# Statistical analysis plan

# The BETAMI-DANBLOCK trial

# Table of content

1.	Administrative information	3
	1.1 Trial registration numbers	3
	1.2 Protocol version used for preparation of the statistical analysis plan	3
	1.3 Contributors for preparation of the statistical analysis plan	3
	1.4 Signatures	4
	1.5 SAP Revision	4
2.	Introduction	5
	2.1 Background and rationale for the DANBLOCK-BETAMI study	5
	2.2 Objectives	<del>(</del>
3.	Study methods	7
	3.1 Trial design and randomization	7
	3.2 Type, dose, and administration of drug	7
	3.3 Framework, sample size and power calculation	7
	3.3.1 Study power calculation for the combined BETAMI-DANBLOCK trial	8
	3.4 Interim analysis for effect	9
	3.5 Timing of final analysis and outcome assessments	9
4.	Statistical principles	9
	4.1 Confidence interval and P values	9
	4.2 Protocol deviations	10
	4.3 Analysis population	10
5.	Trial population	11
	5.1 Screening	11
	5.2 Inclusion and exclusion criteria	11
	5.3 Information to be included in the CONSORT flow diagram	12
	5.4 Adherence, dosage, withdrawal and loss to follow-up	13
	5.4.1 Dosage and adherence to BB therapy	13
	5.4.2 Withdrawal of informed content	13
	5.4.3 Loss to follow up	14
	5.5 Data collection	14
	5.6 Patient characteristics in main publication	15

6.	Analysis and endpoints	16
	6.1 Endpoints	16
	6.1.1 Primary endpoint	16
	6.1.2 Secondary endpoints	16
	6.2 Analyses	17
	6.2.1 Analysis of the primary endpoint	17
	6.2.2 Analyses of key secondary endpoints	18
	6.2.3 Additional analyses	18
	6.2.4 Planned subgroup analyses	19
	6.2.5 Secondary endpoints and data to be included in substudies	19
	6.3 Missing data	21
	6.4 Harms	21
	6.4.1 Safety endpoints	21
	6.4.2 Adverse events	22
	6.4.3 Details of guidelines for stopping the trial early	22
7	Data handling and record keeping	22
8	Supplementary material	23
	BETAMI, protocol version 10.0, 22.11.2023	23
	DANBLOCK, protocol version 2.1, 08.07.2024	23
	Definition of endpoints and standard operating procedures for adjudication	23
9	References	24

### 1. Administrative information

The trials "Danish Trial of Beta Blocker Treatment After Myocardial Infarction Without Reduced Ejection Fraction" (DANBLOCK) and "BETablocker Treatment After Acute Myocardial Infarction in Patients With Preserved Left Ventricular Systolic Function" (BETAMI) are separate trials until end of follow-up. At end of follow-up the trials will be combined and the primary results will be published as one study. This statistical analysis plan (SAP) describes data handling and planned analyses for the combined BETAMI-DANBLOCK trial.

### 1.1 Trial registration numbers

The Danish Trial of Beta Blocker Treatment After Myocardial Infarction Without Reduced Ejection Fraction (DANBLOCK) trial: EudraCT Number 2018-002699-42, NCT03778554.

The BETablocker Treatment After Acute Myocardial Infarction in Patients With Preserved Left Ventricular Systolic Function (BETAMI) trial: EudraCT 2018-000590-75, NCT03646357.

### 1.2 Protocol version used for preparation of the statistical analysis plan

The combined trial does not have a joint protocol. The individual trials are conducted, monitored etc. according to their own protocols:

DANBLOCK: Protocol version 2.2, 08.07.2024 (attached in supplementary materials).

BETAMI: Protocol version 10.0, 22.11.2023 (attached in supplementary materials).

The present SAP only presents our predefined plan for joint analyses of the two trials.

# 1.3 Contributors for preparation of the statistical analysis plan

- BETAMI: Dan Atar, Sigrun Halvorsen, John Munkhaugen
- DANBLOCK: Eva Prescott, Michael Hecht Olsen, Christian Torp-Pedersen, Anna Meta Kristensen

- Statisticians: Theis Lange and Morten Wang Fagerland

The SAP has been approved by the DANBLOCK and BETAMI steering committees.

