



BETABLOCKER TREATMENT AFTER ACUTE MYOCARDIAL INFARCTION IN REVASCULARIZED PATIENTS WITHOUT REDUCED LEFT VENTRICULAR EJECTION FRACTION (BETAMI): RATIONALE AND DESIGN OF A PROSPECTIVE, RANDOMIZED, OPEN, BLINDED END POINT STUDY

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Background Current guidelines on the use of β -blockers in post-acute myocardial infarction (MI) patients without reduced left ventricular ejection fraction (LVEF) are based on studies before the implementation of modern reperfusion and secondary prevention therapies. It remains unknown whether β -blockers will reduce mortality and recurrent MI in contemporary revascularized post-MI patients without reduced LVEF.

Design BETAMI is a prospective, randomized, open, blinded end point multicenter study in 10,000 MI patients designed to test the superiority of oral β -blocker therapy compared to no β -blocker therapy. Patients with LVEF $\geq 40\%$ following treatment with percutaneous coronary intervention or thrombolysis and/or no clinical signs of heart failure are eligible to participate. The primary end point is a composite of all-cause mortality or recurrent MI obtained from national registries over a mean follow-up period of 3 years. Safety end points include rates of nonfatal MI, all-cause mortality, ventricular arrhythmias, and hospitalizations for heart failure obtained from hospital medical records 30 days after randomization, and from national registries after 6 and 18 months. Key secondary end points include recurrent MI, heart failure, cardiovascular and all-cause mortality, and clinical outcomes linked to β -blocker therapy including drug adherence, adverse effects, cardiovascular risk factors, psychosocial factors, and health economy. Statistical analyses will be conducted according to the intention-to-treat principle. A prespecified per-protocol analysis (patients truly on β -blockers or not) will also be conducted.

Conclusions The results from the BETAMI trial may have the potential of changing current clinical practice for treatment with β -blockers following MI in patients without reduced LVEF.

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Background

β -Blockers have been used in long-term secondary prevention following acute myocardial infarction (MI) irrespective of its severity following publication of the pertinent landmark studies in the 1980s.¹⁻³ Since then, implementation of acute coronary reperfusion/revascularization, introduction of high-sensitive troponins, and the use of modern secondary preventive treatments⁴ have changed both the MI diagnostics and the short- and long-term prognosis for MI patients.^{5,6}

Current international guidelines on the management of coronary heart disease therefore call into question the efficacy of β -blockers in contemporary post-MI patients without heart failure, and the strength of recommendations differs across diagnosis and continents.⁷⁻¹⁰ The European Society of Cardiology 2017 ST-elevation myocardial infarction (STEMI) guidelines recommend β -blockers to be started in-hospital and continued long-term following MI, with a class IIa level of evidence B recommendation.⁷ In the European Society of Cardiology 2015 guidelines for non-STEMI (NSTEMI), early β -blocker therapy has a class I, level B recommendation for patients with persistent ischemic symptoms, whereas there is no clear recommendation for long-term β -blocker treatment in patients without heart failure.⁸ Recent American Heart Association guidelines recommend β -blockers as a class I indication for all patients with STEMI who do not have a contraindication¹¹ and as class IIa indication for patients with NSTEMI and a normal left ventricular function.¹⁰

The only randomized large-scale β -blocker trial conducted in recent years,¹² 2 large meta-analyses of randomized controlled trials,^{13,14} and a large US registry study using propensity score analysis¹⁵ failed to verify the short- (30 days) and long-term (≥ 12 months) survival benefit of β -blockers in contemporary post-MI patients without heart failure that was observed in the older studies. In a recent systematic review and meta-analysis of observational studies in nearly 200,000 contemporary post-MI patients where the majority did not have heart failure or reduced left ventricular ejection fraction (LVEF), we found that β -blocker treatment was associated with a 26% reduction in all-cause mortality after a median follow-up time of 2.7 years.¹⁶ However, when controlling for study bias, particularly the effect of small studies, the association between β -blocker therapy and mortality disappeared. β -Blockers did reduce rates of recurrent MI and angina in the studies from the reperfusion era in the meta-analysis from Bangalore et al,¹³ but the benefit appeared to be short term (30 days) and at the expense of increase in heart failure, cardiogenic shock, and drug discontinuation. Notwithstanding, patients experiencing heart failure or arrhythmias following an MI have an unquestionable indication for treatment with β -blockers.^{17,18}

The β -blocker doses used in current clinical practice¹⁹⁻²¹ are lower than used in the landmark trials.¹⁻³ Unfortunately, information about β -blocker types, doses, persistence, and new prescriptions is lacking in most prospective cohort

studies conducted in the postrevascularization era.¹⁶ Furthermore, studies comparing the effect of high versus low β -blocker doses on cardiac outcomes report conflicting results.¹⁹⁻²¹ Randomized clinical trials are therefore needed to investigate the effect of β -blocker doses for cardiac prognosis.

