BEtablocker Treatment After Acute Myocardial Infarction in Patients Without Reduced Left Ventricular Systolic Function (BETAMI)

Protocol Identification Number: BETAMI

EudraCT Number: 2018-000590-75

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SIGNATURE PAGE

Title: **BEtablocker Treatment after Acute Myocardial Infarction in patients without reducedleft ventricular ejection fraction (BETAMI).**

Protocol ID no: **BETAMI**

EudraCT no: **2018-000590-75**

I hereby declare that I will conduct the study in compliance with the Protocol, ICH GCP and the applicable regulatory requirements:

Name	Title	Role	Signature	Date
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John Munkhaugen	MD PhD	Study Co-Chair WP leader, secondary prevention and biobank	(e-sign)	22.11.23
Vidar Ruddox	MD PhD	Scientific Study Secretary	(e-sign)	22.11.23
Sigrun Halvorsen	MD PhD	Member of Executive Steering Group	(e-sign)	22.11.23
Morten Wang Fagerland	PhD	Study statistician	(e-sign)	22.11.23
Toril Dammen	MD PhD	WP leader, psychosocial factors	(e-sign)	22.11.23

SIGNATURE PAGE, PRINCIPAL INVESTIGATOR / COORDINATING INVESTIGATOR

Title:	**BEtablocker Treatment after Acute Myocardial Infarction in patients without reduced left ventricular ejection fraction (BETAMI).**
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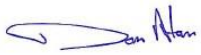
Name	Title	Signature	Date
Dan Atar	Prof.		22.11.2023

PROTOCOL SYNOPSIS

Protocol title: **BEtablocker Treatment after Acute Myocardial Infarction in patients without reduced left ventricular ejection fraction (BETAMI).**

Sponsor	Oslo University Hospital
Phase and study type	Prospective, randomized, open, blinded end-point (PROBE) study.
Investigational Medical Product (IMP) (including active comparator and placebo):	The study aims to investigate whether oral betablocker (BB) therapy is superior to no such treatment following an acute myocardial infarction (AMI).
Centers:	20 hospitals in Norway
Study Period:	Actual date of first patient enrolled: 2-OCT-2018 Anticipated recruitment period: 5.4 years Estimated date of last patient completed: 10-DEC-2024 Follow-up period at end of inclusion at least 0.5 years
Treatment Duration:	Estimated (non) treatment duration per patient: range 0.5 –6 years
Follow-up:	Subjects will be followed up for at least 0.5 –6 (mean 3) years for the primary and secondary endpoints.

Collaboration with the DANBLOCK trial from Denmark	In all, 2250 patients have been included during a 3.5 years months period (per April 2022) indicating a total inclusion period of >10 years to enroll 10 000 patients. After careful discussions, the BETAMI steering committee consider such a long recruitment period not feasible neither from scientific or an ethical point of view. Therefore, negotiations with the parallel DANBLOCK (NCT03778554)study Steering Committee, featuring an almost identical study design, has led to decision to merge the two final databases for endpoint analysis. However, each country (Norway and Denmark), respectively, retain their responsibility and financial plan for execution of their respective original studies.
Objectives	The primary objective is to test whether oral BB therapy reduces the risk of major adverse cardiovascular event (MACE; i.e. all-cause death, non-fatal MI, ischemic stroke, malignant ventricular arrhythmias, coronary revascularization, cardiac arrest with successful resuscitation due to cardiac cause, and incident heart failure compared to no such therapy, in post-AMI patients treated with PCI or thrombolysis without reduced LVEF. The key secondary objectives are: • To study whether oral BB therapy reduces the risk of each of the components of the primary end-point separately, compared to no such therapy To assess clinical outcomes linked BB therapy including outcomes in the following subgroups: age (tertiles), gender (men vs. women), BB dosage tertiles (dosage at randomization) and, LVEF subgroups (preserved LVEF: ≥50% vs. mid-range LVEF: 40-49%) The key secondary objectives are: • To study whether oral BB therapy reduces the risk of cardiovascular death compared to no such therapy • To study whether oral BB therapy reduces the risk of stable and unstable angina compared to no such therapy • To study whether oral BB therapy reduces the risk of atrial fibrillation, atrial flutter or other atrial tachyarrhythmias compared to no such therapy • To study whether oral BB therapy increases the risk of hospitalization for bradycardia, syncope, AV-block, implantation of pacemaker, ICD, or CRT. • To study whether oral BB therapy increases the risk of hospitalization for chronic obstructive pulmonary disease, asthma or peripheral artery disease. • To study whether oral BB therapy increases the risk of hospitalization or outpatient visit for new-onset or dysregulated diabetes

- To study whether oral BB therapy affects the following patient related outcomes: quality of life, angina, dyspnoea, anxiety, depression, sexual dysfunction or sleep disorders
- To conduct a cost-utility analysis in relation to quality of life and a health economic evaluation including drug use, health care utilization, employment, income, and benefit take-up
- To assess study safety

Exploratory biobanking objectives:

- To study the proportion and predictors of non-adherence with BB, statins and other cardiovascular drugs assessed by direct methods quantifying drug concentrations in blood
- Identify pharmacokinetic, pharmacogenetic and pharmacodynamic markers associated with side-effects and suboptimal response to treatment with cardiovascular drugs

Post-trial objective:

- To perform a joint analysis of the data from the BETAMI/ DANBLOCK (Denmark) study and the REDUCE (NCT03278509) and REBOOT (NCT03596385) trials. This analysis will increase power and precision for clinical decisions on both primary and secondary endpoints.

Endpoints:

Primary endpoint:
Time to all-cause mortality, non-fatal MI, ischemic stroke, malignant ventricular arrhythmias, coronary revascularization, cardiac arrest with successful resuscitation due to cardiac cause, and incident heart failure since randomization

Key secondary endpoints:

- Each of the components of the primary study end-point.
- Subgroup analyses as elaborated above.

Safety endpoint:

- A composite of malignant ventricular arrhythmias, incident heart failure, new MI or all-cause death a t 30 days after randomization assessed after 18 months follow-up and at study end.
- All-Cause Mortality: obtained from the Norwegian Population Registry at study end.
- Suspected Unexpected Serious Adverse Reaction (SUSARs) reported continuously by local investigators obtained from the study database.

Assessment of primary study end points

The primary study end-points will be obtained through linkage to the Norwegian Cardiovascular Disease Registry and the Population Registry.

Assessment of safety end points	• The safety endpoints will be under the responsibility of the primary investigators at all participating centers and collected at day 30 through direct telephone contact with the patient and from hospital medical records. A safety analysis will be performed 18 months after study start and at study end through linkage to the Norwegian Cardiovascular Disease Registry and the Norwegian Population Registry. • All serious adverse events, including potential endpoints will be collected from the Norwegian Cardiovascular Disease Registry and the Norwegian Population Registry at study end.
Assessment of secondary registry-based study end points	In addition to SAE reporting, data will be collected through linkage to the following national registries: The Norwegian Population Registry (Folkeregisteret), the Cause of Death Registry, the Norwegian Patient Registry, the Norwegian Cardiovascular Disease Registry, the Norwegian Prescription Database, the Norwegian registry for income, the FD-Trygd database (social security micro data for research) and the Control and payment of reimbursements to health service providers (KUHR) database
Study Design:	This is a **prospective, randomized, open blinded end-point (PROBE)** study. Patients with AMI will be randomized 1-8 days following PCI or thrombolysis, and allocated to either prescription of a BB or to no such prescription
Main Inclusion Criteria:	• An AMI diagnosis verified according to the "Universal Definition of AMI" and treatment with PCI and/or thrombolysis during the AMI hospitalization
Main Exclusion Criteria	• No clinical diagnosis of heart failure. • LVEF < 40% or significant LV akinesia in ≥ 3 segments regardless of LVEF by visual assessment • Conditions requiring BB therapy • Contraindications to BB treatment • End-stage somatic disease, dementia, psychosis and other conditions could put the subject at significant risk, confound the study results, interfere significantly with the subject participation in the study, or rendering informed consent unfeasible • Women of childbearing potential
Sample Size:	Estimated 5600 patients in Norway (N=2900) and Denmark (N=2700)

Power Calculation	Incident rates obtained from the subpopulation with AMI as the indication for treatment with PCI in the NORSTENT trial provided the background for sample size considerations indicating a 5-year event rate of 17% for the initial primary endpoint (Mortality 6.9% and AMI 10.1%). With a randomization ratio of 1:1, a sample size of 4671 patients (794 events) will provide a power of 80% to detect a difference of 18.7% primary endpoints with no BB treatment and 15.3% primary endpoints with BB treatment. This corresponds to a hazard ratio of approximately 1.22. To allow for a slightly lower overall event rate and some information loss due to drop-outs and crossover between groups the total sample size of the trial will be 5000 patients. However, preliminary data from Denmark indicates that the prevalence of the initial primary endpoint is significantly lower than estimated. A new power calculation for the joint BETAMI – DANBLOCK trial 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 around 950 events in total. Only one analysis of the primary endpoint on the combined BETAMI and DANBLOCK sample will be performed.
Efficacy Assessments:	Not applicable
Safety Assessments:	Subjects will be interviewed by phone after a standardized protocol by a specially trained study nurse after 30 days for the assessment of the composite safety endpoints. A safety analysis will be performed as soon as data from 1667 patients (1/3 of the population) at 30 days are available. Data on the 30 days safety endpoint will also be collected at end-of follow-up from Norwegian Cardiovascular Disease Registry and the Population Registry.

Type and Dosage of BB Treatment	Information will be collected from a telephone interview with the patients at day 30, from the Norwegian Prescription Registry at study end
Statistical Analysis	Statistical analyses will be conducted according to the intention-to-treat principle. Clinical endpoints will be assessed by using Cox-regression and Kaplan-Meier curves Oslo Centre for Biostatistics and Epidemiology (OCBE) is responsible for all statistics. A statistical analysis plan (SAP) describing all details in this respect will be produced prior to database lock together with the study statistician from the DANBLOCK trial.
Clinical Endpoint Committee (CEC)	Adjudication of all end-points according to pre-specified and standardized criteria will be performed by a CEC blinded to study assignment.
Data Safety Monitoring Board	This committee consisting of two senior cardiologists and one trial-science statistician will overview safety and will have access to unblinded data.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or special term	Explanation
AMI	Acute myocardial infarction
BB	Betablocker
CAD	Coronary artery disease
CAG	Coronary angiogram
CEC	Clinical Endpoint Committee
CV	Cardiovascular
DSMB	Data Safety Monitoring Board
ESC	European Society of Cardiology
GP	General Practitioner
IeCRF	Electronic Case Record Form
IMP	Investigational medicinal product
LVEF	Left ventricular ejection fraction
NORMI	Norwegian myocardial infarction Registry
NORSTENT	Trial of Drug Eluting Stent Versus Bare Metal Stent to Treat Coronary Artery Stenosis
NSTEMI	Non-STEMI (Non-ST-elevation myocardial infarction)
PCI	Percutaneous coronary intervention
PROBE	Prospective, randomized, open label, blinded endpoint evaluation
PROMS	Patient-reported outcome measures (on sociodemographic, clinical and psychosocial factors)
STEMI	ST-elevatiom myocardial infarction
UAP	Unstable angina pectoris

1 INTRODUCTION

1.1 Background – Myocardial Infarction

Acute Myocardial Infarction (AMI) remains one of the leading causes of heart failure, sudden cardiac death all-cause mortality and disability-adjusted life-years (DALY) globally(1-3). Furthermore, costs related to MI management represent a significant economic burden to healthcare systems(4). Treatment for an AMI aims to reduce initial and late events and disease progression. Although separate guidelines have been developed for different presentations of the AMI, ST-segment elevation (STE) MIs and non (N)-STEMIs, the two have in common that a coronary angiogram (CAG) is recommended during hospital admission. The CAG will, with certain exceptions, reveal one or more occluded/stenotic coronary arteries as a result of an atherosclerotic process, termed coronary artery disease (CAD). CAD remains the single most frequent cause of death in Europe, whatever the severity, is estimated to account for >12% of all deaths(2).