# 1.4 Signatures

Sponsor, BETAMI	Sponsor, DANBLOCK	
Name: Dan Atar	Name: Eva Prescott	
Signature:	Signature:	
Date: 19-MAR-2025	Date: <u>19-MAR-2025</u>	
Senior Statistician, BETAMI	Senior statistician, DANBLOCK	
Name: Morten Wang Fagerland	Name: Theis Lange	
Signature: Morten Wang Fagerland	Signature: They lange	
Date: 19-MAR-2025	Date: 20-MAR-2025	

# 1.5 SAP Revision

Date of revision	Revision	Justification for revision
March 18, 2025	Changes in subgroup	We have updated the SAP to align with the SAP
	analyses	used in the REBOOT trial to facilitate an
	Extension of the follow-up	individual patient data meta-analysis. The
	period	follow-up period has been extended due to
	Definition of the intention-	lower-than-expected event rates. Additionally,
	to-treat approach	the subgroup analysis for beta-blocker dosage
	Definition of adherence	has been revised from tertiles to a comparison of

Inclusion of a secondary	> vs. ≤ the median dose of metoprolol (or its
endpoint in the main	equivalent), as all tertile groups were originally
publication	set at 50 mg. Similarly, the subgroup analysis for
	age was adjusted from tertiles to ≥70 vs. <70
	years. The intention-to-treat approach has been
	further clarified, and the definition of adherence
	was modified, as the original definition was not
	applicable within the registries.
	The secondary endpoint hospitalization for
	pacemaker implantation, second- or third-degree
	atrioventricular block was moved from
	substudies to be included in the main paper.

### 2. Introduction

# 2.1 Background and rationale for the DANBLOCK-BETAMI study

Beta-blockers (BB) have been widely used and recommended by international guidelines after myocardial infarction (MI) based on landmark trials conducted in the 1980s. <sup>1–3</sup> However, since then, several factors have led to questioning the continued use of BB therapy in a modern secondary preventive setting. <sup>4</sup> These factors include revisions in the criteria for MI and the use of highly sensitive troponins, which can now classify patients previously diagnosed with unstable angina as experiencing a MI. <sup>5</sup> Additionally, primary percutaneous coronary intervention (PCI) and new

secondary preventive medical therapies such as statins and antihypertensive medications have been introduced.<sup>6,7</sup> These developments have reduced the risk of myocardial scarring and, consequently, the risk of fatal arrhythmias and heart failure (HF), which are conditions where BB therapy has been known to be beneficial.

Despite wide-spread use and tolerability patients treated with BB report side-effects, i.e. sexual dysfunction, cold hands and feet and fatigue.<sup>8</sup> A lower compliance to BB treatment compared to other cardiovascular medications is seen and is thought to be related to side effects.<sup>9</sup> On the other hand, BB treatment reduces angina symptoms, which has profound effects on quality of life. Thus, the benefit of BB treatment on survival outlook needs to be weighed against the impact on side effects as well as quality of life.

BB have an ubiquitous role in patients with reduced left ventricular ejection fraction (LVEF). <sup>10</sup> For patients with mid-range or preserved LVEF no randomized controlled trials have been performed testing the continued efficacy of BB therapy in a modern secondary preventive setting. The lack of evidence in the reperfusion era has resulted in divergence between guideline recommendations. In patients with ST-segment elevation MI the European Society of Cardiology (ESC) recommends BB therapy with a class 2A recommendation, level of evidence (LOE) B. <sup>11</sup> On the contrary, the American College of Cardiology/American Heart Association (ACC/AHA) has a class I recommendation, LOE B. <sup>12</sup> The ESC has no recommendation on long-term BB therapy in patients with acute coronary syndromes presenting without STEMI and preserved LVEF <sup>13</sup>, whereas BB therapy are recommended long-term by AHA/ACC with a class IIA recommendation, LOE C. <sup>14</sup>

# 2.2 Objectives

The aim of the BETAMI-DANBLOCK study is to evaluate the effectiveness and safety of BB therapy after MI. The study will investigate whether BB therapy is superior to no BB therapy

following MI in patients with normal or mildly reduced LVEF in terms of reducing the risk of cardiovascular events. The primary endpoint is a composite of all-cause mortality, recurrent MI, coronary revascularisation (with PCI or coronary artery bypass graft (CABG)), ischemic stroke, incident HF, or malignant ventricular arrhythmia including resuscitated cardiac arrest of cardiac origin.