In a recent Norwegian nationwide study, 82% of post-MI patients received β -blockers at discharge, a figure that only decreased by 5% after 12 months of follow-up.²² Similar estimates are reported internationally but with large variations between countries.²³ Although β -blockers are considered relatively safe and inexpensive, they do have well-known and common adverse effects¹⁻³ that may have deteriorating effect on quality of life, functional status, and health economic aspects such as the ability to work and health care utilization. Furthermore, adherence to other (potentially more efficacious) secondary preventive medications may diminish as a result of concomitant use of β -blockers.²⁴

In both current clinical practice guidelines and contemporary studies, there is at present a questionable rationale for β -blockers, and the important question arises whether β -blocker treatment still improves clinical outcome in contemporary revascularized post-MI patients without reduced LVEF.

Study design and methods

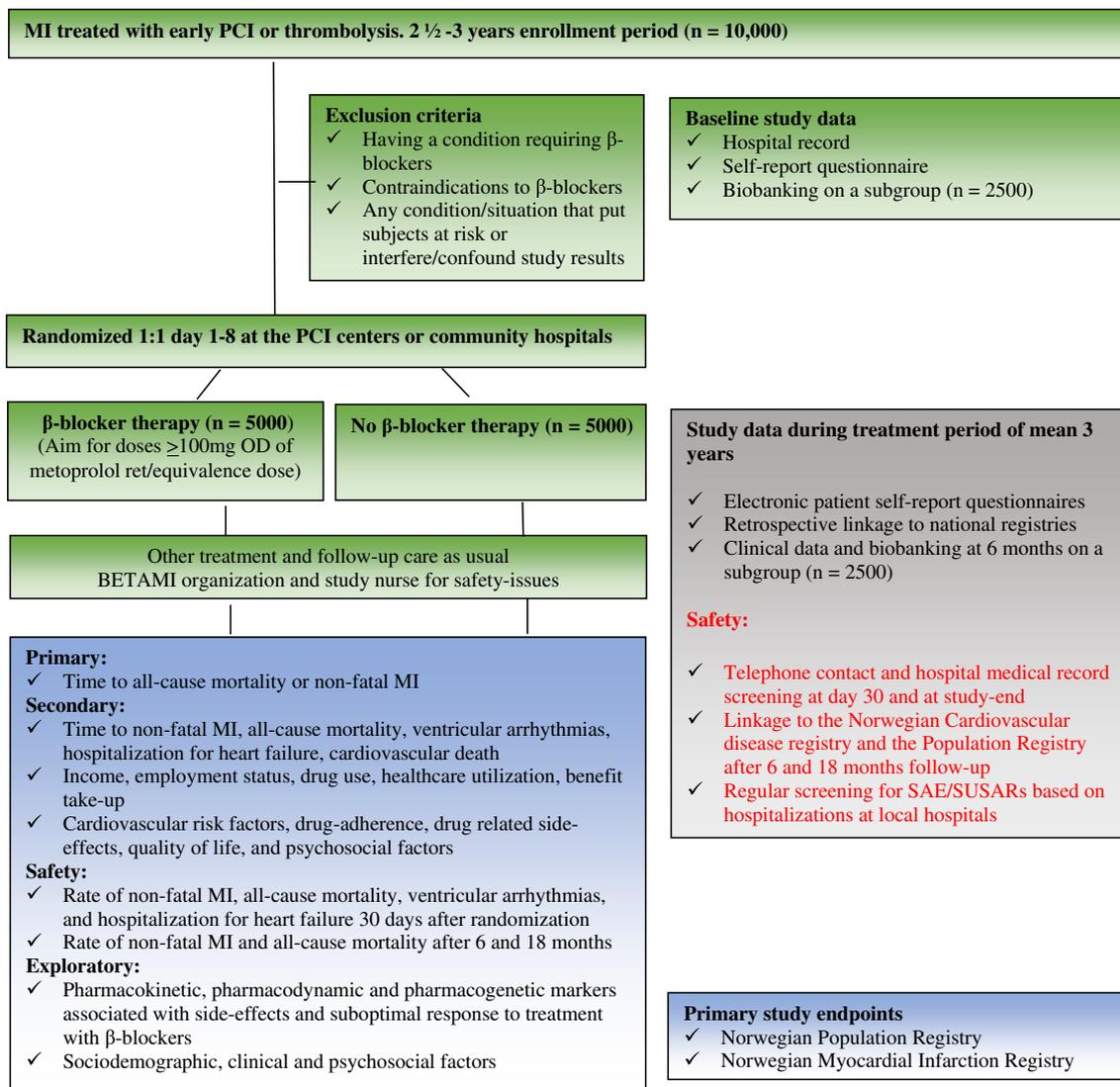
Study objectives and hypothesis

The primary objective is to test whether oral β -blocker therapy reduces the risk of all-cause mortality or nonfatal MI compared to no such therapy in post-MI patients without reduced LVEF. The working hypothesis is that “ β -blocker treatment” is still superior to “no β -blocker treatment” in such patients in terms of all-cause mortality and recurrent MIs over an average follow-up period of 3 years.