Initial treatment during the first phase of an AMI, being partial or total occlusion, is to restore coronary blood flow in the diseased vessel and thus myocardial perfusion. This can be done either by pharmacologic reperfusion or by percutaneous coronary intervention (PCI), or, in some cases by surgery (coronary artery bypass grafting, CABG). Further treatment, including secondary prophylaxis depends on individual risk assessment.

The comprehensive AMI registry in Sweden (SWEDEHEART) reported in 2015 the yearly incidence of STEMI to be 66/100000 and of NSTEMI to be 132/100000 individuals. In the Norwegian Myocardial Infarction Registry (NORMI) report from 2015, these incidence figures were 64 / 100 000 and 184 / 100 000, respectively. The higher Norwegian incidence of NSTEMI is due to the fact that SWEDEHEART does not include small AMIs treated in other hospitals than major intensive care units. In Norway 12 612 individuals were registered with at least one AMI, and the total number was 13 397. NSTEMIs constituted 75% of all AMIs, and 30 days survival rate was 90 %(6). The rate of STEMI patients < 80 years treated with primary PCI was 80%, and of NSTEMI patients < 80 years undergoing early CAG was 76%, of whom about the half also underwent PCI. Based upon these figures it is reasonable to assess that 65% of AMI patients at present are being treated with PCI or thrombolysis during their index hospitalization in Norway(6).

Appropriate secondary preventive treatment and high adherence with recommended drug treatment and lifestyle changes are crucial to prevent disease progression after hospital discharge(5). The general practitioners (GPs) are the key actors to initiate, coordinate, and provide long-term secondary preventive management as they deliver most of the preventive consultations(5). Efforts to support their clinical work with secondary prevention is apparently needed as we have recently demonstrated that a majority of post-MI patients in Norway has an unfavourable lifestyle and poor coronary risk factor control(7). We have also shown that 65% were on social disability benefits, whereas the prevalence of comorbid depression, anxiety, type D (distressed) personality, and insomnia ranged 18-45%(8). Long-term follow-up data on lifestyle behaviour, risk factor management and the mediating socio-economic, clinical and psychosocial predictors are strongly requested in guidelines(5). Such knowledge is of utmost importance to i. determine quality and outcome of care, ii. develop empirically-based interventions, and iii. develop psychosocial and clinical screening instruments and risk prediction models that help clinicians to individualize lifestyle, drug management and follow-up care(5, 9). Comprehensive datasets in large populations are required for such analyses(10).

1.2 Background - Therapeutic Information

BBs have been a part of secondary prophylaxis following AMI irrespective of its severity for decades. Three studies published in the early eighties are credited for the introduction of secondary prophylactic BB treatment; the BHAT trial (11), the Norwegian Timolol study (12) and the Gothenburg Metoprolol trial (13). In the European Society of Cardiology (ESC) guidelines from 2013 on treatment of stable coronary disease, it is argued that the present efficacy of BBs is uncertain because the studies on post-MI patients were

conducted prior to the implementation of acute coronary revascularization and modern secondary prophylactic treatment(14). Similar ESC guidelines on STEMI assert long-term BB therapy as well established, but recognize the uncertainties referred to above(2). In the 2015 guidelines for NSTEMI, early BB therapy is recommended for patients with persistent ischemic symptoms, provided this is not contraindicated, and that patients without severe heart failure can be offered long-term therapy(15). In the American guidelines for management of stable ischemic disease from 2012, it is pointed out that BBs are efficacious in patients who have suffered myocardial infarction in the last three years (16, 17). Notwithstanding, patients experiencing heart failure or arrhythmias following an AMI have an unquestionable indication for treatment with BBs (14, 18).

In a large meta-analysis of randomized trials, BBs did not show effect post-AMI in the contemporary revascularization period (1991-2013) as opposed to the mortality reduction seen in the pre-revascularization period (1966-1991) (19). Recently, Puymirat et al (20) reported that early BB use in post AMI patients was associated with reduced 30-days mortality based upon propensity score matched cohorts comprising 502 patients in each group. However, discontinuation of BBs after one year was not associated with different five-year survival. In a large registry study of post-AMI patients without heart failure, Dondo et al (21) did not observe any mortality benefit from BB versus non-BB after 30 days, 6 or 12 months in a propensity analysis comprising 16 683 patients, regardless of their LVEF level (Tatendashe Bernadette Dondo, personal communication). Reduced mortality with BB treatment is still evident in study populations with reduced left ventricular ejection fraction (LVEF)(22).

In the last two decades BBs have been shown to reduce mortality and morbidity for a broad range of patients with a reduced LVEF in sinus rhythm. Recently, the ESC suggested there should be a third intermediate prototype of LVEF distribution, called mid-range LVEF (40-49%), thereby creating a clear separation between reduced LVEF (< 40%) and preserved LVEF ≥ 50% (23). In a recent meta-analysis of double blind, placebo-controlled randomized trials, Cleland et al (24) could show that for patients with heart failure in sinus rhythm and LVEF < 40% (n = 13442 patients) BB reduced all cause mortality (log rank p<0.001). These benefits, although less pronounced, also applied to the much smaller subgroup of patients with LVEF 40-49% (n = 575, log rank p = 0.042), whereas no benefit was seen the small group of patients with LVEF ≥ 50% (n= 244). The smaller number of patients with LVEF > 40% may not allow any firm conclusion on the efficacy of safety of BBs for mid-range and preserved LVEF.

BBs are still frequently prescribed in clinical practice to CAD patients even if cardiac function is preserved: In the study by Puymirat et al (20), BBs were given to 76.5% which dropped by 11% after one year. In an observational study of patients hospitalized for CAD events (80% AMI, 10% with heart failure) in two Norwegian Hospitals, the use of BBs among patients without heart failure was 83% at discharge and 70% after a median follow-up period of 1.7 years (range 6 months – 3 years) (25).

BB treatment introduces side effects that may have deteriorating effect on quality of life, functional status and health economic aspects such as the ability to work. Looking back to the pioneering BB trials, more patients in the BB group of the BHAT trial (11) reported tiredness, bronchospasm, diarrhea, and cold hands or feet. The excessive withdrawal rate in the BB group during the first month of the Norwegian Timolol study (12) was mainly due to bradycardia and hypotension. Finally, in the Gothenburg Metoprolol trial(13), more patients were withdrawn from treatment in the BB group because of suspected cardiovascular reactions. In a more recent review, Messerli et al (26) pointed out that acquisition cost of BBs is minimal, but certainly adverse events with this drug class is not.

1.3 eHealth

The Norwegian Directorate of eHealth (NDE) uses eHealth as a term to describe healthcare practice supported by electronic processes and communication. eHealth refers to tools and services using information- and communication-technologies that can improve the healthcare system as a whole, including prevention and monitoring of medical conditions and diseases. eHealth has been recognized as important in the development of patient centered health care. This study will, by the regular questionnaires that are

planned, be able to explore if certain standardized instruments for measuring generic health status might predict unfavorable disease progression in the follow up of patients with established CHD.

1.4 Study Rationale

The landmark studies which established the rationale for the routine use of oral betablocker after AMI were published more than thirty years ago (11-13). Since then, the implementation of acute coronary revascularization (the term 'revascularization' is in this protocol defined as primary PCI or thrombolysis for STEMI and with "early" PCI (i.e. during index hospitalization) for NSTEMI), and the use of modern secondary preventive treatments have changed the short and long-term prognosis for MI patients substantially. It is therefore possible that in this context BBs may have lost some of their effectiveness.

Based on contemporary studies there is at present a questionable rationale for a treatment which may influence quality of life and cause treatment withdrawal of both BBs and other secondary prophylactic drugs. Therefore, the important question arises whether BB treatment gives a net health benefit in patients who have received revascularization therapy post-AMI and who do not have clinical heart failure and/or evidence of LV systolic dysfunction.

1.5 Risk/Benefit

The BETAMI study has been designed as a multi-center, prospective, randomized, open blinded end-point (PROBE) study to provide definite evidence on the effects of oral BB therapy on all-cause mortality and recurrent MI in AMI patients treated with early revascularization and no clinical signs of heart failure and/or LVEF ≥ 40% by visual estimation or the Simpron`s biplane method.. The choice of a combined endpoint is explained by the high number of re-infarctions and by the importance of these two clinical endpoints (death and re-MI). Moreover, a meta-analysis using data from BETAMI and the similar REDUCE study conducted in Sweden, will provide evidence on the effects of oral BB therapy on all-cause mortality. Detailed information on the rationale for the study doses is provided in Section 5.1.

The greatest risk in this study is related to the risk of adverse cardiovascular events in the study group that *does not* receive beta blockers. This also includes patients with established CAD who were taken off their beta blocker at study inclusion. Strict study inclusion and exclusion criteria are pursued in order to mitigate that risk. Safety monitoring procedures further seek to minimize the risk of study participation. The study will have predefined termination criteria at predefined point in the study timeline. The use of BBs is associated with a risk to develop side effects which are well known to medical practitioners and are handled as a part of routine practice. Thus, these issues are not within the scope of this study as they are already known and present in everyday practice.

The greatest benefit will be to answer the question whether or not all AMI patients without heart failure or reduced LVEF should be given a betablocker, or if it certain subpopulations should not.

1.6 Secondary coronary prevention, biomarkers and drug adherence

Background and rationale for the work package (WP) covering secondary prevention, biomarkers and drug adherence is presented in *Appendix A.*

1.7 Health Economic Aspects

Background and rationale for the WP covering health economic aspects is presented in *Appendix B.*

1.8 Study Hypothesis

- 'BB treatment' is superior to 'No BB treatment' in patients who have received revascularization therapy for AMI (either PCI or, in some cases, thrombolysis), in terms of re-infarction, ischemic stroke, malignant ventricular arrhythmias, coronary revascularization, incident heart failure, cardiac arrest with successful resuscitation due to cardiac cause or all-cause death, over a mean of 3 years of follow-up period.