# 3. Study methods

# 3.1 Trial design and randomization

DANBLOCK and BETAMI are prospective, randomized, controlled, open-label clinical trials evaluating the benefits of long-term oral BB therapy in MI patients with normal or mildly reduced LVEF. Patients will be randomized 1:1 to BB treatment or no BB treatment. In DANBLOCK patients are stratified by LVEF, whereas patients are stratified by site in BETAMI.

# 3.2 Type, dose, and administration of drug

If a patient is randomized to BB therapy the treatment is given orally. The type and dose of BB will be left at the discretion of the treating physician. The highest tolerated dose is recommended.

Generic drug and accepted dosages will be:

- 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 (DANBLOCK)

#### 3.3 Framework, sample size and power calculation

The trial will be analyzed as an ordinary superiority trial and was designed to achieve a prespecified number of adjudicated events under modelled event rates. Actual number of (nonadjudicated) events will be monitored by linkage to Norwegian and Danish national registries. The last patient included will be followed for a minimum of 12 months.

#### 3.3.1 Study power calculation for the combined BETAMI-DANBLOCK trial

The original power calculation in BETAMI estimated a total of 794 first events to provide a power of 80% to detect a relative risk reduction of approximately 20% (11% primary end points with no BB vs 9% primary end points with BB; hazard ratio of 1.22). In DANBLOCK it was assumed that with a hazard ratio of 1.2 for the non-treated group compared to the treated the DANBLOCK trial had 80% power to detect the effect with an accumulation of 900 first events of the primary endpoint. Original sample size and power calculations for DANBLOCK and BETAMI can be seen in the protocols in supplementary material.

The primary analysis in the combined BETAMI-DANBLOCK trial will be conducted as a Cox model adjusted for site (and hereby country). To illustrate the expected power, the power obtained with a true treatment effect of a hazard ratio of 0.83 and 50 equal sites is presented below. It becomes clear that if the follow-up is concluded with 950 first events one will have about 80% power which is considered acceptable and 950 primary events were thus the aim of the study. The inclusion will be stopped when it is anticipated that this number of events will be reached within a minimum of a 12-month follow-up period or a reasonable time thereafter. The decision to stop the trial will be at the discretion of the combined steering committee.

Event count	Power
300	0.3511
400	0.4397
500	0.5295
600	0.6053
700	0.6751

800	0.7304
900	0.78
1000	0.8159
1100	0.8531
1200	0.8844
1300	0.911
1400	0.9255

### 3.4 Interim analysis for effect

No interim analyses are planned.

# 3.5 Timing of final analysis and outcome assessments

The final analyses will be performed when follow-up has ended, and all endpoints have been adjudicated. The minimum follow-up period will be 12 months.

Primary, secondary, and safety endpoints are collected and monitored through registry linkage, hospital medical records, and questionnaires throughout the trial. Patient Reported Outcome (PRO) questionnaires are collected at baseline and 12 months after randomization in both studies. In DANBLOCK, PRO-questionnaires are also collected after 3- and 24-month follow-up. In BETAMI, PRO-questionnaires are collected after 30 days, 6 months, and 18 months follow-up.

# 4. Statistical principles

#### 4.1 Confidence interval and P values

For the primary endpoint, the level of significance will be 5% and a confidence interval (CI) of 95% will be reported. The secondary outcomes will also be assessed with a level of significance of 5% and a CI of 95%, however, as no adjustment of multiplicity is planned for the secondary outcomes

any significant finding for these will be considered exploratory. Statistical comparisons will be performed using two-sided significance tests.