The key secondary objectives are to study whether β -blocker therapy reduces the risk of each of the primary end points separately, risk of cardiovascular (CV) death, and risk of hospitalization for ventricular arrhythmias or heart failure compared to no such therapy. Furthermore, to assess clinical outcomes linked to β -blocker therapy in subgroups according to treatment doses (ie, dose tertiles), LVEF (preserved LVEF: $\geq 50\%$ vs midrange LVEF: 40%-49%), drug-related adverse effects, drug adherence, CV risk factors, quality of life, anxiety, depression, symptom burden (angina, dyspnea), sexual dysfunction, and sleep disturbance. A cost-utility analysis of treatment with β -blocker therapy in relation to quality of life and a health economic evaluation including drug use, health care utilization, employment, income, and benefit take-up will also be conducted.

Exploratory biobanking objectives include direct determination of the proportion and predictors of nonadherence with β -blockers, statins, and other CV drugs assessed by liquid chromatography-tandem mass spectrometry

Figure 1



BETAMI study flowchart.

methods quantifying drug concentrations in blood. Pharmacokinetic, pharmacodynamic, and pharmacogenetic markers associated with adverse effects and suboptimal response to treatment with β -blockers and other CV drugs will also be explored.

Study design

This is a prospective, randomized, open, blinded end point (PROBE) superiority multicenter study conducted in Norway. The study flowchart is shown in Figure 1. In all, 10,000 patients will be included from 10 participating centers (n = 8 with percutaneous coronary intervention [PCI], n = 2 without PCI). *Reperfusion therapy* is defined as primary PCI or thrombolysis for STEMI, and “early” PCI (ie, during index

hospitalization) for NSTEMI. Patients will be electronically randomized to open prescription of a β -blocker or no such treatment. All other documented secondary prophylactic drugs will be prescribed according to existing guidelines⁴ as judged by the responsible attending physician.

Oslo University Hospital (OUH) is the sponsor for this investigator-initiated trial. Center of Regional Research Support (CRRS), OUH, is the clinical and data coordinating center. The trial has received grant support from the Health South-East research program in Norway (grant 2017205). Other than mediating financial support, the sponsor is not involved in the conduction of this study. The Steering Committee (SC), comprising representatives from all PCI centers and selected non-PCI centers in Norway, in

cooperation with CRRS, including statisticians at the Oslo Center of Biostatistics and Epidemiology, is the responsible body for the design and execution of the trial, related statistical analyses, and all aspects of manuscript preparation, including drafting and editing of the paper and its final content.

Study population, entry criteria, and inclusion procedures

All patients with a first or recurrent MI treated with PCI or thrombolysis will be screened for eligibility by study nurses or the treating physicians. PCI procedures will be performed according to standard operating procedures at the treating hospitals.⁷⁻¹⁰ Inclusion and randomization of the patients will be performed by treating physicians at PCI centers and selected high-volume community hospitals within 8 days following PCI or thrombolysis. A prerequisite for participation is that there is no clinical sign of heart failure at the time of randomization according to the assessment of the responsible physician and that LVEF is estimated to be $\geq 40\%$ by an echocardiographic examination. Previous treatment with a β -blocker is not an exclusion criterion for study enrolment. Based on data from a recent Norwegian post-MI study,²⁵ we expect that this subgroup will comprise 10%-15% of the total sample population. Patients can participate in any other study that does not directly alter the effect of β -blocker treatment. Further details on inclusion and exclusion criteria are summarized in Table I.

Randomization and interventions with study drug (dosage and administration)

If all eligibility criteria are met and written informed consent is provided, patients will be electronically randomized to open prescription of β -blocker or no such treatment in a 1:1 ratio. Block randomization (with block sizes 4, 6, and 8 in random order) stratified by study center will be conducted online (<http://www.betami.org>) through a Web-based application.

Prescription of the dose and type of β -blocker therapy will be left at the discretion of the community site physician. Accepted generic drug and dosages include metoprolol succinate up to a total dose of 200 mg daily, bisoprolol up to a total dose of 10 mg daily, or carvedilol up to a total dose of 50 mg daily. In general, doses >100 mg OD of metoprolol ret/equivalence dose of the other 3 β -blockers will be recommended when clinically tolerated. Patients will be encouraged to continue the prescribed β -blocker until the end of the study. Patients randomized to no β -blockers will be discouraged to use β -blocker therapy as long as there is no other indication than strictly secondary prevention after MI.

All study patients will receive a BETAMI information letter (ID-card size) stating that they participate in a clinical trial, containing information about the sponsor and contact

Table I. Enrollment criteria

Inclusion criteria (all the following)

- 18 y 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 1 value above the 99th percentile upper reference limit and with at least 1 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)
- Must have been treated with PCI for culprit lesion 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

Exclusion criteria (any of the following)