2 STUDY OBJECTIVES AND RELATED ENDPOINTS

	Objectives	Endpoints	Assessments
Primary	To study whether oral BB therapy reduces the risk of all-cause death, non-fatal MI, ischemic stroke, malignant ventricular arrhythmias, coronary revascularization, cardiac arrest with successful resuscitation due to cardiac cause, and incident heart failure since randomization compared to no such treatment, in patients with acute MI treated with PCI or thrombolysis without reduced LVEF	Time to all-cause death, non-fatal MI, ischemic stroke, ventricular arrhythmias, coronary revascularization, cardiac arrest with successful resuscitation due to cardiac cause, and incident heart failure *	Ref. Section 7.1. Obtained from Norwegian Cardiovascular Disease Registry at study end
Secondary	To study whether oral BB therapy reduces the risk of each of the components of the primary end-point separately, compared to no such therapy	Time to all-cause death, re-infarction, ischemic stroke, ventricular arrhythmias, coronary revascularization, cardiac arrest with successful resuscitation due to cardiac cause or incident heart failure*	Ref. Section 7.1. Obtained from the Norwegian Cardiovascular Disease Registry at study end
	To study whether oral BB therapy reduces the risk of cardiovascular death compared to no such therapy	Time to cardiovascular death*	Ref. Section 7.1. Obtained from the Norwegian Cause of Death Registry at study end

	Objectives	Endpoints	Assessments
	To study sociodemographic, clinical, and psychosocial characteristics (PROMS and clinical data) between the two study arms and in the total sample	Time to non-fatal MI, all-cause mortality, ventricular arrhythmias, ischemic stroke, coronary revascularization, cardiac arrest with successful resuscitation due to cardiac cause, hospitalization for heart failure, and cardiovascular death*	Ref. Section 7.1. Obtained from the Norwegian Cause of death Registry and the Norwegian Cardiovascular Disease Registry at study end
	To assess study safety	1.Rate of ventricular arrhythmias, heart failure, new MI or all-cause death 30 days after randomization analysed at 18 months follow-up and at study end. 2. All-cause death analyzed at study end	Ref. Section 7.2. Collected by direct telephone contact at 30 days and from hospital medical records at local hospitals throughout the study analysed at 18 months follow-up. Obtained from the Norwegian Population Registry and Norwegian Cardiovascular Disease Registry at study end
	To assess clinical outcomes linked BB therapy including outcomes in the following supbgroups: age (tertiles), gender (men vs. women), treatment subgroups (i.e. BB doses), LVEF subgroups (preserved LVEF: ≥50% vs. mid-range LVEF: 40-49%), quality of life, anxiety, depression, symptom burden (angina, dyspnea), sexual dysfunction and sleep disturbances.	Time to non-fatal MI, all-cause mortality, malignant ventricular arrhythmias, ischemic stroke, coronary revascularization, cardiac arrest with successful resuscitation due to cardiac cause, and incident heart failure*	Ref. Section 7.1. Obtained from the Norwegian Cardiovascular Disease Registry at study end

	To conduct a cost-utility analysis in relation to quality of life and a health economic evaluation including drug use, health care utilization, employment, income, and benefit take-up, controlling for death and relevant demographic variables.	Costs and benefits from a societal perspective, and net gain for public budgets.	Ref. Section 7.3. Obtained by patient self-report (SF-12) and from the Norwegian registry for income, the FD-Trygd (social security micro data for research) database, the Norwegian Prescription Database, the KUHR (control and payment of reimbursements to health service providers) database and the Norwegian Patient Registry. These data will be retrieved after patient enrollment is completed
Exploratory biobanking objectives:	To study the proportion and predictors of non-adherence with BB, statins and other cardiovascular drugs assessed by quantifying drug concentrations in blood Identify pharmacokinetic, pharmacogenetic and direct drug-related markers associated with side-effects and suboptimal response to treatment with cardiovascular drugs	Association with traditional cardiovascular risk factors, drug adherence, self-reported side-effects, and the primary and secondary study end-points Association with traditional cardiovascular risk factors, drug concentration measurements, self-reported side-effects, and the primary and secondary study end-points	Ref. Section 7.1-7.5 Obtained from the Norwegian Population Registry, the Norwegian Cardiovascular Disease Registry, the Norwegian Prescription Database and collected from self-reported questionnaires, and a clinical examination with blood sample collection and biobanking at baseline (all patients) and after 6 months follow-up (sub-sample).
Post-trial objective:	To perform a joint analysis of the data from this study with that of the REDUCE (NCT03278509) and REBOOT (NCT03596385) trials. This analysis will comprise >19000 patients, giving increased power and precision to make clinical decisions on both primary and secondary endpoints.	Time to non-fatal MI, all-cause mortality, ischemic stroke, ventricular arrhythmias, coronary revascularization, cardiac arrest with successful resuscitation due to cardiac cause , hospitalization for heart failure, and cardiovascular death*	Ref. Section 7.1. Obtained from the Norwegian Cardiovascular Disease Registry at study end

*time since randomization

3 OVERALL STUDY DESIGN

This is a multi-center, prospective, randomized, open label, blinded endpoint evaluation (PROBE) multicenter superiority study. It will include a total of 3000 patients in Norway with AMI who are treated with early coronary revascularization therapy (primary PCI or thrombolysis for STEMI and with "early" PCI (i.e. during index hospitalization) for NSTEMI). Patients will be electronically randomized to open prescription of a BB or no such treatment. All other documented secondary prophylactic drugs will be prescribed according to existing guidelines.

3.1 Recruitment Plan

In Norway, approximately 12.600 patients have an AMI each year, of which 65% are treated with a revascularization procedure, and hence theoretically eligible for study participation(6). Based on the study inclusion and exclusion criteria and previous experience with patient inclusion in recent similar randomized trials in Norway(27), we estimated that that some 4500-5000 patients may be included per year, indicating a recruitment period of 2 ½ to 3 years to enrol 10 000 patients in Norway. However, after an inclusion period of 8 months, we have experienced that the true inclusion rate is significantly lower.

In all, 2250 patients have been included during a 3.5 years period (per March 2022) indicating a total inclusion period of >10 years to enroll 10 000 patients. After careful discussions, the BETAMI steering committee consider such a long recruitment period not feasible neither from scientific nor an ethical point of view. Therefore, negotiations with the parallel DANBLOCK (NCT03778554) study Steering Committee, featuring an almost identical study design, has led to decision to merge the two final databases for endpoint analysis. However, each country (Norway and Denmark), respectively, retain their responsibility and financial plan for execution of their respective original studies. Further, we have decided to reduce the number of patients to be enrolled from 10 000 to aprox. 5 600. To maintain statistical power, we also increase the primary composite end-point, so that the same number of events will be observed (see updated sample size calculation in Section 9.6.1).

The first patient was enrolled October 2nd 2018. With an inclusion duration of 5.5 years, the mean/median follow-up period at end of inclusion is approximately 0.5 year; hence, the subsequent mean follow-up period will be 3 years or even longer in case of fewer primary end points occurring than expected. The total study duration from inclusion of the first patient to completion of the last included is estimated to 6 years.

Study Period	Actual date of first patient enrolled: 2-OCT-2018
	Anticipated recruitment period: 5.5 years
	Estimated date of last patient completed: 10 DEC 2024
	Estimated follow-up period at end of inclusion 0.5 years
Treatment Duration:	Until end of study period (mean 3 years after randomization)
Follow-up:	Expected range of follow-up is 0.5-6 years after randomization.

4 STUDY POPULATION

4.1 Selection of Study Population

PCI procedures will be performed according to generally accepted techniques, and is anticipated that most patients will have drug-eluting stents. The term PCI includes patients who are treated with balloon dilatation only. Subsequent antiplatelet and eventual triple therapy will be performed according to recommendations given by the respective PCI-centers.

All AMI patients who have been treated with a revascularization procedure will be screened for eligibility. Patients should be considered for inclusion in the study in the general ward / intensity care unit when stabilized the first days following PCI or thrombolysis, under the responsibility of the investigator in charge of patients` visits in the PCI center acting as the patients` local hospital as well, or at local hospitals after

discharge, at the latest within 8 days following PCI or thrombolysis. This recruitment strategy will allow a clinical and, in most cases, an echocardiographic evaluation with measurement of LVEF. In a pilot study of 159 consecutive post-AMI patients treated with primary PCI for STEMI or NSTEMI who underwent an echocardiographic examination after 3-7 days, 11% had LVEF <40%(28). Thus, nearly 90% of these patients may be potentially eligible for a trial like BETAMI. However, our experiences after trial commencement is that only half of these population are actually enrolled. Enrolled patients can participate in any other study that does not directly alter the effect of BB treatment. A prerequisite for participation is that patients fulfill all inclusion and exclusion criteria according to the assessment of the responsible physician performing the randomization procedure.

4.2 Number of Patients

2 900 patients will be included in the Norway part of this trial and 2 700 patients will be included in the Danish part of the trial.

4.3 Inclusion Criteria

To be eligible for inclusion in the study, subjects must fulfill the following criteria at inclusion:

- 18 years or older
- Diagnosed with an acute MI type I according to the "Universal Definition of MI" (Defined as a detection of a rise and/or fall of cardiac biomarker value, preferably troponin, with at least one value above the 99th percentile upper reference limit and with at least one of the following; a) symptoms of ischemia, b) new or presumed new significant ST-segment-T wave changes or new left bundle branch block, c) development of pathological Q waves, d) imaging evidence of new loss of viable myocardium or e) identification of an intracoronary thrombus by CAG) (18)
- Must have been treated with PCI or thrombolysis during current hospitalization
- Signed informed consent and expected cooperation of the patient according to ICH/GCP and national/local regulations
- Have a national personal identification number and not be expected to emigrate during study

4.4 Exclusion Criteria

Study subjects must not meet any of the following criteria:

- Having a condition where BB-therapy is required, including but not limited to:
  - Arrhythmias
  - Hypertension
  - Cardiomyopathies
  - Clinical diagnosis of heart failure
  - LVEF < 40% by echocardiography (by measurement and not only visual assessment for STEMI patients)
  - Left ventricular akinesia in ≥ 3 segments regardless of the LVEF

- Contraindications to BB-therapy:
  - Bradyarrhythmias
  - Hypotension
  - Severe peripheral artery disease
  - Previously known side-effects causing withdrawal
  - Severe chronic obstructive pulmonary disease
  - Women of childbearing potential (a woman is considered of childbearing potential, i.e. fertile, following menarche and until becoming post-menopausal unless permanently

sterile)
  - Known hypersensitivity to any ingredient of the IMP
  - Other, according to the responsible investigator

- End-stage somatic disease with short life expectancy, dementia, psychosis and other conditions could put the subject at significant risk, confound the study results, interfere significantly with the subject participation in the study, or rendering informed consent unfeasible

Previous treatment with a BB is not an exclusion criterion for enrollment into the BETAMI study. Enrolled patients can participate in any other study that does not directly alter the effect of BB treatment

5 TREATMENT

Patients will be electronically randomized to open prescription of either a BB or no such treatment in a 1:1 fashion within 1 – 8 days following the invasive procedure and after written, informed consent. Block randomization (with block sizes 4, 6, and 8 in random order), stratified by study centre and LVEF above vs. below 50% (preserved vs. mid-range), will be conducted through a web-based application (Viedoc™). All other documented secondary prophylactic drugs will be prescribed according to existing guidelines as judged by the responsible investigator.

5.1 Drug Identity, Supply and Storage

Drugs will be prescribed to the BB group as per clinical practice. Patients will upon discharge from the ward receive standard reimbursed prescriptions either on paper or electronically (so-called “blåresept”), hence no trial specific labelling of trial drugs will be performed. Exemption to requirements of trial specific labelling and batch registration has been given by Norwegian Medicines Agency (NoMA).