#### 4.2 Protocol deviations

Protocol deviations are only related to adherence to assigned treatment.

Adherence to assigned treatment will be evaluated at six months. Patients in the BB group will be considered adherent at six months if they fill at least two prescriptions from one month before to six months after randomization. To account for packages containing >180 tablets, as well as cases where patients have been down-titrated due to side effects or have only taken half a tablet daily, a buffer period of 6 months will be added.

BB naïve patients randomized to no BB therapy will be considered adherent until they redeem a prescription for BB therapy. Patients previously treated with BB randomized to no such therapy will be considered adherent unless they redeem a BB prescription within 3 to 6 months after randomization. This period was chosen to allow for a gradual discontinuation of treatment.

Participants adherent to randomization group at six months are considered adherent for the full follow-up period.

### 4.3 Analysis population

All major treatment comparisons between the randomized groups will be performed according to the principle "intention-to-treat" (ITT), i.e., participants will be analysed, and endpoints counted in the group to which they were assigned at randomization, irrespective of later crossover. Patients who withdrew consent or were randomized in error (e.g., did not suffer from an MI or were already randomized leading to a duplicate) will not be included in the ITT full analysis set. Patients who were lost to follow-up will be included.

# 5. Trial population

### 5.1 Screening

Patients admitted to the hospital for MI will be screened for in- and exclusion criteria at all participating centers. However, only selected sites in DANBLOCK and one site in BETAMI are consecutively reporting the reasons for not being included in the trial. Patients fulfilling the study entry criteria will be registered in the eCRF. Collected screening data will be summarized and presented in the main publication.

Information on all individuals experiencing MI during the study trial period is available through national registries. However, LVEF-values are not available in the Danish registries making it difficult to extrapolate to a screening population.

#### Screening data registered in the eCRF:

- Age
- Sex
- Site
- Inclusion criteria including the date of index event and LVEF-value
- Exclusion criteria (see below)

#### 5.2 Inclusion and exclusion criteria

	DANBLOCK	BETAMI
Inclusion criteria		
MI definition	Universal definition of MI	Universal definition of MI type 1
Time to randomization	Within 14 days following MI	Within 7 days following MI

Age	≥18 years		
LVEF	> 40%	≥40%	
Revascularization	No specified criteria	PCI or thrombolysis	
Exclusion criteria	Clinical evidence of heart fa	Clinical evidence of heart failure	
	Pregnancy or of childbearin	Pregnancy or of childbearing age not using safe anticonception	
	throughout the study period	throughout the study period	
	Lack of signed informed con	Lack of signed informed consent or lack of expected	
	cooperation during follow-u	cooperation during follow-up	
	Decline to participate		
	Any medical condition where BB treatment is indicated		
	according to the treating physician		
	Any medical condition when	Any medical condition where BB treatment is contraindicated	
	according to the treating physician		

# 5.3 Information to be included in the CONSORT flow diagram

- Number of sites with screening and estimated number of patients assessed for eligibility
- Estimated number of patients excluded and reason for exclusion
- Number of patients randomized
- Number of patients allocated to BB or no BB
- Number of loss to follow-up
- Number of patients excluded from analyses and reasons for exclusion

## 5.4 Adherence, dosage, withdrawal and loss to follow-up

#### 5.4.1 Dosage and adherence to BB therapy

A landmark summary of adherence to allocated study arm will be performed six months after inclusion of each patient. Participants will be described according to whether they became non-adherent before six months or experienced the main outcome; whatever occurs first.

As previously described patients in the BB group will be considered adherent at six months if they fill at least two prescriptions from one month before to six months after randomization. To account for packages containing >180 tablets, as well as cases where patients have been down-titrated due to side effects or have only taken half a tablet daily, a buffer period of 6 months will be added.

BB naïve patients randomized to no BB therapy will be considered adherent until they redeem a prescription for BB therapy. Patients previously treated with BB randomized to no such therapy will be considered adherent unless they redeem a BB prescription within 3 to 6 months after randomization. This period was chosen to allow for a gradual discontinuation of treatment.