- Having a condition where β -blocker therapy is required, including but not limited to:
 - Arrhythmias
 - Hypertension
 - Cardiomyopathies
 - Clinical diagnosis of heart failure
 - LVEF $<40\%$ by echocardiography
 - Significant left ventricular akinesia and/or thrombus formation regardless of the LVEF
- Contraindications to β -blocker- therapy:
 - Bradyarrhythmias
 - Hypotension
 - Severe peripheral artery disease
 - Previously known adverse effects causing withdrawal
 - Severe chronic obstructive pulmonary disease
 - Others, according to the responsible investigator
- Any condition (eg, psychosis, dementia) or situation that, in the investigators' opinion, could put the subject at significant risk, confound the study results, interfere significantly with the subject participation in the study, or render informed consent unfeasible
- Women of childbearing potential using inadequate birth control, pregnancy, and/or breastfeeding. Adequate contraception includes oral, injected, or implanted hormonal methods of contraception; placement of an intrauterine device or system; vasectomized partner; or sexual abstinence.
- Short life expectancy (<1 y) due to noncardiac comorbid conditions

Abbreviations: ICH/GCP: International Council for Harmonisation /Good Clinical Practice.

information to the local Primary investigator (PI) and study nurse and to a Central Study Monitor (CSM) at the CRRS, as well as the treatment allocation. Patients will be instructed to wear the ID card in case of medical contact or primary care visits that may influence adherence to treatment.

Data collection and monitoring

A detailed overview of data collected at baseline, during the treatment follow-up period, and at the study end is shown in Table II. Baseline data will be obtained from hospital records and discharge letters (medication, comorbidity, cardiac rehabilitation, blood pressure, and weight and height measurements), echocardiographic examinations, and a self-report questionnaire about lifestyle behavior, psychosocial factors, and quality of life. Relevant standard blood samples (ie, hematology, clinical chemistry,

Table II. Study data collection

Time and assessments	Baseline	Treatment period (0-2 y following randomization)				End point
		1-8 d following randomization	Day 30	Every 6th month	6 m 18 m	
Recruitment, inclusion/exclusion evaluation*	X					
Informed consent and randomization†	X					
Collection of relevant hospital record data‡	X	X			X††	
Self-reported questionnaires (PROMs)§	X	X			X††	
eCRF (patient self-report)¶		X	X			
Collection of fasting blood samples for analyses and biobanking¶	X	X††			X††	
Safety assessment obtained from medical records and linkage to national health registries#		X			X X	
Assessment of primary and secondary study end points from national registries**						X

* 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.

† Randomization and collection of informed consent will be performed at baseline by the treating physician or the site PI.

‡ Relevant hospital record data at baseline and after 6 months (on a subsample of n = 2,500) 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); electrocardiographic and echocardiographic findings (if performed) with emphasis on myocardial function and associated cardiac disorders; prescribed medical treatment at discharge; cardiac rehabilitation (content, duration, referral rate); and information about CV risk factors like blood pressure, pulse, weight, and height. A self-report questionnaire will be completed by all patients at baseline and on a subsample (n = 2,500) after 6 months of follow-up. The questionnaire comprises lifestyle behavior (smoking history, physical activity), muscle pains (numeric rating scales 0-10), and sexual dysfunction (Female Sexual Function Index and The International Index of Erectile Function)

§ Symptom burden (New York Heart Association functional, Canadian Cardiovascular Society functional classification of angina), anxiety and depression (the Hospital Anxiety and Depression Scale, PHQ-2), type D personality (DS-14 questionnaire), insomnia (Bergen Insomnia scale, Nightmare Frequency Questionnaire, and average sleep length), and health-related quality of life (Short Form-12).

¶ All patients will be complete a brief an electronic questionnaire at day 30 following randomization and every 6 months thereafter. The online forms will include brief screening questions covering (1) status on β-blocker treatment and concomitant treatment with antiplatelets and statins; (2) lifestyle behavior (smoking, physical activity), drug adherence, and perceived drug-related adverse effects; (3) secondary preventive follow-up visits; and (4) screening questions on generic health status, depression, anxiety, muscle pains, sexual dysfunction, fatigue, and insomnia.

¶ Blood sample collection at baseline and after 6 months of follow-up will be performed by the local study nurse or a bioengineer. The following nonfasting blood tests will be included: HbA1c, hemoglobin, hsCRP, creatinine, cardiac biomarkers (max. troponin-T/1), ALT, LDL cholesterol, and HDL cholesterol. 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 2,500 patients.

Safety data after 30 days will be collected from a standardized telephone interview with all patients. The screening questions include occurrence of events since discharge, particularly hospitalizations for subsequent CV events, or reiteration of study procedures. The hospital records will be reviewed by the site PI if patients report hospitalization for subsequent CV events on the telephone interview. Safety assessment after 6 and 18 months of follow-up include nonfatal MI and all-cause death collected from the Norwegian Cardiovascular Disease Registry and the Norwegian Population Registry.

** The primary and secondary study end points will be obtained at study end by linking study data to administrative registries (income, social security micro data, health care utilization, drug prescription), clinical CVD (myocardial infarction, heart failure, arrhythmias, coronary angiography) registries, and the Cause of Death Registry after patient enrollment is completed.

and lipids) will be analyzed at community site hospitals. In addition, blood samples from a random subsample of 2,500 patients will be sent to the central laboratory for interlaboratory validation, analyses of CV biomarkers and pharmacokinetic, pharmacodynamic, and pharmacogenetic markers, as well as biobanking for future research. The echocardiographic records will be analyzed for a variety of functional and prognostic parameters.

