB members will be independent and will not be involved otherwise in the trial. They will formally review the accumulating data after 3 months and every 6 months thereafter to ensure there is no avoidable increased harm to patients. The DSMB may recommend trial termination due to excess risk associated with no treatment with BB as described above. All final decisions regarding trial modifications rest with the Steering Committee. The responsibilities of the DSMB are described in a contract (appendix 5).

Statistical analysis plan and supervision

The primary analysis will be intention-to-treat analysis, i.e. patients will be counted in the group to which they were assigned at randomization regardless of later cross-over. Additionally, a secondary per-protocol analysis will be performed, where compliant BB-users are considered exposed during follow-up. Outcome analysis will be assessed by using cumulative incidence and Cox-regressions. Level of significance will be 0.05. No interim analyses are planned. A detailed statistical analyses plan will be developed by the project management and SC and will be published through clinicaltrials.gov and EudraCT. Statistical analysis will be supervised by Theis Lange, Institute of Biostatistics, University of Copenhagen.

GCP -Good Clinical Practice

The study will be performed according to the most recent approved study protocol, ICH-GCP guidelines and applicable regulatory requirements and legislation. The study will be monitored by the Danish GCP-unit.

Danish Medicines Agency (Lægemiddelstyrelsen - DMA)

The study has been approved by the Danish Health and Medicines Authority.

The Committee on Health Research Ethics (Videnskabsetiske Komitéer)

The study has been approved by the regional Ethics Committee

The Danish Data Protection Agency (DDPA)

The study will adhere to 'Databeskyttelsesforordningen' and 'Databeskyttelsesloven' and will be approved by the Danish Data Protection Agency.

International collaboration

To resolve the question of BB treatment after MI an adequately powered trial is needed. Two Scandinavian and one Spanish/Italian trial have been funded and initiated: The Swedish REDUCE trial the Norwegian BETAMI, and the Spanish/Italian REBOOT. Similar trials in the UK (REDUCE-UK) are planned but have not yet acquired funding. Both the BETAMI and the REDUCE trial are powered for a conventional superiority trial to detect a HR of >1.20 with a combined outcome of recurrent MI and death. However, more patients are needed to identify smaller but clinically relevant benefits of BB treatment and resolve the question of mortality. With a total number of events of 2800 between the tree trials, we will have 80% power to detect a 10% reduction in the primary outcome. This will also allow for subgroup analyses including midrange LVEF40-49/>=50%, men/women, young/elderly, NSTEMI/STEMI and MI with vs. without significant lesions (MINOCA). The trials are collaborating closely on design to ensure that an international individual patient meta-analysis can be performed.

A formal collaboration with the Swedish REDUCE trial (PI Thomas Jernberg) and the Norwegian BETAMI trial (PI Dan Atar) has been established to coordinate the studies. A Scandinavian collaborative committee will be formed and there will be mutual representation in the national steering committees. The DANBLOCK trial will include patients with MINOCA, i.e. MI patients with no obstructive CAD. An international (Swedish/Norwegian/Australian/US/UK) trial is being undertaken to test the effect of BB (and ACE/ARB) on patients with MINOCA – the MINOCA BAT trial. A formal collaboration with the PI Bertil Lindahl has been established to ensure that the DANBLOCK study results can be pooled in a similar manner.

Ethical and regulatory requirements

Ethical considerations

The project requires approval by the Danish Health Data Board, the Danish Data Protection Agency and the National Ethics Committee. All legislation on handling of personal data will be adhered to.

The aim of the present study is to evaluate the effectiveness and the risk-benefit balance of BBs after MI in real-life practice. Treatment with BBs will be used according to summary of product characteristics and therefore it is not necessary to distribute the BBs free of charge to patients. This is according to the Danish Board of Health rules since section 3 paragraph 13, no. 2 is fulfilled and we have been exempted from the general rule by the DMA.

The treatment with beta BB is current standard and we see no risk in participating in this arm of the trial. For the control group who receive no beta-blocker treatment there may be an increased risk of adverse outcome. This is monitored by the DSMB with the process described above. Side-effects will be reported according to the reference documents for the BB's used.

The study has been registered at EudraCT and will be registered at clinicaltrials.gov once approvals have been obtained.