Participants adherent to randomization group at 6 months are considered adherent for the full follow-up period. The landmark summary will preferably be performed in both cohorts but is dependent on acceptable time to updated registries.

Substudies and secondary analyses focusing on BB-dosage and adherence are planned.

#### 5.4.2 Withdrawal of informed content

Patient consent withdrawals are possible at any time during follow-up and the day of withdrawal will be registered. Time to withdrawal will be summarized. Patients who withdraw consent or were randomized in error (e.g., did not suffer from an MI or were already randomized leading to a duplicate) will not be included in the ITT full analysis set.

#### 5.4.3 Loss to follow up

Loss to follow-up is expected negligible due to almost complete coverage by the national registries.

Loss to follow-up will be registered in the national registries and reported as day of loss to follow-up (emigration).

#### 5.5 Data collection

#### Data collected at baseline:

- Demographics
- Major comorbidities
- Procedures performed during index event (CAG, PCI, CABG)
- Lifestyle (smoking status and body mass index)
- Laboratory data, including eGFR, Hba1c, troponin, CKMB and lipids
- Patient reported outcomes on symptoms and quality of life measures
  - Measures for quality of life: 12-Item Short Form Survey (SF-12, BETAMI) and EuroQol-5 dimension questionnaire (EQ5D, DANBLOCK).
  - Measures of depression and anxiety: Hospital Anxiety and Depression Scale
     (HADS) and Patient Health Questionnaire (PHQ)-2 (BETAMI).
  - Measures of sexual dysfunction: The International Index of Erectile Function
     (IIEF) and Female Sexual Function Index (FSFI), (short versions).
  - Measures of sleeping disorder: Bergen insomnia Scale, Nightmare Frequency
     Questionnaire (BETAMI) and average sleep duration (BETAMI).

- Angina burden following MI: New York Heart Association classification (NYHA);
   Canadian Cardiovascular Society grading of angina pectoris (CCS); Seattle Angina
   questionnaire (SAQ) (for those who report angina symptoms).
- Measures of personality: Type D (distressed) personality disorder (BETAMI).

#### Data collected during follow-up:

Primary, secondary, and safety endpoints are collected through registry linkage, questionnaires, and hospital medical records throughout the trial as previously described. In addition, patient reported adherence and hospitalization will be assessed by questionnaires every 3 months in DANBLOCK and after 30 days in BETAMI. Follow-up data also includes the BETAMI biobank at 6 months (BETAMI only).

### 5.6 Patient characteristics in main publication

#### Data at baseline:

- Demographics
  - o Age, sex, country and education
- Major cardiovascular risk factors and comorbidities
  - Hypertension, hyperlipidaemia, chronic kidney disease, diabetes, smoking, family history of cardiovascular disease and BMI
  - Previous cardiovascular disease: MI, coronary artery disease, PCI, CABG, stroke,
     peripheral artery disease, atrial fibrillation/flutter.
- Type of MI (NSTEMI/STEMI)
- LVEF-value
- Procedures performed at index event (CAG, PCI, CABG)
- Type and dosage of BB at randomization (for patients randomized to BB therapy)

- Prior BB therapy
- Medications related to CVD (antiplatelets, statins, ezetimibe, angiotensin inhibitors, anticoagulants, antidiabetics)

#### Details of how baseline characteristics will be descriptively summarized

Baseline characteristics will be presented as numbers with percentages for categorical variables and medians with interquartile ranges for continuous variables.

# 6. Analysis and endpoints

### 6.1 Endpoints

#### 6.1.1 Primary endpoint

A composite of all-cause mortality, recurrent MI (primary and secondary diagnosis in the
administrative patient registries), revascularisation with PCI or CABG, ischemic stroke,
incident HF, or malignant ventricular arrhythmia (including resuscitated cardiac arrest of a
cardiac cause)

It is noted that the original BETAMI primary endpoint was a composite of all-cause mortality or non-fatal MI and the original DANBLOCK primary endpoint was a composite of all-cause mortality, MI, stroke, unstable angina, or HF.