At 30 days following randomization and every 6 months thereafter until the end of study, an electronic Case Report Form (eCRF) will be made available for the patients to complete. An SMS reminder will be issued in case of missing responses. Paper version of the questionnaires will be available and sent by post to those who do not respond. The forms will include brief screening questions covering (1) status on β-blocker treatment; (2) concomitant treatment with antiplatelets and statins; (3) lifestyle behavior, drug adherence, and perceived CV drug-related adverse effects; (4) participation in cardiac rehabilitation and other secondary preventive follow-up visits; and (5) screening questions on generic health status, depression, anxiety, muscle pains, fatigue, sexual dysfunction, and insomnia. These symptoms are known adverse effects to both β-

blocker therapy and other CV drugs as well as common complications to the MI itself. Study participants will not be informed that these symptoms could be β-blocker adverse effects to prevent that the lack of placebo drug effect will influence the patient's response to these questions. To further minimize this risk, the mean score for each item during follow-up will be used in the final analyses.

Each study site will be monitored regularly by the CSM/CRRS according to Good Clinical Practice standards.

Safety monitoring and reporting

Thirty days after randomization, all patients will be contacted by telephone by specially trained study personnel and interviewed after a standardized written protocol for occurrence of events since discharge with emphasis on hospitalizations for subsequent CV events. Hospital records will be screened for the safety end points (ie, rate of ECG-documented ventricular arrhythmias, hospitalization for heart failure, recurrent MI or all-cause mortality) by the local study nurse and/or site PI (a) if patients report hospitalization for CV events or (b) if the patients do not respond to the phone call. Further safety monitoring will be based on rates of recurrent MI and all-cause death obtained

from the Norwegian CV Disease Registry and the Population Registry after 6 and 18 months of follow-up. In addition, the PIs at each participating center are responsible for reporting serious adverse events and suspected unexpected serious adverse reactions to the Data and Safety Monitoring Board (DSMB) according to Good Clinical Practice and the requirements put forward by the Norwegian Medicines Agency.

A subsample of 2,500 patients from both treatment arms will be invited to a subsequent visit at the hospital outpatient clinic after 6 months of follow-up to repeat the baseline examination and the self-report questionnaire and to collect blood samples for analyses of drug-related biomarkers and concentrations of β -blockers and other CV drugs.

Outcome measurements and definitions

Patients will be followed up for a minimum of 2 years, giving a likely mean follow-up of 3 years (range 2-4 years), with regard to the primary and secondary end points described in Figure 1. Assessment of the primary outcome will be obtained from the Norwegian Population Registry and the Norwegian Myocardial Infarction Registry at study end. Assessment of the other secondary study end points will be ascertained through administrative registries (income, social security micro data, health care utilization, drug prescription) and clinical CV disease (myocardial infarction, heart failure, arrhythmia, coronary angiography) registries and the Cause of Death registry. All these registries have a mandatory reporting system (no attrition), and a unique personal identifier enables us to link the study participants to the registries.

Statistical considerations

Sample size

Sample size calculation was made for the primary end point which is a composite of all-cause mortality or recurrent MI. Incidence rates were obtained from the NORSTENT trial²⁶ indicating a 3-year event rate of 11% for the primary end point in the MI population (all-cause mortality: 4.5% and recurrent MI: 7.5%). Assuming a recruitment period of 2.5-3 years, a 3-year mean follow-up period, and a randomization ratio of 1:1, a sample size of 7,940 patients (794 events) will provide a power of 80% to detect a relative risk reduction of approximately 20% (11% primary end points with no β -blocker treatment vs 9% primary end points with β -blocker treatment; hazard ratio of 1.22). Based upon estimated dropout rates, we expect crossover between groups in the range of 10%-15%, particularly from the β -blocker group to the non- β -blocker group. In addition, expected withdrawals will be cases where non- β -blocker group patients require β -blocker treatment for other emerging indications. Also, we allow for a slightly lower overall event rate (9% instead of 10%) such that the total sample size of the trial will be 10,000 patients (5,000 per treatment group).

Statistical analyses

The primary statistical analyses will be conducted according to the intention-to-treat principle. A secondary/sensitivity analysis will be performed on the per-protocol set of patients (patients truly on β -blockers or not). The Oslo Center of Biostatistics and Epidemiology will be responsible for the statistical quality of the trial. The primary end point is time to all-cause mortality or nonfatal MI, assessed after all patients have completed a minimum of 2 years of follow-up. The null hypothesis is that the rate of all-cause mortality or MI in the β -blocker group is equal to the rate in the group without β -blocker, whereas the alternative hypothesis (2-sided) is that the rate of all-cause mortality or MI in the group with β -blocker is greater than or smaller than the rate in the group without β -blocker. A Cox regression model will be used with prescription of β -blocker (yes/no) and study site as covariates because these factors were used to stratify the randomization. A hazard ratio for prescription of β -blocker versus no β -blocker with a 95% CI will be estimated, and a test of a hazard ratio equal to 1 will be performed. The survival curves for the 2 groups (β -blocker vs no β -blocker) 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.