5.2 Dosage and Drug Administration

BB is administered orally. Dosages used in the pivotal BB trials described above [12-14] were very high, and do not reflect contemporary management. Pilot data from 80 consecutive AMI patients treated with PCI over a 3 months period in Drammen, Norway (dr. Elise Sverre, personal communication) shows that the majority of coronary patients was discharged with metoprolol succinate ranging from 25 to 100 mg OD (mean 75 mg OD). Nationwide mean dosage is 60mg daily.

To reflect contemporary management, for which this study is designed to test, there will not be a defined minimum dosage. The type and dose of BB will be left at the discretion of the PI. Generic drug and accepted dosages will be:

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

5.3 Concomitant Medication

All concomitant medication will be registered at baseline. Information about drug use during follow up will be obtained by linkage to the NorPD.

All other drugs with documented secondary prophylactic effect are permitted (e.g. statins, platelet inhibitors, oral anticoagulants, antihypertensive medication including ACE inhibitors / aniogtensin receptor antagonists). In fact, there are no prohibited medications unless for patients randomized to BBs, the use of

verapamil or diltiazem are considered to be prohibited, and patients who require such therapy will be withdrawn.

5.4 Subject Compliance

Patients will be asked to report BB use to the study nurse at 30 days and in the self-report system every 6 months until study end.

5.5 Drug Accountability

Drug accountability is not applicable (ref. section 5.1), but BB type and doses will be registered from the self-report system

5.6 Subject Numbering

Each subject is identified in the study by a unique subject number, which is assigned electronically after the subject has signed the Informed Consent Form. Once assigned the subject number cannot be re-used for any other subject.

6 STUDY PROCEDURES

Table 1. Schedule of activities

	Baseline	**Treatment period (0-2 years following randomization)**			
Time and assessments	1-8 days following randomization	Day 30	Every 6th month	Six months	study end
Recruitment, inclusion/exclusion evaluation[1)]	X				
Informed consent and randomization[2)]	X				
Collection of relevant hospital record data[3)]	X	X			x
Self-reported questionnaires (PROMs)[4)]	X	X	X*	X*	
Other self-reported questionnaires[5)]		X	X		
Collection of fasting blood samples for analyses and biobanking[6)]	X			X*	
Safety assessment obtained from medical records and national registries[7)]		X			X

1. Recruitment and inclusion/exclusion evaluation will be performed at baseline by a dedicated study nurse or the treating physician at PCI centers or community hospitals.
2. Randomization and collection of informed consent will be performed at baseline by the site-PI or delegated staff.
3. Relevant hospital record data at baseline will be registered in an eCRF by specially trained study nurses at each site. The following variables will be recorded: Age, gender, ethnicity, medical history, index cardiac event (NSTEMI, STEMI), angiographic findings, coronary treatment (PCI with or without stent implantation, thrombolysis) and echocardiographic findings (if performed) with emphasis on LVEF (40-49% and >=50%), a standard 12-lead ECG, prescribed medical treatment at hospitalization and at discharge, cardiac rehabilitation (content, duration, referral rate) and relevant information about cardiovascular risk factors (blood pressure, pulse, weight, height) provided in hospital discharge letters. The following blood sample will be recorded from the hospital record: HbA1c, haemoglobin, hsCRP, creatinine, cardiac biomarkers (max. CK-MB and/r Troponin-T/I, Brain Natriuetic Peptide), ALT, lipid profile (total cholesterol, HDL cholesterol, and LDL cholesterol.
4. A self-report questionnaire will be completed by all patients at baseline and after 6, 12, and 18 months follow-up. The questionnaire comprises lifestyle behaviour (smoking history, diet, alcohol, physical activity), generalized muscle pains (the Brief Pain Inventory Questionnaire), anxiety and depression (the Hospital Anxiety and Depression Scale and Patient Healthg Questionnaire-2), Type D personality (DS-14 questionnaire), insomnia (Bergen Insomnia scale), Nightmare Frequency Questionnaire, and average sleep length, health-related quality of life (Short Form-12), sexual dysfunction (Female Sexual Function Index and The International Index of Erectile Function) and symptom burden (New Your Heart Association functional, Canadian Cardiovascular Society functional classification of angina).
5. All patients will complete an electronic questionnaire at day 30 following randomization and at 6, 12 and 18 months follow-up. The online forms will include brief screening questions covering i. status on BB treatment,treatment with statins, ii. lifestyle behaviour (smoking, physical activity), drug adherence, and perceived drug related side- effects, iii. secondary preventive follow-up visits, iv. screening questions on generic health status, angina, dyspnoa, depression, anxiety, muscle pains, sexual dysfunction, fatigue and insomnia.
6. Biobanking for biomarker analyses and pharmacokinetic, pharmacodynamics and pharmacogenetic markers will be collected at baseline and after 6 months from both treatment arms on a subgroup of 500 patients.
7. Safety data after 30 days will be collected from a standardized telephone interview with all patients. The screening questions include: i. occurrence of events since discharge, particularly hospitalizations for subsequent cardiovascular events or reiteration of study procedures, ii. current medication, particularly BB treatment including dosages. The hospital records will be reviewed by the site PI if patients report hospitalization for subsequent cardiovascular events on the telephone interview. Safety data will also be collected from registries at study end.

6.1 Data collected at baseline:

6.2.1 Informed Consent and Randomization

Informed consent must have been given voluntarily by each subject before any study specific procedures are initiated, ref. Section 11.3. The informed consents will be systematized in a secure IT solution provided by Medinsight (Informed Consent Form Registry), ref. Section 11.3.1

A subject who has signed the informed consent form and has been assigned a subject identification number generated by Viedoc™ is considered registered (but not yet randomized). A subject who has been assigned to one of the two groups and has been assigned a randomization number is considered randomized.

All subjects will receive a study specific ID card stating that they participate in a clinical trial, containing information about the sponsor and contact information to the local PI/study nurse as well as the treatment allocation. This ID card will also include information that states that the patient, next of kin or the patient`s treating physician at the hospital and/or family doctor must inform the BETAMI investigators as soon as possible, when a diagnosis is established, about relevant cardiovascular events, for example stable angina pectoris , UAP, new AMI, ventricular arrhythmias, heart failure or death. The card will explain that the BETAMI investigators will *not* be made aware of this information unless specifically informed.

6.2.2 Data registered from the hospital medical records

- Age, gender, ethnicity
- Medical history, current cardiac status (NSTEMI, STEMI), angiographic findings, coronary treatment and echocardiographic findings (if performed), with emphasis on LVEF, and standard 12-lead ECG.
- Prescribed medical treatment at hospitalization and at discharge, content, duration and referral rate to cardiac rehabilitation programs. This information should be exchanged between PCI centers, local hospitals and the patient's treating physician, as per normal practice.
- Information about cardiovascular risk factors including blood pressure, pulse, height and weight.
- For subjects who have undergone an echocardiography before trial inclusion, where the images are available, these images may later be collected and analyzed by a central facility.

6.2.3 Patient self-report using commonly used and mainly validated questionnaires (See Appendix C)

- Lifestyle behaviour: Smoking history, diet, physical activity and alcohol addiction measured by AUDIT (Alcohol Use Disorders Identification Test).
- Medication with emphasis on BB and dose and secondary prophylactic treatment
- Generalized muscle pains (Brief Pain Inventory)
- Psychosocial factors:
    - Anxiety and depression: The Hospital Anxiety and Depression Scale (HADS)(29), contain 14 item covering symptoms of anxiety (HADS-A) and depression (HADS-D). It focuses on affective and cognitive symptoms and there are no somatic symptoms. Cut-off scores $\geq$8 on each subscale define doubtful cases and $\geq$11 define definite cases(29). Patient Health Questionnaire-2 (PHQ-2) a 2-item screening questionnaire for depression.

- Type D personality: DS-14 questionnaire(30), contains 14 items, with 7 items each on subscales of negative affectivity and social inhibition. To be categorized with type D personality a score ≥10 points on both subscales is required.

- Bergen Insomnia scale(31): Contains 6 items about sleep onset, maintenance of sleep and early morning wakening. In addition the average sleep duration will be measured

- Short Form-12 (SF-12)(32): Provides information on mental and physical health status and may be used for measurement of the patients quality of life and for health economic evaluation.

- Sexual dysfunction (Female Sexual Function Index and The International Index of Erectile Function)

- Symptom burden (New Your Heart Association functional, Canadian Cardiovascular Society functional classification of angina).)

6.2.4 Laboratory evaluations and biobanking

Standard blood samples (i.e. haematology, clinical chemistry and lipids) will be analysed at local hospitals and recorded from the hospital medical records. In addition, blood samples from a subsample of 500 patients from selected study centers at the south-eastern part of Norway (mainly OUS Ullevål, Akershus, Haukeland and Sykehuset i Østfold Kalnes) that are previously not treated with BBs or statins. Blood samples will be sent to the central laboratory at OUS for analyses of cardiovascular and drug-related biomarkers and biobanking. Details on the collections, shipment of samples and reporting of results will be prepared in a laboratory manual.

Hematology
The following tests are included in the haematology: HbA1c and haemoglobin,

Clinical chemistry
The following tests are included in the chemistry: hsCRP creatinine, CK, cardiac biomarkers (max. CK-MB and/r Troponin-T/I), and ALTwill be measured.

Fasting lipid profile
The following tests are included in the non-fasting lipid profile including total cholesterol, HDL cholesterol, LDL cholesterol and non-HDL cholesterol.

Pharmacological biomarker analyses
Concentrations of BBs in blood will be quantified by a direct liquid chromatography-tandem mass spectrometry (LC-MS/MS) methods and pharmacokinetic (concentrations), pharmacogenetic (known CYP enzymes) and direct drug-related markers (drug related metabolites) associated with side-effects and suboptimal response to treatment with BBs and other cardiovascular drugs will be explored.

6.3 Data Collected During Treatment and Follow-up

6.3.1 Safety data and online self-reported questionnaires

For this trial, NoMA has accepted that safety reporting will be limited to a selected number of safety parameters, i.e. the investigators do not have to report all adverse events occurring during the course of the trial.

The Steering Committee has chosen the following events considered important for safety reasons: Hospitalizations for heart failure, serious heart rhythm disturbances (ventricular tachycardia), new

myocardial infarction and death. With the present design and safety conduct, all these adverse events of special interest (AESI) will be included and handled as SAEs.

All patients will be contacted by telephone regarding the safety parameters malignant ventricular arrhythmias, incident heart failure, new myocardial infarction and all-cause death, as well as BB treatment including dosages, 30 days after randomisation. The interviews will be performed by trained site staff according to a standardised written protocol (ref. Appendix E).

Hospital records will be checked by trial staff for all patients who report such events and for all patients not reached. In addition, the ID card (ref. section 6.2.1 and Appendix D) will contain information encouraging reporting of relevant cardiovascular events to the site staff.

Further safety monitoring will be based on rates of all-cause death and the composite end-point of malignant ventricular arrhythmias, incident heart failure, new myocardial infarction and all-cause death from the Norwegian CVD Registry at study end.