All events included in the primary endpoint will be collected from the Norwegian and Danish Patient registries. All first events of each component of the primary endpoint (except all-cause mortality) will be adjudicated by a clinical endpoint adjudication committee. Please see supplementary material for the definition of endpoints.

#### 6.1.2 Secondary endpoints

#### Key secondary endpoints

The following secondary endpoints will be included in the main publication:

- Each of the components of the primary endpoint, i.e.: All-cause mortality, recurrent non-fatal
   MI, revascularisation with PCI or CABG, ischemic stroke, incident HF, and malignant
   ventricular arrhythmia
- Hospitalizations for pacemaker implantation, second- or third-degree atrioventricular block

#### Other secondary endpoints

Planned analyses of other secondary endpoints are described under 6.2.5

### 6.2 Analyses

The primary analysis will be performed on combined data between the two trials. Data will be transferred from the Norwegian data center to the Danish data center by an encrypted and password protected transfer method and according to a signed data transfer agreement and in accordance with the signed informed consent of each patient.

#### 6.2.1 Analysis of the primary endpoint

The primary assessment will involve an intention-to-treat comparison among all randomized participants of the effects of allocation to BB versus no BB on time to first occurrence during the scheduled treatment period of the primary endpoints. Main secondary assessments will involve intention-to-treat comparisons among all randomized participants of the effect of allocation to BB on time to first occurrence of secondary endpoints.

The primary endpoint is time to one of the components of the primary endpoint (time to first event), assessed after the last patient included has completed a minimum of 12 months of follow-up. The null hypothesis is that the rate of the composite primary endpoint in the allocation groups are equal.

The primary analysis will be a Cox proportional hazards regression model with randomization group (prescription of BB) as the main covariate. The analysis will be adjusted for site and LVEF (the stratification factors in the randomization). A hazard ratio (HR) for BB vs no-BB with a 95% CI will be estimated, and a P-value for the null hypothesis of a hazard ratio equal to 1 will be computed. In addition, the survival curves for the 2 groups (BB and no-BB) will be estimated and plotted with the Kaplan-Meier estimator.

#### Decision rule:

- If the estimated HR is < 1 and the 95% CI does not contain 1, superiority of BB will be accepted
- If the estimated HR is > 1 and the 95% CI does not contain 1, superiority of no BB will be accepted
- If the 95% CI contains 1, no superiority will be accepted

# 6.2.2 Analyses of key secondary endpoints

The key secondary endpoints to be included in the main publication are in section 6.1.2. All-cause mortality will be analyzed in the same manner as the primary endpoint. All other secondary endpoints will be analyzed with a Fine-Gray competing risk regression model, with all-cause mortality as the competing risk and the same covariates as in section 6.1.2. Cumulative incidence curves will be plotted for the two groups. All analyses of secondary endpoints will be interpreted as explanatory.

#### 6.2.3 Additional analyses

An analysis of the primary endpoint will be done in which follow-up time is limited to 12 months. The analysis will be performed and presented as described in section 6.2.1, with the addition of right censoring at 12 months. The results of this analysis will be interpreted as exploratory.

#### 6.2.4 Planned subgroup analyses

The following subgroup analyses are planned in the primary publication:

- Sex (Men and women)
- Age ( $\geq$ 70 and <70 years of age)
- Country (Denmark and Norway)
- Type of MI (NSTEMI/STEMI)
- LVEF-value (Mildly reduced and preserved)
- BB dosage (> and  $\le$  the median of metoprolol in mg or equivalent dosage)
- Rhythm (Previous or current atrial fibrillation, no atrial fibrillation)
- BB therapy prior to index-MI (Yes, no)
- Hypertension (Present at index-MI, not present at index-MI)
- Diabetes (Present at index-MI, not present at index-MI)

The subgroup analyses will be performed by adding an interaction term in the Cox model (as described in Section 6.2.1) between prescription of BB and the subgroup-defining factor. A HR with 95% CI for BB vs no BB will be estimated for each subgroup and presented in a forest plot.