Secondary end points will be analyzed in a similar manner as the primary end points, with Cox regression models and Kaplan-Meier survival curve estimation or other suitable statistical methods detailed in the statistical analysis plan. 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 SC.

Safety analysis

After one-third ($n = 3334$) and two-thirds ($n = 6668$) of the patients, respectively, have completed 30 days of follow-up, the DSMB will analyze the 30-day safety end point. The DSMB will recommend to the executive SC that the trial is stopped if one of the treatment arms has 50% more events than the other. A 95% Koopman CI 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, triggering a recommendation from DSMB to SC to stop the study.

The safety end point of nonfatal MI and all-cause mortality, to be assessed at 6 and 18 months by the DSMB, will not be subjected to a predefined stopping criterion. The recommendation to either continue or stop the trial because of an unbalance in MI and mortality between the treatment arms will be at the discretion of the DSMB.

Study organization

SC and DSMB

The National SC composed of the study chair (D. A.) and co-chair (J. M.), work-package leaders (T. D., K. H. H., N. T. V.,

J. M., M. W. F.), and the PIs of the participating centers approved the study design, protocol, and amendments issued to the DSMB and the participating centers. The DSMB consisting of 3 international experts will overview safety and will have access to unblinded data. The DSMB provides advice on modifying or stopping the study as needed. However, the final decisions regarding changes in the study protocol remain in the hands of the SC. The DSMB members will not be a part of the study organization and must not have any competing interests as judged by the SC.

Clinical end point committee and adjudication

Adjudication of safety points at 30-day follow-up according to prespecified and standardized criteria will be performed by a clinical end point committee (CEC) blinded to study assignment. The CEC will not evaluate the primary study end points at study end because these are directly derived from the Norwegian Population Registry and the Norwegian Myocardial Infarction Registry which are valid and reliable.²⁷ The interrater reliability for STEMI and NSTEMI diagnoses obtained from the Norwegian Myocardial Infarction Registry was excellent (agreement coefficient >0.95) compared to hospital medical records reviews by experienced audit nurses blinded to the registry data.²⁷ Both registries are also complete²⁸ because of the mandatory reporting system and the personal identity numbers given to all citizens in Norway. The secondary study outcomes obtained from administrative and clinical CV disease registries with lower validity and completion rates will be adjudicated with hospital medical records at study end by CEC blinded to the registry data.

Data coordination and site management

Data collection and coordination will be under the responsibility of the CRRS. Continuous site monitoring will be performed by a CSM engaged by the CRRS in cooperation with the SC.

Ethical and other regulatory approvals

The study will be conducted in accordance with the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice and applicable regulatory requirements. All patients must provide written informed consent. Registration of patient data will be carried out in accordance with national personal data laws. The study protocol, including the patient information and informed consent form, has been approved by the Joint Regional Ethics Committee in Norway (number 2018/455) and the National Medicines Agency (number 18/02571-6). The trial protocol has been registered at the European Clinical Trials Database (EudraCT) (number 2018-000590-75) and at <http://register.clinicaltrials.gov> (number 2018-000590-75).

Trial status and timeline

In Norway, approximately 12,500 patients have an MI each year, of whom approximately 65% are treated with PCI (a minority with thrombolysis for STEMI) and hence are theoretically eligible for study participation.²⁸ Based on the study inclusion and exclusion criteria and previous experience with patient inclusion in similar randomized trials, a conservative estimate is that 10,000 patients may be enrolled over a 2½- to 3-year period. The first patients will be enrolled on October 1, 2018. With an inclusion duration of 3 years, the mean follow-up time at end of inclusion is approximately 1.5 years; hence, the subsequent follow-up period will be approximately 2 years and will last until all patients have completed a minimum of 2 years of follow-up. The total study duration from inclusion of the first patient to completion of the last included will be 4½ years. Thus, the final results of primary end point are expected in March 2023.

Scandinavian collaboration: joint analysis of BETAMI, REDUCE-SWEDEHEART, and DANBLOCK

A large number of patients are needed to identify the benefits of β -blockers in patient (ie, men/women, young/elderly) and treatment (β -blocker doses) subgroups and to resolve the question of all-cause mortality. The REDUCE-SWEDEHEART in Sweden (ClinicalTrials.gov Identifier: NCT03278509) is, to our best knowledge, the only ongoing randomized controlled β -blocker trial on contemporary post-MI patients without heart failure. REDUCE-SWEDEHEART is also designed as a superiority trial and will include 7,000 patients with comparable entry criteria and equal primary study end point to BETAMI. A similar superiority trial in Denmark (DANBLOCK) has been designed and is currently seeking funding.

After completion of the primary analyses of the Scandinavian trials, a prespecified posttrial joint analysis of data is planned. Together, these trials will comprise at least 17,000 patients. We then have a power of 79% to detect a relative difference between the treatment groups in all-cause mortality of approximately HR = 1.22 (event rates: 4.5% vs 3.7%). The power to detect the same relative difference in recurrent MI is 94% (event rates: 7.5% vs 6.1%). The increased power and precision of this joint analysis facilitate clinical decision making on both primary and secondary end points, in addition to increased generalizability through a broader patient population.