Informed consent

Patients are recruited on the basis of in- and exclusion criteria. The first contact can be during hospital admission for MI, shortly thereafter by telephone or mail or at their first appointment at the cardiac rehabilitation. They will be informed about the background and design of the trial. If they are interested in participating, a consultation at the hospital or by telephone (if the patient prefers this option) will be scheduled and they will be provided with oral and written information about the trial along with the brochure 'Your rights as a participant in biomedical research'. They are encouraged to bring a companion

and ask questions. Before signing the consent form the patient will be given ample time to re-consider. Should the patient need further time, a follow-up meeting will be scheduled. If the patient consents, the form is signed ("Samtykkeerklæring") either by mail or in person and the patient receives a copy of the informed consent.

Patients are informed that they may at any time withdraw their consent to participate in the trial without consequences for their treatment in the department of cardiology. The patients are informed that information from their patient records will be retried by study personnel and used in this study. The patients are specifically informed and asked about their consent to this in the patient information. This information will be used to assess AEs, SAEs, SUSARs, endpoints, etc.

All study personnel will undergo training by the local principal investigator in study design, patient treatment, safety and other study related issues before they are involved in patient contact. The study personnel involved will be doctors and nurses employed at the department of cardiology or the cardiac rehabilitation.

Compensation for any treatment injury to the participants will be through 'Patienterstatningen'.

Trial sponsorship and financing

The study is investigator initiated by the principal investigator and members of the working group on cardiovascular prevention and rehabilitation under the DCS. The study has received support from the Danish Heart Foundation covering costs for the first year of the trial and the Novo Nordisk Foundation. There are no financial interests in the trial.

Communication

A website will be developed for information on study rationale and description of the trial. An e-mail and telephone number will be dedicated to questions on the trial and answered 24/7.

Publication policy

When the study is completed, and results are analysed and reported the study will be submitted for an international journal and results will be made publicly available. The results will also be reported at EUDRACT and ClinicalTrials.gov. Both positive, negative and inconclusive results will be published.

All individuals who have contributed significantly to the study, including local MD s responsible for the trial conductance, will be acknowledged and if they fulfil the requirements of co-authorship in accordance with the Vancouver convention they will be invited to participate in the process of publication.

Time line

Approval from the Committee on Health Research Ethics	December 2018
Approval from the Danish Data Protection Agency	December 2018
Approval from the Danish Medicines Agency	December 2018
First patient randomized	December 2018
Last patient randomized	January 2024
End of follow up	December 2024
Data analysis complete (+4 months)	April 2025
Publication of study results (+3-8 months)	October 2025

Reference list

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Appendix 1: Patient information

Appendix 2: eCRF and eQuestionnaires

Appendix 3: Definition of endpoints and adjudication

Appendix 4: Data Safety Monitoring Board

Kristian Thygesen, Independent Cardiologist, Denmark

Chris Gale, Independent Cardiologist, UK

Biostatistician TBD

Appendix 5: DSMB contract

Appendix 6: Product resume for beta blockers

Has been forwarded separately to DMA

Appendix 7: Budget

Appendix 8: List of PI's (Updated 22.12.2021)

Region Hovedstaden	
Amager Hospital	Jens Brønnum Schou
Bispebjerg Hospital	Eva Prescott
Bornholms sygehus	Kjeld Skødebjerg Kristensen
Frederiksberg Hospital	Eva Prescott
Gentofte Hospital	Gunnar Gislasson
Glostrup Hospital	Jawdat Abdulla
Herlev Hospital	Mette Mouridsen
Hvidovre Hospital	Jens Hove
Nordsjællands Hospital	Louise Schierbeck
Sjælland	
Holbæk Sygehus	Michael Hecht Olsen
Nykøbing F. Sygehus	
Næstved Sygehus	John Larsen
Roskilde Sygehus	Martin Snoer
Slagelse Sygehus	Jens Lomholdt
Syddanmark	
OUH Odense Universitetshospital	Gro Egholm
OUH Svendborg Sygehus	Jess Lambrechtsen
Sydvestjysk Sygehus	Kristian Korsgaard Thomsen
Sygehus Sønderjylland	Ghassan Jadou
Sygehus Lillebælt	Ann Bovin
Sygehus Lillebælt, Kolding	Monica Poenaru
Midtjylland	
Aarhus Universitetshospital	Michael Mæng
Hospitalsenhed Midt	Nikolaj Thure Krarup
Hospitalsenhed Vest	Morten Bøttcher
Regionshospitalet Horsens	Morten Krogh Christiansen
Silkeborg Hospital	Lars Frost (inkluderer ikke længere)
Nordjylland	
Aalborg Universitetshospital	Svend Eggert Jensen
Regionshospital Nordjylland	Peter Bisgaard Stæhr