During the follow-up visits, all study patients will be asked to complete electronic questionnaires at 30 days after randomization and every 6 months thereafter until the end of study. The system (ViedocMe) will be set up to issue a reminder if the online forms are not completed. Paper version of the questionnaires will be available.

Online forms (Appendix C) will include brief screening questions covering the following information:

- Status on BB treatment
- Concomitant treatment with statins.
- Lifestyle behaviour, drug adherence and perceived drug related side-effects
- Participation in cardiac rehabilitation programs and visits to primary care physicians
- Screening questions on generic health status, depression, anxiety, muscle pains, symptoms (dyspnoa and angina), sexual dysfunction, fatigue and insomnia

6.3.2 Clinical follow-up with laboratory evaluations, biobanking and completion of the baseline self-reported questionnaire

A subsample of 500 study patients will be invited to a visit at the local hospitals 6 months after randomization. Study data collected during the follow-up visit will be registered from a self-report questionnaire and from blood sample collections with biobanking. The study variables and procedures include those described above (see 6.2.*)*.

6.4 Linkage to National Registries

6.4.1 The Norwegian Prescription Database

The Norwegian Prescription Database (NorPD) registers all pharmacy dispenses in Norway. Actual drug use is not registered, thus we will follow an intention-to-treat principle. For the individual patient, information on the Anatomical Therapeutic Chemical code, the date of dispensation, the quantity and dosage dispensed, and reimbursement codes will be retrieved. A dataset including the patients' unique personal identifiers, clinical data, treatment allocation and study end-points will be sent to NorPD who pseudonymize the dataset

prior to linkage. Importantly, the pseudonymized dataset which is returned to the researchers, still includes prescription data on the individual patient.

6.6.2 Administrative registries for income and social security programs (FD-Trygd)

Data on income, employment and benefit take-up will be retrieved from the FD-trygd database (social security micro data for research) and tax-return data (income registry), together with demographic variables such as marital status, place of residence (bosted) and education.

6.6.3 Health care utilization - the Norwegian Patient Registry and the KUHR database

Data on health care utilization, with primary focus on cardiovascular vs. non-cardiovascular events, will be retrieved from the KUHR database (control and payment of reimbursements to health service providers) and from the Norwegian Patient Registry (NPR). Together KUHR and NPR will give a detailed description of health care utilization for the patients included in this study.

6.4.4 The Cause of Death Registry

Cause of death, which is relevant for the long-term follow-up, will be retrieved from the Cause of Death Registry.

6.5 Withdrawals and Procedures for Stopping Data Collection

Once randomized into the study, all patients will be assessed until study closure unless informed consent is withdrawn for study participation. Patients can withdraw their consent to participate at any time during follow-up without prejudice to further treatment. Data collection will stop at the time of withdrawal.

All randomized patients will be included in the study population. Patients who withdraw or are withdrawn from the study after randomization will not be replaced.

6.6 Procedures for Discontinuation

6.6.1 Patient Discontinuation

Subjects will not be discontinued from the trial, but cross over from one arm to the other will be recorded. BB prescription to subjects in the “non BB” arm will be done at the discretion of the treating physicians.

6.6.2 Trial Discontinuation

The whole trial may be discontinued upon DSMB recommendation. After 1/3 (1667) of the patients have completed 30 days follow-up, the DSMB will analyze the safety endpoint (rate of ventricular arrhythmias, heart failure, new MI). 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. 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.

6.7 End of Study

The Steering Committee is responsible for the decision to end the study, either due to safety reasons or when a sufficient number of patients is deemed to have been followed up for a sufficient time period. We estimate that study closure will happen in Dec 2024. Upon trial end, patients will be sent a letter (ref. Appendix F) describing that the study has been closed, and that all further treatment(s) with betablockers (or no betablocker treatment) and other concomitant medications will be fully up to the preferences and choices of the patient's physician and the patient based on prevailing national and international guidelines.

The sponsor and principal investigator(s) will inform all investigators, the relevant Competent Authorities and 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 Ethics Committees will be informed within 15 days.

7 ASSESSMENTS

7.1 Primary and Secondary Endpoint Assessments

Assessment of the primary endpoints (MACE; all-cause mortality, non-fatal MI, ischemic stroke, ventricular arrhythmias, coronary revascularization, cardiac arrest with successful resuscitation due to cardiac cause , and incident heart failure since randomization) and the other secondary cardiovascular study end-points will be obtained from the Cardiovascular Disease Registry of Norway and the Norwegian Population Registry at study end except for cardiovascular death which will be retrieved from the Cause of Death Registry.

7.2 Safety Assessments

Assessment of safety will be obtained from hospital medical records at the participating hospitals after 30 days, follow-up. All patients will be contacted by telephone by a specially trained study nurse and interviewed after a standardized written procedure. Hospital records will be screened for safety end-points by the local study nurse or site-investigator if patients a) report hospitalization for cardiovascular events or b) if the patients do not respond to the phone call.

Assessment of safety at study end will be based on rates of all-cause death and the composite end-point of malignant ventricular arrhythmias or resuscitated cardiac arrest, incident heart failure, new MI , and all-cause death obtained from the Norwegian CVD Registry.

The CSC will, in cooperation with the Department of Research Support (DRS) conduct a control of all safety end points as provided from the SAE and SUSAR reports at 30 days and provide it for the data and safety monitoring board (DSMB)

7.3 Health Economic Assessments

Assessment of income and employment will be obtained from adminstrative registries for income and social security programs (FD-Trygd) at study end. Assessment of drug use will be obtained from the Norwegian Prescription Database at study end. Assessment of health care utilization will be obtained from the KUHR (control and payment of reimbursements to health service providers) database and from the Norwegian Patient Registry at study end. Cause of death in the long-term health economic follow-up will be obtained from the Cause of Death Registry. In addition a health economic analysis in terms of quality of life will be performed based on self-reported data (SF-12).

7.4 Traditional cardiovascular risk factors and drug related side-effects

Assessment of traditional cardiovascular risk factors and side-effects will be obtained from hospital records and the self-report questionnaires at baseline and from the eCRF after 30 days, 6, 12 and 18 months follow-up.

7.5 Adherence Assessments

Assessment of drug adherence will be obtained by patient self-report from the eCRF during follow-up and from the Norwegian Prescription Database at study end.

8 SAFETY MONITORING AND REPORTING

8.1 Adverse Events

Traditional Adverse Event reporting, i.e. reporting side effects of the IMP to the sponsor is not within the scope of this trial. Prophylactic treatment with BBs following an AMI has been standard of care since the seventies, and the side effects are well known, as described in Section 1.

The main objective of this trial is to assess whether treatment with BB in the selected patient population reduces the risk of death or new MI, compared to no such treatment. Side effects of BB treatment are mainly relevant in terms of investigating their effect on the subjects' general condition with regard to quality of life, health care utilization, employment and benefit take up.

8.2 Serious Adverse Events (SAEs)

A Serious Adverse Event is defined as any untoward medical occurrence that at any dose:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above.

Medical and scientific judgment is to be exercised in deciding on the seriousness of a case. Important medical events may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the subject or may require intervention to prevent one of the listed outcomes in the definitions above. In such situations, or in doubtful cases, the case should be considered as serious. Hospitalization for administrative reason (for observation or social reasons) is allowed at the investigator's discretion and will not qualify as serious unless there is an associated adverse event warranting hospitalization.

A pre-planned hospitalization admission (ie, elective or scheduled surgery arranged prior to the start of treatment) for pre-existing condition is not considered to be a serious adverse event.

All serious adverse events (SAEs) will be reported according to GCP. SAEs will be reported by the Investigator via the eCRF system (Viedoc™) as soon as possible, and no more than 24 hours following the knowledge of such an event.

8.3 Suspected Unexpected Adverse Events (SUSARs)

The Sponsor's Medical Officer will review all SAEs reported as related to the trial drug and evaluate whether the event is expected according to the Reference Safety Information (RSI). The SPC (section 4.8 «Bivirkninger») of the IMPs is used as Reference Safety Information (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 that are fatal or life-threatening is recorded and reported as soon as possible to the Competent Authorities in any case no later than seven (7) days after knowledge by the sponsor of such a case, and that relevant follow-up information is subsequently communicated within an additional eight (8) days.

All other suspected serious unexpected adverse reactions will be reported to the Competent Authority concerned concerned as soon as possible but within a maximum of fifteen (15) days of first knowledge by the sponsor.

SUSARs will be reported using the CIOMS form.

8.4 Safety and Reporting

Clinical end-points and safety items are similar and safety end points new MI, malignant ventricular arrhythmias, hospitalization for heart failure, and all-cause mortality. They will all be validated by the Clinical Endpoint Committee (CEC). In addition, the Data Safety Monitoring Board (DSMB) will overview the outcomes throughout the study. Please see Section 6.3and 7.2were this is described in detail.

8.4.1 Annual Safety Report

A yearly safety report to the Competent Authority is not relevant in this trial. The Competent Authority will receive reports from the Data Safety Monitoring Board (ref. Section 8.5).

8.4.2 Clinical Study Report

The adverse events and serious adverse events occurring during the study will be discussed in the safety evaluation part of the Clinical Study Report.

8.5 Data Safety Monitoring Board (DSMB)

The DSMB consists of three international experts who will review all safety parameters death, hospitalization for heart failure, ECG-documented ventricular arrhythmia and recurrent AMI at day unblinded as well as the rate. This review will take place after the first 30 days of follow up, and at study end. The DSMB members will not be a part of the study organization and must not have any competing interests as judged by the Executive Steering Committee.

A DSMB charter, detailing the committee's activities and responsibilities, will be created prior to the inclusion of the first patient.

9 DATA MANAGEMENT AND MONITORING

9.1 Case Report Forms

9.1.1 Electronic Case Report Forms (eCRFs)

The Clinical Data Management System (CDMS) used for the eCRF in this study is Viedoc™. The setup of the study specific eCRF in the CDMS will be performed by the Clinical Trial Unit at Oslo University Hospital. The eCRF system will be FDA Code of Federal Regulations 21 Part 11 compliant.

The designated investigator staff will enter the data required by the protocol into the eCase report forms (eCRF). The Investigator is responsible for assuring that data entered into the eCRF is complete, accurate, and that entry is performed in a timely manner. The signature of the investigator will attest the accuracy of the data on each eCRF. If any assessments are omitted, the reason for such omissions will be noted on the eCRFs. Corrections, with the reason for the corrections will also be recorded.

At 30 days and at 6, 12 and 18 months thereafter, eCRFs/PROMs will be made available for the patients to fill in electronically, using the web-based application ViedocMe. An SMS reminder will be issued in case of missing responses. The patient accesses ViedocMe from any web-browser enabled platform, i.e. using their smartphone, tablet computer or PC. This accounts for eCRFs used for eHealth assessments as well.

After database lock, the investigator will receive a digital copy of the subject data for archiving at the investigational site.

9.1.2 Paper Case Report Forms (pCRF)

Paper forms are only relevant for patient reported data (questionnaires), which will be produced by the Clinical Trial Unit, Oslo University Hospital.

The data will be entered into Viedoc™ by the study staff.

9.2 Source Data

Source data are all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies).

The medical records for each patient should contain information which is important for the patient's safety and continued care, and to fulfill the requirement that critical study data should be verifiable.