Discussion

The BETAMI trial will provide definitive evidence on the effects of oral β -blocker therapy on all-cause mortality and recurrent MI in revascularized post-MI patients without reduced LV function. This is an important clinical issue because of the lack of scientific evidence for a treatment

prescribed to most patients with one of the leading chronic diseases worldwide.²⁹ The varying prescription rates of β -blockers and the potential negative consequences of adverse effects for drug adherence, quality of life, functional status, and social and economic aspects further encourage a scientific reevaluation of the potential benefits or risks associated with current clinical practice.

The 3 old landmark trials demonstrated a significant 28%-40% relative reduction of all-cause mortalities in patients treated with β -blockers.¹⁻³ Two of these studies also found a 16%¹ and 30%³ reduction in occurrence of reinfarctions, respectively. Only the BHAT trial evaluated the incidence of a new diagnosis of heart failure and could not show any difference between propranolol and placebo.¹ No previous studies have shown any prophylactic effect of β -blockers on the development of subsequent heart failure among patients without heart failure at baseline. A superior design with the composite outcome all-cause mortality or recurrent MI has therefore been chosen for the present study. In line with another large trial conducted the past years,³⁰ we have chosen a PROBE design which makes the study more practically and economically feasible than a double-blinded placebo-controlled study. An inevitable limitation with PROBE design is that the lack of placebo in itself introduces a theoretic overestimation of β -blocker's effect on the patient-reported outcomes during follow-up because no effect inherent to placebo tablets will be amenable to subtraction from the active drug study arm.

BETAMI will be a pragmatic study, and patient recruitment and baseline registrations will be conducted as part of routine clinical practice. Patients previously treated with β -blockers will also be included to increase the generalizability of the study results and to reduce the total inclusion time. Norway is well experienced with and has a good infrastructure for running large multicenter studies, and the estimated inclusion rate in BETAMI is in line with the rate in recent nationwide post-MI trial.²⁶ Thus, the estimated inclusion period of 2.5-3 years appears feasible.

Dosages used in the pivotal β -blocker trials were very high (ie, about 80% of the patients had taken more than 90% of the prescribed target doses) and do not reflect contemporary practice.¹⁻³ In Norwegian revascularized post-MI patients without heart failure, the prescribed dosages equipotent to metoprolol succinate over the first 12 months ranged from 25 to 100 mg (mean 60 mg) daily.²² Treatment with suboptimal β -blocker doses could therefore potentially partly explain why the beneficial effects of β -blocker are not reproduced in observational studies conducted in the postrevascularization period.¹²⁻¹⁶ The impact of β -blocker doses on cardiac outcomes has recently been addressed in several observational studies.^{19,21} Whereas lower 1-year in-hospital mortality following MI was observed in patients treated with $\geq 50\%$ versus $< 50\%$ of the β -blocker target doses in 1 study,¹⁹ 2 other studies^{20,21} found no benefits on survival or cardiac outcomes in patients treated with β -blocker doses approximating those

used in the landmark trials compared with lower doses. An important caveat for these findings is that they do not represent randomized clinical trial results. Because there is, at present, no firm rationale for the optimal β -blocker dose in contemporary post-MI patients without heart failure or reduced LVEF, we have chosen a pragmatic dosage recommendation that reflects contemporary management, for which this study is designed to test. There will not be a defined minimum dosage, and the decision about the β -blocker dosage is left up to the discretion of the treating physicians. However, it will be recommended to aim for doses > 100 mg OD of metoprolol ret/equivalence when clinically tolerated. This will, to our opinion, contribute to an adequate β -blocker dose in the intervention arm across the participating centers.

Most studies showing improved outcome with β -blockers have been conducted in patients with symptomatic heart failure and LVEF $< 40\%$, who have already been treated with an angiotensin inhibitor.¹⁴ In the present study, patients with a clinical diagnosis of heart failure will be excluded. The cutoff value introduced for LVEF has been a matter of debate, especially because the ongoing REDUCE trial will only include patients with LVEF $\geq 50\%$. Such a high level will inevitably reduce inclusion rates, but concerns of safety have been raised for selecting the lower level of $\geq 40\%$. In a recent meta-analysis of PCI-treated patients with STEMI and preserved LVEF, however, Misumida et al³¹ found no differences in a favorable mortality outcome of β -blockers versus no β -blockers in a subgroup analysis stratified according to the definition of LVEF being $> 40\%$ or $> 50\%$. In a large recent UK registry study,¹⁵ where patients with a diagnosis of heart failure had been carefully excluded, no differences in lack of mortality reduction were found among patients with LVEF $\geq 50\%$ versus all patients who had LVEF measured, with a cutoff level of $\geq 30\%$ (B. Dondo, personal communication). Recently, a meta-analysis of randomized trials of β -blockers in heart failure reported an insignificant mortality reduction in patients with midrange LVEF (40%-49%), but this finding was based on only 570 randomized patients as opposed to a highly significant mortality benefit among 13,355 patients with reduced LVEF ($< 40\%$).¹⁴ By introducing a cutoff value of $\geq 40\%$, the BETAMI study gives a valuable opportunity to evaluate patients without reduced LVEF and stratify patients with midrange (ie, LVEF 40%-49%) versus preserved LVEF (ie, LVEF $\geq 50\%$) for clinical outcome in post-MI patients without clinical evidence of heart failure. It is well known that an LVEF below 35%-40% is a precise predictor of mortality but does not have similar predictive value above 40%.³² We have previously shown that a modern echocardiographic technique, left ventricular global longitudinal strain, has superior accuracy for prognostic information compared to traditional measures when LVEF is above 40%.³³ A BETAMI substudy including traditional and modern echocardiographic methods will be analyzed for myocardial function and prognostic information.