#### 6.2.5 Secondary endpoints and data to be included in substudies

The following substudies are planned for later publications. Study data and planned analyses are not described in detail, as they will not be part of the main publication.

- To describe BB dosage and adherence obtained from the prescription registries.
- To determine whether long-term treatment with BB therapy reduces:
  - Cardiovascular mortality obtained from the Cause of Death Registry.
  - Hospitalization or electrical cardioversion for atrial fibrillation/atrial flutter and other tachyarrhythmia obtained from the Norwegian and Danish Patient Registry

- Hospitalization for unstable and stable angina obtained from the Norwegian and Danish Patient Registry, self-reported questionnaires, and hospital medical records.
- Exercise capacity measured as VO2-peak at cardiac rehabilitation obtained from the Danish cardiac rehabilitation registry (DANBLOCK only).
- To determine whether long-term treatment with BB therapy increases:
  - Hospitalization for bradycardia, AV-block, syncope or implantation of a pacemaker obtained from the Norwegian and Danish Patient Registry
  - Hospitalization for asthma and chronic obstructive pulmonary disease obtained from the Norwegian and Danish Patient Registry.
  - Hospitalization for dysregulated blood pressure and blood pressure control obtained from the Danish registries (DANBLOCK only).
  - Hospitalization or out-patient visit for new-onset or dysregulated diabetes
    obtained from the Norwegian/Danish Patient Registry and from the Danish
    cardiac rehabilitation registry (DANBLOCK only).
  - New-onset peripheral artery disease or hospitalization for peripheral artery disease obtained from the Norwegian and Danish Patient Registry.
- To determine whether assigned group affects the following PRO:
  - Quality of life, symptoms of depression, anxiety, sexual dysfunction and sleep disorders (both trials). Type D personality (BETAMI only).
- Comparison of locally adjudicated endpoints, registry-based endpoints and endpoints adjudicated by a blinded clinical endpoint adjudication committee (DANBLOCK)
- MINOCA (DANBLOCK)\*

- Comparison of clinical characteristics of trial participants and the entire Norwegian post-MI population with LVEF >40% (BETAMI)
- To determine whether long-term treatment with BB affects drug metabolism and biomarkers (BETAMI biobank).
- Joint meta-analyses with the ongoing REDUCE (ClinicalTrials.gov Identifier: NCT03278509), REBOOT (NCT03596385), and CAPITAL-RCT studies are planned.
   These are also superiority trials with comparable study entry criteria. The statistical analysis plan for these meta-analyses will be outlined in detail elsewhere.

Substudies marked with \* will be performed as joint analyses with the REBOOT trial.

# 6.3 Missing data

Follow-up is through registry linkage as previously described. We anticipate no missing data on the primary or main secondary outcomes, with the exception of loss to follow-up due to emigration. Follow-up will be censored at the time of emigration. In secondary adjusted analyses (for later publications) missing data will be handled through multiple imputation.

#### 6.4 Harms

#### 6.4.1 Safety endpoints

The following safety endpoints will be reported in the main publication:

- A composite of all-cause mortality, recurrent MI, incident HF, malignant ventricular
  arrhythmia or resuscitated cardiac arrest at 30 days following randomization: A table with
  number and frequencies obtained from the Norwegian and Danish Population Registries and
  adjudicated by a clinical endpoint adjudicating committee.
- All-Cause Mortality: A table of all deaths within the follow-up period with number and frequency in each group obtained from the Norwegian and Danish Population Registries.

Suspected Unexpected Serious Adverse Reaction (SUSARs): A table of all SUSARs within
the follow-up period with number and frequency in each group. Reported by local
investigators and obtained from the study databases.

#### 6.4.2 Adverse events

All serious adverse events, including potential endpoints, are captured in the study database to be used for safety assessments and are reported continuously to regulatory authorities.

#### 6.4.3 Details of guidelines for stopping the trial early

Two independent Data Safety Monitoring Boards (DSMB) are overviewing safety for DANBLOCK and BETAMI. The DSMB will recommend to the executive steering committees that the trials are stopped if one of the treatment arms has 50% more events than the other. All final decisions regarding trial modifications rest with the steering committees and are not subject to a pre-defined stopping criterion. The recommendation to either continue or stop the trials 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 trials are 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 principal investigator for each study will inform all investigators, relevant authorities and ethics committees of the termination.