To achieve this, the medical records of each patient should clearly describe at least:

- That the patient is participating in the study, e.g. by including the enrollment number and the study code or other study identification;
- Date when Informed Consent was obtained from the patient and statement that patient received a copy of the signed and dated Informed Consent;
- Results of all assessments confirming a patient's eligibility for the study;
- Diseases (past and current; both the disease studied and others, as relevant);

- Surgical history, as relevant;
- Treatments withdrawn/withheld due to participation in the study;
- Results of assessments performed during the study;
- Treatments given, changes in treatments during the study and the time points for the changes;
- Visits to the clinic / telephone contacts during the study, including those for study purposes only;
- Non-Serious Adverse Events and Serious Adverse Events (if any) including causality assessments;
- Date of, and reason for, discontinuation from study treatment, and vice-versa crossover from no-BB arm to BB-treatment;
- Date of, and reason for, withdrawal from study;
- Date of death and cause of death, if available;
- Additional information according to local regulations and practice.

Specify and provide details if any source data will be recorded directly into the Case Report Form (meaning that for the defined parameters, CRF is source data and not the hospital records).

A source data list will be agreed upon for each site specifying the source at a module or a variable level.

9.3 Study Monitoring

The investigators at local hospitals will be visited on a regular basis by the Clinical Study Monitor, who will check the following:

- Informed consent process
- Reporting of safety data
- Adherence to protocol
- Maintenance of required regulatory documents
- Facilities and equipment's (example: pharmacy, BP devices, etc.) if applicable
- Data completion on the CRFs including source data verification (SDV).

The monitor will review the relevant CRFs for accuracy and completeness and will ask the site staff to adjust any discrepancies as required.

Sponsor's representatives (e.g. monitors, auditors) and/or competent authorities will be allowed access to source data for source data verification in which case a review of those parts of the hospital records relevant to the study will be required.

9.4 Confidentiality

The investigator shall arrange for the secure retention of the patient identification and the code list. Patient files shall be kept for the maximum period of time permitted by each hospital. The study documentation

(CRFs, Site File etc) shall be retained and stored during the study and for 25 years after study closure). All information concerning the study will be stored in a safe place inaccessible to unauthorized personnel.

9.5 Database management

Data management will be performed by the Clinical Trial Unit, Oslo University Hospital. The Data management procedures will be performed in accordance with the department's SOPs and ICH guidelines. The data management process will be described in the study specific data handling plan and the study specific data handling report after database closure.

Data entered into the eCRF will be validated as defined in the data validation plan. Validation includes, but is not limited to, validity checks (e.g. range checks), consistency checks and customized checks (logical checks between variables to ensure that study data are accurately reported) for eCRF data and external data (e.g. laboratory data). A majority of edit checks will be triggered during data entry and will therefore facilitate efficient 'point of entry' data cleaning.

Data management personnel will perform both manual eCRF review and review of additional electronic edit checks to ensure that the data are complete, consistent and reasonable. The electronic edit checks will run continually throughout the course of the study and the issues will be reviewed manually online to determine what action needs to be taken.

Manual queries may be added to the system by clinical data management or study monitor. Clinical data managers and study monitors are able to remotely and proactively monitor the patient eCRFs to improve data quality.

All updates to queried data will be made by authorized study center personnel only and all modifications to the database will be recorded in an audit trail. Once the queries have been resolved, eCRFs will be signed by electronic signature Any changes to signed eCRFs will be approved and resigned by the Investigator.

Once the full set of eCRFs have been completed and locked, the Sponsor will authorize database lock and all electronic data will be sent to the designated statistician for analysis. Subsequent changes to the database will then be made only by written agreement.

The data will be stored in a dedicated and secured area at Oslo University Hospital. Data will be stored in a de-identified manner, where each study participant is recognisable by his/her unique trial subject number. The data will be stored until 31.12.2038.

Adverse events and medical history will be coded from the verbatim description (Investigator term) using the Medical Dictionary for Regulatory Activities, MedDRA. Prior and concomitant medications and therapies willbe coded according to <name of dictionary>.

Once the database has been completed and locked, the Sponsor will authorise database lock and all electronic data will be sent to the designated statistician for analysis. Subsequent changes to the database will then be made only by written agreement.

9.6 Determination of Sample Size and Power Calculation

9.6.1 Sample Size

The trial will include a total of 2900 patients from Norway with AMI who are revascularized. As previously described the remaining 2700 patients will be included from the Danish DANBLCOCK trial.

Incident rates obtained from the subpopulation with AMI as the indication for treatment with PCI in the NORSTENT trial [16] provide the background for sample size considerations and indicate a 5-year event rate

of 17% for the primary endpoint (Mortality 6.9% and AMI 10.1%). Assuming a recruitment (5.5 years) and post-trial follow-up (0.5 years) period of 6 years, a 3-year mean follow-up period, and a randomization ratio of 1:1, a sample size of 4671 patients (794 events) will provide a power of 80% to detect a difference of 18.7% primary endpoints with no BB treatment and 15.3% primary endpoints with BB treatment. This corresponds to a hazard ratio of approximately 1.22. To allow for a slightly lower overall event rate and some information loss due to drop-outs and crossover between groups the total sample size of the trial will be 5 000 patients.

After careful discussions in the common BETAMI-DANBLOCK executive steering committee and with the study statisticians, it has been decided that the primary composite study endpoint by the elements mentioned in 2.0 and in the synopsis (all-cause mortality, non-fatal MI, coronary revascularization, ischemic stroke, malignant ventricular arrhythmia, cardiac arrest with successful resuscitation due to cardiac cause, and incident heart failure since randomization) will be a time-to-event outcome. A new power calculation for the joint BETAMI - DANBLOCK trial has therefore been made 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 around 950 events in total. Only one analysis of the primary endpoint on the combined BETAMI and DANBLOCK sample will be performed.

9.7 Randomization

9.7.1 Allocation- sequence generation

Eligible patients will be allocated in a 1:1 ratio between BB and no BB, using a computer randomization procedure stratified by centre. Block randomization with block sizes 4, 6, and 8 in random order will be used.

Details of block size and allocation sequence generation will be provided in a separate document that is unavailable to those who enroll patients or assign treatment.

9.7.2 Blinding and emergency unblinding

Not applicable.

9.8 Population for Analysis

The following populations will be considered for the analyses:

- The primary statistical analyses will be conducted according to the intention-to-treat (ITT) principle.

- Safety population: Includes all subjects who have received at least one dose of study medication. Subjects who withdraw from the study will be included in the safety analysis. A list of withdrawn subjects, preferably with the reasons for withdrawal, will be established.

9.9 Planned analyses

The main statistical analysis is planned when all patients have been followed for a minimum of 0.5 years, all data have been entered, verified and validated, and the database has been locked.

Oslo Centre for Biostatistics and Epidemiology (OCBE) will be responsible for the statistical quality of the trial. Prior to the main statistical analysis, the data base will be locked for further entering or altering of data. A statistical analysis plan (SAP) describing all the statistical methods will be produced prior to database lock in close collaboration with the DANBLOCK statistician. The SAP will also describe the analyses set (ITT and PP) and all endpoints in detail. The treatment allocation will be revealed after the database lock and used in the

statistical analysis.

Deviation from the original statistical plan will be described and justified in the Clinical Study Report. Amendments to plan can be done until day of DB lock.

9.10 Statistical Analysis

9.10.1 Statistical hypothesis (superiority test)

Null hypothesis: The rate of the primary composite MACE endpoint in the group with prescription to BB is equal to the rate of MACE in the group without prescription to BB.

Alternative hypothesis (two-sided): the rate of MACE in the group with prescription to BB is greater than or smaller than the rate of MACE in the group without prescription to BB.

9.10.2 Primary analysis

The primary endpoint is time to MACE, assessed after all patients have completed a minimum of 0.5 years follow-up. A Cox regression model with prescription of BB (yes/no) and study site as covariates will be used. A hazard ratio for prescription of BB vs no BB with a 95% confidence interval will be estimated, and a test of a hazard ratio equal to one will be performed.

The survival curves for the two groups (BB vs no BB) will be estimated and plotted with the Kaplan-Meier estimator and the equality of the survival curves will be tested with the log-rank test.

The primary analysis will be performed on the ITT population.

9.10.3 Secondary analyses

Secondary endpoints will be analyzed in a similar manner as the primary endpoints, with Cox regression models and Kaplan-Meier survival curve estimation – or other suitable statistical methods – as detailed in the SAP, to be completed before database lock.

9.10.4 Safety analyses

After 1/3 (1667) of patients have completed 30 days follow-up, the DSMB will analyze the safety endpoint (rate of ventricular arrhythmias, heart failure, new MI or all-cause death 30 days after randomization). 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 criteria for such a recommendation is deemed to have been met. The recommendation to either continue or stop the trial because of an unbalance in event between the treatment arms will be at the discretion of the DSMB. The composite safety endpoint as well as all-cause mortality will also be assessed at study end.

Other safety analysis may be performed by the DSMB during the course of the trial, and include descriptive statistics and tabulations of safety parameters.

The DSMB charter, to be completed before inclusion of the first patient, will contain more details of the committee's activities and responsibilities.

9.10.5 Exploratory analyses using biobanking

1. To study the proportion of post MI patients that is non-adherent with BBs, statins and other cardiovascular drugs assessed by indirect (self-report and pharmacy registry) and novel direct methods quantifying drug concentrations in blood.
2. To study the association between clinical and psychosocial predictors of drug non-adherence measured with direct and indirect methodology.
3. To identify direct drug-related markers that predict statin-associated muscle symptoms and validate these against self-reported symptoms.
4. To explore the association between side-effects of cardiovascular drugs, clinical factors, cardiovascular drug concentrations and pharmacogenetic factors.

9.10.6 Other analyses

Other exploratory analyses of primary, secondary, and exploratory variables, on the whole trial sample or in selected subgroups, may be performed if appropriate. The decision to perform such analyses will be made by the executive steering committees on basis of the collected data.

9.10.7 Post-trial joint analysis

After completion of the primary analysis of the trial, a joint analysis of the data from this trial with that of the REDUCE trial in Sweden – provided this trial is completed – will be performed. In this analysis, a larger population from Norway/Denmark and Sweden will be available, giving increased power and precision to make clinical decisions on both primary and secondary endpoints, including total mortality, in addition to increased generalizability through a broader patient population.

10 STUDY MANAGEMENT

10.1 Investigator Delegation Procedure

The principal investigator is responsible for making and updating a “delegation of tasks” listing all the involved co-workers and their role in the project. He will ensure that appropriate training relevant to the study is given to all of these staff, and that any new information of relevance to the performance of this study is forwarded to the staff involved.

10.2 Protocol Adherence

Investigators ascertain they will apply due diligence to avoid protocol deviations.
All significant protocol deviations will be recorded and reported in the Clinical Study Report (CSR).

10.3 Study Amendments

If it is necessary for the study protocol to be amended, the amendment and/or a new version of the study protocol (Amended Protocol) must be notified to and approved by the Competent Authority and the Ethics Committee according to EU and national regulations.

10.4 Audit and Inspections

Authorized representatives of a Competent Authority and Ethics Committee may visit the study centers to perform inspections, including source data verification. Likewise the representatives from sponsor may visit the center to perform an audit. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice (ICH GCP), and any applicable regulatory requirements. The principal investigator will ensure that the inspectors and auditors will be provided with access to source data/documents.

11 ETHICAL AND REGULATORY REQUIREMENTS

The study will be conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice and applicable regulatory requirements. Registration of patient data will be carried out in accordance with national personal data laws.

11.1 Ethics Committee Approval

The study protocol, including the patient information and informed consent form to be used, must be approved by the regional ethics committee before enrolment of any patients into the study.

The investigator is responsible for informing the ethics committee of any serious and unexpected adverse events and/or major amendments to the protocol as per national requirements.

11.2 Other Regulatory Approvals

The protocol will be submitted and approved by the applicable competent authorities before commencement of the study.

The protocol will also be registered in www.clinicaltrials.gov and the European Clinical Trials Database (EudraCT) as before inclusion of the first patient.

11.3 Informed Consent Procedure

The investigator is responsible for giving the patients full and adequate verbal and written information about the nature, purpose, possible risk and benefit of the study. They will be informed as to the strict confidentiality of their patient data, but that their medical records may be reviewed for trial purposes by authorized individuals other than their treating physician.

It will be emphasized that the participation is voluntary and that the patient is allowed to refuse further participation in the protocol whenever she/he wants. This will not prejudice the patient's subsequent care. Documented informed consent must be obtained for all patients included in the study before they are registered in the study. This will be done in accordance with the national and local regulatory requirements. The investigator is responsible for obtaining signed informed consent.

A copy of the patient information and consent will be given to the patients. The signed and dated patient consent forms will be filed in the Investigator Site File binder.

11.3.1 Informed Consent Form Registry – Medinsight

The consent forms will be scanned and stored in a secure, encrypted, and access controlled database at OUH (Medinsight).

The "Informed Consent Form Registry" in Medinsight is approved by the Information Security Manager (Personvernombud) at OUH.

Site staff will, on an ongoing basis, send validated paper copies of the informed consent (IC) signature pages by post/courier to the Sponsor. The signature pages must contain the subject's trial ID and 11-digit personal ID. Dedicated staff will scan the signature pages into the Informed Consent Form Registry and record the subject's corresponding ID information, as well as information regarding what the subject has consented to (participation in the trial, genetic analyses, information regarding use of certain medications). The data will be verified by a second person and the verification documented. The paper copies at OUH will be destroyed after verification.

For every version of the IC forms, the full text will be scanned into the registry. In case of amendments to the IC forms, all versions will be available, as well as information regarding which version each subject has signed.

11.4 Subject Identification

The investigator is responsible for keeping a list of all patients (who have received study treatment or undergone any study specific procedure) including patient's date of birth and personal number, full names and last known addresses.

The patients will be identified in the CRFs by patient number, initials and date of birth (define as applicable).

11.5 User involvement

The BETAMI user group has been established with coronary patients (n=2), user group representatives (n=2), primary physicians (n=4), cardiac nurses (n=3), and clinical cardiologists (n=2). The research group will choose a representative from this group that will be a member of the Study Steering Committee and participate at their meetings.

The user group has discussed BB treatment in clinical practice together with members of the BETAMI research group during the planning phase. The group has also provided valuable input on the practical study implementation and the development and revision of the PROMS. The user group will participate in the development of written study information to patients, primary physicians and clinical cardiologists at the local hospitals. The user group will include central members of the major CAD patient organizations in Norway (Nasjonalforeningen for folkehelsen and Landsforeningen for Hjerte og Lungesyke). They will be pivotal in disseminating the BETAMI trial design, the importance of high compliance with the study protocol and the future study results to to patients, healthcare providers, authorities and the lay public. The BETAMI website (wwe.betami.no/wwwbetami.org) is about to be established.

12 TRIAL SPONSORSHIP AND FINANCING

Oslo University Hospital is the sponsor of the trial, which is funded by KLINBEFORSK (South-Eastern Norway Regional Health Authority) and the Norwegian Research Council. Further applications for funding for sub-studies and researchers will be submitted in due course.

13 TRIAL INSURANCE

The Principal investigator has insurance coverage for this study through membership of the Drug Liability Association (see http://www.laf.no for more details). This coverage harmonizes with the time period from randomization until end-of-study. In case of data collection and analysis after 5 and 10 years this will be performed in a separate trial.

14 PUBLICATION POLICY

Upon study completion and finalization of the study report the results of this study will either be submitted for publication and/or posted in a publicly assessable database of clinical study results.

The results of this study will also be submitted to the Competent Authority and the Ethics Committee according to EU and national regulations.

All personnel who have contributed significantly with the planning and performance of the study (Vancouver convention 1988) may be included in the list of authors.

15 APPENDICES

15.1 APPENDIX A – Background secondary coronary prevention (clinical, registry and biobank)

Burden, temporal trends, and cardiovascular risk factor control in CHD patients

Coronary heart disease (CHD) is the single leading cause of disability-adjusted life-years (DALY)(3) and premature death globally(1). Costs related to CHD management represent a significant economic burden to the healthcare system in Europe(4). Population aging and reduction in short-term mortality due to widespread use of coronary revascularization and effective medical treatment(4), have contributed to worldwide increases in the number of patients in need for optimal secondary prevention. Appropriate treatment and high adherence with secondary preventive drug treatment to obtain lipids and blood pressure (BP) at targets, metabolic control in diabetic patients, and appropriate lifestyle changes after AMI are crucial to prevent disease progression and recommended with the highest level of evidence in clinical practice guidelines(5).

However, cardiovascular risk factor control after CAD events in clinical practice today is poor (33)with an unfavourable trend over time has been documented(34) . Since the mid-1990s, the proportion of European CAD patients with obesity increased by 13% and with diabetes increased by 11%, while the proportion of daily smokers and patients with elevated BP remained nearly unchanged (34). Only cholesterol management has improved due to the increased prescription of statins (34). Norway did not participate in these multi-centre studies, but a recent cross-sectional study in 1127 patients (NORwegian CORonary [NOR-COR] Prevention Project) documented that cardiovascular risk factor control in CHD patients in two Norwegian counties was in line with European data(7). *Unpublished NOR-COR data from the sub-group (i.e. 65% of the NOR-COR sample population) treated with percutaneous coronary intervention (PCI) without clinical heart failure reveals a similar prevalence of cardiovascular risk factors as in the total study group (John Munkhaugen, personal communication).*

Unfavourable lifestyle and risk factor management contribute significantly to the high (18-20%/year) arisk of subsequent cardiovascular events in patients surviving an AMI(35, 36).Twenty-eight percent of the registered MIs in 2013 Norway were recurrent events(37) and even though the risk of recurrent MI has declined in patients older than 65 years between 2001 and 2008, it is concerning that no decline was observed in younger patients(38). ***These data are concerning and encourage further studies on temporal trends and cardiovascular risk factors in clinical CHD populations (39-41).***

The reasons for unfavourable lifestyle behaviour and risk factor control after MIs are complex and the mechanisms are not yet well understood. The factors are often categorised as related to the *patient,* the *treatment*, the *healthcare provider*, and *healthcare system (42)*. Examples of patient and treatment related factors are demographic background(40), socio-economic status(43-45), factors related to the CHD and other somatic comorbidities(46-48), psychological distress(49, 50) , personality(51, 52), complex treatment, treatment non-adherence and side-effects(48, 53). Poor discharge information and transition of patients between the hospital wards and primary physicians, the content and the duration and structure of CR programs are examples of healthcare and system factors of relevance (49, 54).

The cross-sectional NOR-COR study have identified several potentially modifiable clinical and psychosocial factors associated with (a) persistent smoking(8), (b) unfavourably elevated blood pressure(55), (c) unfavourably elevated LDL-cholesterol(56), (d) subclinical inflammation (Munkhaugen et al, resubmitted Eur J of Prev Cardiology after revision in January 2017) and (e) poor metabolic control in diabetes (Munkhaugen et al, under review BMC Cardiovascular Disorders), respectively. Suboptimal secondary preventive drug prescription, low drug adherence, drug-related side-effects, low participation rate in CR, and high level of psychosocial distress were among the most frequently potentially modifiable factors identified.

Identification of potentially modifiable factors of importance for risk profile and prognosis remains a public health priority(39, 40). In most previous large-scale studies in CHD populations, cardiovascular risk factors and clinical and demographic factors for the individual patient are measured one point in time (34, 36). ***The natural course of coronary risk factors and the mediating predictors of risk factor control over time on cardiac prognosis needs to be better clarified for the development of i. empirically-based***

interventions(25), ii. risk prediction models that help clinicians to individualize drug management and select patients for treatment with novel and more expensive drug therapy(9)***, iii. psychosocial and clinical screening instruments for early identification of subgroups of CHD patients in need of personalized management and extended follow-up care. Comprehensive datasets in large populations are required for such analyses***(10).

Risk prediction in patients with established CHD

The assessment of CVD risk and the prevention of recurrent events in patients suffering from cardiovascular disease represent an opportunity for major public health gains (57). Informal methods of risk prediction have traditionally been used to guide which individuals may benefit from therapy (58). However, due to variation in the observed and unobserved risk factors and the fact that clinicians are not good at estimating the likelihood of an outcome, risk assessment based on informal methods is not optimal(59, 60). Multivariable risk models in the setting of primary prevention have been intensely studied, in contrast to patients with established cardiovascular disease, where much less data are available(58). The SMART (Second Manifestations of Arterial disease) risk score for 10-year risk of myocardial infarction, stroke, or vascular death is among the very few risk prediction models developed for patients with established cardiovascular disease(9). The variables included in the model were age, sex, current smoking, diabetes, blood pressure, cholesterol, coronary artery disease, cerebrovascular disease, peripheral artery disease, creatinine, and high-sensitivity C-reactive protein. ***The present project will include a large number of patient related variables that may be used for the development prediction models for CHD patients.***

Non-adherence with cardiovascular drug therapy

Drug adherence is defined as the extent to which a patient takes medications as prescribed by their healthcare providers[12,13]. While significant resources are allocated to develop new CV drug treatments, 'simple' non-adherence to existing medications has become well-recognized, but yet an undermanaged challange(61). In a secondary care settings, non-adherence undermines evidence-based therapy, contributing to hundreds of thousands of deaths annually and unnecessary healthcare expenditures exceeding hundreds of billions of dollars in the US and Europe alone (62). International data indicate that only 50-60% of patients remain adherent with CV (i.e. antiplatelets, statins and antihypertensive) drugs within one year of initial prescription[10,25]. Non-adherence is associated with a significant increased risk of long-term adverse events and mortality in patients with established CHD[12,13]. Adherence has traditionally been monitored by patient self-report questionnaires[22]. Pill counts, prescription fill rates, and electronic pillboxes[24] are other indirect methods that all may overestimate drug intake, due to recall bias and/or patient overestimation[9]. Rates of prescription refill obtained from pharmacy registries, provide the most accurate data on adherence with cardiovascular drugs today[9]. In a recent Norwegian study, guideline- recommended secondary preventive drugs were prescribed to most patients discharged from hospital after MI and 12 months after the index MI, 84 % of patients were still on aspirin, 84 % on statins, 77
% on BBs and 57 % on ACEI/ARB(63). However, few drug and dose adjustments were made during follow-up.