# 7 Data handling and record keeping

Data is collected for participants who enter the randomized phase of the trial. All data are entered into web-based electronic data systems (DANBLOCK: RedCap, BETAMI: Viedoc). A participant

list will be linked to the national registries for collection of endpoints. A combined dataset for the two trials will be prepared and stored at secured Danish servers. This dataset forms the basis for all statistical analyses, which will be performed by Danish and Norwegian statisticians in collaboration. Internal database quality-control checks will be performed.

# 8 Supplementary material

BETAMI, protocol version 10.0, 22.11.2023

DANBLOCK, protocol version 2.1, 08.07.2024

Definition of endpoints and standard operating procedures for adjudication

#### 9 References

- 1. Freemantle N, Cleland J, Young P, et al. Beta Blockade after myocardial infarction: systematic review and meta regression analysis. *BMJ* 1999; 318: 1730–1737.
- 2. Friedman LM. A randomized trial of propranolol in patients with acute myocardial infarction. I. Mortality results. *JAMA* 1982; 247: 1707–1714.
- 3. Hjalmarson Å, Herlitz J, Málek I, et al. Effect on mortality of metoprolol in acute myocardial infarction. A double-blind randomised trial. *Lancet (London, England)* 1981; 2: 823–827.
- 4. van Diepen S, Armstrong PW. Learning whether to subtract beta-blockers: it's about time. *Eur Heart J* 2021; 42: 915–918.
- 5. Thygesen K, Alpert JS, Jaffe AS, et al. Fourth Universal Definition of Myocardial Infarction (2018). *J Am Coll Cardiol* 2018; 72: 2231–2264.
- 6. Zhou B, Danaei G, Stevens GA, et al. Long-term and recent trends in hypertension awareness, treatment, and control in 12 high-income countries: an analysis of 123 nationally representative surveys. *Lancet* 2019; 394: 639–651.
- Colantonio LD, Wang Z, Chen L, et al. Trends in High-Intensity Statin Therapy After
   Myocardial Infarction Among U.S. Adults, 2011-2019. *J Am Coll Cardiol* 2022; 79: 1870–1872.
- 8. Ko DT, Hebert PR, Coffey CS, et al. Beta-blocker therapy and symptoms of depression, fatigue, and sexual dysfunction. *JAMA* 2002; 288: 351–357.
- 9. Gislason GH, Rasmussen JN, Abildstrøm SZ, et al. Long-term compliance with betablockers, angiotensin-converting enzyme inhibitors, and statins after acute myocardial infarction. *Eur Heart J* 2006; 27: 1153–1158.

- 10. Dargie HJ. Effect of carvedilol on outcome after myocardial infarction in patients with left-ventricular dysfunction: The CAPRICORN randomised trial. *Lancet* 2001; 357: 1385–1390.
- 11. Ibanez B, James S, Agewall S, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2018; 39: 119–177.
- 12. O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of st-elevation myocardial infarction: A report of the American college of cardiology foundation/american heart association task force on practice guidelines. *J Am Coll Cardiol*; 61. Epub ahead of print 29 January 2013. DOI: 10.1016/j.jacc.2012.11.019.
- 13. Collet JP, Thiele H, Barbato E, et al. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J* 2021; 42: 1289–1367.
- 14. Amsterdam EA, Wenger NK, Brindis RG, et al. 2014 AHA/ACC Guideline for the management of patients with non-st-elevation acute coronary syndromes: Executive summary: A report of the American college of cardiology/American heart association task force on practice guidelines. *Circulation* 2014; 130: 2354–2394.
- 15. Hansson L, Hedner T, Dahlöf B. Prospective randomized open blinded end-point (PROBE) study. A novel design for intervention trials. Prospective Randomized Open Blinded End-Point. *Blood Press* 1992; 1: 113–9.