However, pharmacy registry data also have their limitations since they cannot document tablet intake[9]. Furthermore, assessment of refill compliance from registries is laborious, and not feasible in daily clinical practice. Hence, drug adherence is rarely monitored in routine clinical practice[9], and when performed, the outcome is uncertain. Directly observed therapy with subsequent measurement of the active drug or its biological markers, and spot measurements of drug and/or metabolites in blood are regarded the most objective and accurate measurements of drug adherence[9]. Liquid chromatography-tandem mass spectrometry (LC-MS/MS) is the reference methodology for quantitative bioanalysis of cardiovascular drugs[26]. In a study of 84 patients with apparent treatment resistant hypertension who were taking on average five antihypertensive drugs, there were no detectable drug concentrations in serum samples from 35% of the patients, and 66% of the patients fulfilled the criteria of non-adherence[27]. Measurements of active drug or metabolites of antihypertensive drugs have recently been shown effective in improving blood pressure control in patients with resistant hypertension in a small pilot study[28]. LC-MS/MS methodology for measuring the blood levels of several clinical relevant secondary preventive drugs in blood is available(64). Recently, LC-MS/MS methodology for blood concentration

measurements of several cardiovascular drugs has also been established in Norway (NT Vethe and Mimi Opdal, Oslo University Hospital, Personal communication).

The reasons for non-adherence to cardiovascular medications are complex, multifactorial and probably related to both patient factors (composed treatment, side-effects, demographic and social factors, psychological distress[9]), and the healthcare provider[9]. The frequency, duration and structure of follow-up care are factors of relevance[9].

The main requirements challenges to improve drug adherence are[3,11]***:i. identifying patients who do not take their prescribed cardiovascular drugs measured with direct and indirect tests, ii elucidating causes of non-adherence, measured with reliable measures of adherence, and ii. exploring the relative importance of drug non-adherence in risk of subsequent cardiovascular events.***

Individual variations in cardiovascular drug therapy and drug related side-effects

The blood level of cardiovascular drugs is individual and determined by dosage, absorption, distribution, metabolism, excretion, drug-interactions and the liver and kidney function (65). Altered drug metabolism of CV drugs in the individual patient may be due to genetic polymorphisms or other drug and non-drug related biomarkers(65-69), which can lead to reduced or increased effect of consumed medication leading to side effects or poor treatment response. The prevalence of statin intolerance in clinical practice, including mainly side-effects from the musculoskeletal system, reaches 30% in observational studies (70, 71) and is an independent predictor of failure to reach the therapeutic target for LDL-C in CHD patients (72). Furthermore, side-effects with antihypertensive drug therapy is a common barrier to patients' adherence to BP lowering medication (73). Patients experiencing many side-effects might therefore have stopped their medication themselves resulting in poor risk factor control and cardiac prognosis. ***Knowledge on how pharmacokinetic, pharmacogenetic, pharmacogenomic and other drug related biomarkers influence individual drug metabolism and contributes to drug-related side-effects is needed to personalize drug treatment, reduce the burden of side-effects and thereby may improve drug adherence, risk factor control and cardiac prognosis.***

Biomarkers and novel personalized drug therapy

Even though the current challenge in combating CHD(39, 40) is to efficiently target the established CV risk factors that account for most of the CHD events(74, 75), a complex array of genetic, inflammatory and non-inflammatory biomarkers also contributes to the development and progression of CHD(76-78). Recently, specific drug therapy to target residual inflammatory (e.g. interleukin-beta antagonist)(79) and lipid risk (e.g. proprotein convertase subtilisin kexin 9 antibodies)(80) have reduced the risk of cardiovascular events in MI patients, while the sodium–glucose transport inhibitors reduce the risk of cardiovascular death and heart failure hospitalizations in patients with type 2 diabetes and established cardiovascular disease(81). Furthermore, cholesteryl ester transfer protein (CETP) inhibition(82), anti-thrombotic therapy with low-dose factor Xa antagonism in addition to platelet inhibition, and RNA interference which is a novel genetic treatment strategy(83), appear promising in the prevention of CHD(84). These novel drugs provide unique opportunities to personalize secondary prevention(85), but could also potentially increase the healthcare costs related to secondary preventive management markedly(86). Moreover, these drugs are hampered by potentially fatal side-effects(79). In the forthcoming years, several new therapeutic agents that target residual inflammatory, lipid and thrombotic risk will be available.Since these novel treatments have not yet been tested in combination and because of the practical and economic limitations(87), an important challenge is patient selection. ***New knowledge of the relative importance of the genetic, inflammatory and non-inflammatory biomarkers on cardiovascular prognosis and their associations with established cardiovascular, clinical and psychosocial risk factors may be important for the development of risk prediction models that may guide selection of patients for novel drug therapy.***

Psychosocial factors, drug treatment and cardiac prognosis

Comorbid psychosocial distress is prevalent after MI. The rate of clinically significant depressive symptoms has been estimated to be 40-65%, while 15-25% meet the criteria for major depression(49). The prevalence of anxiety symptoms has been estimated to be 25-40%, while type D (i.e. distressed) personality is estimated to be 18-28%(49). *Unpublished NOR-COR data reveals a similar* prevalence of *psychosocial risk factors in the*

sub-group (i.e. 65% of the NOR-COR sample population) treated with PCI without clinical heart failure. In observational studies, depression(88, 89), anxiety(88, 90), type D personality(91) and insomnia(92) increase the risk of coronary events(39, 93) and deteriorate the prognosis and quality of life of patients with established CHD(39, 49). The mechanisms by which psychosocial factors influence prognosis in CHD patients are not completely understood, but it is hypothesized that they are mediated through both direct pathophysiological (as autonomic nervous system dysfunction, genetics, epigenetics inflammatory and non-inflammatory markers) and bio-behavioural (i.e. unhealthy lifestyle, low adherence with medication, low participation in CR) pathways(39, 49, 94). Great variations in levels of psychosocial distress by socio-demographic and somatic background factors make the picture even more complex(49, 95). Available psychological treatments have only small effects on symptoms and quality of life, and no effects on cardiac prognosis have been found(96).

Evidence based pharmacotherapies that potentially modify the symptoms of anxiety, depression and insomnia are available(96, 97). Therefore, knowledge of the proportion of patients with psychosocial distress who was under concomitant active psychotropic drug treatment and the relative influence of drug treatment on cardiac prognosis is needed(96, 97). Moreover, psychotropic drug treatment gives an indication of the proportion of patients with psychosocial distress or psychological diseases prior to the study participation.

Better insight into the mechanisms linking psychosocial factors to cardiac prognosis and the relative influence of concomitant psychotropic drug treatment is required for the development of more efficient and sustained psychosocial interventions(96).

15.2 APPENDIX B – Background Health Economic Aspects

The health economic aspects of this study cover impacts on drug use, health care utilization, employment, and benefit take-up, all of which will be studied separately as well as jointly in the health economic evaluation.

The analysis will exploit rich and detailed administrative data, virtually attrition free, merged together using unique personal identifiers. For drug use we make use of the Drug Prescription database, covering all prescriptions in Norway. It does however not contain information on actual drug use and the analysis will thus follow an "intention to treat" strategy (as we do in the randomization of BB as well).

We will study health care utilization using the KUHR database (control and payment of reimbursements to health service providers), covering all visits to primary health care and private specialists, as well as NPR (the Norwegian Patient Registry), covering all visits to hospitals. Together KUHR and NPR will give a detailed description of health care utilization for the patients included in this study. Health care utilization will be measured in monetary terms. For KUHR this is straightforward since the database contains billing information. For NPR this can be estimated using DRG points.

The FD-Trygd database and tax-return data will be used to study employment, benefit take-up (Disability Insurance (DI), Temporary Disability Insurance (TDI), Unemployment Insurance (UI), Sick Leave (SL) and Social Assistance (SA)) and income from annual labour earnings, earnings from taxable benefits (disability, unemployment) and non-taxable benefits (social assistance etc.). Certain demographic variables, such as marital status, place of residence (bosted) and education, will be used as background variables in these analyses. By using data for the years prior to the AMI, we can characterize patients' labour supply before and after the event. Cause of death will be retrieved from the Cause of Death Registry (CDR) or the National Population Registry.

A follow-up of the patients using data from the above mentioned registries is planned for 5 and 10 years after completing patient enrollment.

All together these data provide insight into the costs and benefits for post-AMI patients, with and without BB treatment, in the short and long term. Firstly, we will try to evaluate costs and benefits from a societal perspective. We then assume that value added from employment equals labour income, and subtract the deadweight loss from raising taxes to cover all public costs (drug subsidies, subsidized treatment and benefits). Secondly, we will try to estimate net gain for public budgets by comparing changes in tax-revenues with total changes in public costs. We believe this may provide valuable insight into future treatment decisions. The study also includes self-reported data on quality of life, as measured by SF-12, which allows for an estimation of costs per quality-adjusted life year (QALY).

15.3 Protocol amendment on safety issues and follow-up of primary and safety endpoints

This document describes in further detail the handling of safety issues and follow-up of primary and safety endpoints in accordance with requirements from the Norwegian Medicines Agency (NoMA), and it complements the Protocol v4.0.

After 30 days, all patients will be contacted by telephone from the site staff and/or Central Study Coordinator to record Adverse Events of Special Interest (AESI):

- Hospitalizations for recurrent MI
- Heart failure
- Malignant cardiac arrhythmias (ventricular tachycardia/fibrillation)

In the instances where telephone contact were unsuccessful, hospital records will be scrutinized for all AESIs

In case of rehospitalizations, hospital records will be scrutinized for all AESIs and other relevant events leading to hospitalization

ASEIs shall be reported to the sponsor similarly to all Serious Adverse Events (SAE)s. Most probably all ASEIs will represent an SAE.

At the end-of-study the Norwegian Cardiovascular Registry and the Norwegian Population Registry will be scrutinized for the occurrence of the combined primary endpoint recurrent myocardial infarction or all cause death. In addition, patients alive at the end-of-study will be contacted by telephone with a question about having been hospitalized for a new myocardial infarction.

The patients and their closest relatives will, through the BETAMI study patient-ID card be informed that all hospitalizations including relevant cardiovascular events (including AESI) should be continuously, and as soon as possible, reported to the Sponsor. A list of the AESIs has to be included in the ID card. In addition, the card will point out that the Sponsor will not receive this information unless it is reported as requested.

In case of a rehospitalization the event has to be reported to the treating physician and then further on to the Sponsor if the event qualifies as an SAE. Most rehospitalizations will represent an SAE (see chapter 8.2 for exceptions). SAEs (in both study-arms) should be reported to the Sponsor as soon as possible and not later than 24 hours after being aware of the event.

The Sponsor shall record all SAEs, including ASEIs at the earliest possible time, and within 24 hours of becoming aware of the event.

The Sponsor shall report all SAEs which, according to the opinion of the PI or Sponsor represent a Suspected Unexpected Serious Adverse Reaction (SUSAR), to the NMA via CIOMS. A SUSAR considered fatal or life-threatening shall be reported to NMA within 7 days, all others within 15 days.

DSMB shall use data from all recorded ASEIs and other SAEs in their safety evaluations. Details of these safety evaluations are provided in the protocol.

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