The use of β -blockers is associated with well-known potentially serious adverse effects such as hypotension and bradyarrhythmias.¹⁻³ The potential risk of participating in BETAMI is therefore related to the risk of adverse CV events in the study patients who *do not* receive β -blockers, including those with established CVD who are taken off their β -blockers at inclusion. Recently, Puymirat et al³⁴ reported that early β -blocker use in post-MI patients was associated with reduced 30-day mortality based upon propensity score matched cohorts comprising 502 patients in each group. However, discontinuation of β -blockers after 1 year was not associated with different 5-year survival. In a large recent registry study of post-MI patients without heart failure, Dondo et al¹⁵ did not observe any mortality benefit from β -blocker versus non- β -blocker after 30 days, 6 months, or 12 months in a propensity analysis comprising 16,683 patients. The strict study inclusion and exclusion criteria and the planned safety analyses based on a careful adverse event monitoring after 30-day follow-up and after 6 and 18 months, in addition to the predefined termination criteria, are pursued to mitigate the risk of study participation.

Other adverse effects of β -blockers reported in the landmark trials include fatigue, dyspnea, depressive symptoms, sexual dysfunction, sleep disorders, muscle pains, cold hands and feet, and weight gain.¹⁻³ Not all these adverse effects are supported by evidence from randomized trials; for example, the association between β -blocker and depression and insomnia, respectively, has yet to be proven. The comprehensive and interdisciplinary data collection from clinical examinations, e-questionnaires, and valid administrative and national registries will provide unique longitudinal outcome data linked to β -blocker therapy. The biobank data will provide new knowledge on how altered drug metabolism due to genetic polymorphisms, and/or drug-drug interactions, potentially reduces or increases the concentrations (and thus the effects) of β -blockers in blood leading to adverse effects or poor treatment response.³⁵ Altogether, the evidence from the CV, pharmacological, genetic, biomarker, and psychosocial substudies may be useful in personalizing secondary prevention and modeling effective and sustained interventions³⁶ that may potentially reduce the burden of adverse effects³⁷ and improve drug adherence,³⁸ CV risk factor control, and cardiac prognosis. The health economic evaluation of costs and benefits related to β -blockers and other secondary preventive drugs will potentially be of importance for future treatment decisions, health care providers, and authorities.³⁹

Conclusion

The results from the BETAMI trial together with the ongoing similar REDUCE-Swedeheart study and the planned DANBLOCK trial will potentially change present clinical practices for treatment with β -blockers following MI in patients without heart failure or reduced LVEF.

Competing interests and disclosures

The authors have no competing interests to declare.

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Author contribution

J. E. O., J. M., V. R., M. W. F., S. H., K. H. H., T. D., T. P., and D. A. contributed to the design of the work. J. M. prepared the figures and drafted the manuscript. All authors critically revised the manuscript and gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper, and its final contents.

References

1. Beta-Blocker Heart Attack (BHAT) Trial. A randomized trial of propranolol in patients with acute myocardial infarction. Mortality results. *JAMA* 1982;247:1707-14.
2. Pedersen T. The Norwegian multicenter study on timolol after myocardial infarction—design, management and results on mortality. *Acta Med Scand Suppl* 1981;651:235-41.
3. Hjalmarson A, Herlitz J, Holmberg S, et al. The Goteborg metoprolol trial. Effects on mortality and morbidity in acute myocardial infarction. *Circulation* 1983;67:26-32.
4. Piepoli MF, Hoes AW, Agewall S, et al. 2016 European guidelines on cardiovascular disease prevention in clinical practice. *Eur J Prev Cardiol* 2016;23:1-96.
5. Fox KA, Steg PG, Eagle KA, et al. Decline in rates of death and heart failure in acute coronary syndromes, 1999-2006. *JAMA* 2007;297:1892-900.
6. Hall M, Dondo TB, Yan AT, et al. Association of clinical factors and therapeutic strategies with improvements in survival following non-ST-elevation myocardial infarction, 2003-2013. *JAMA* 2016;316:1073-82.
7. Ibanez B, James S, Agewall S, et al. 2017 ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J* 2018;39:119-77.
8. Roffi M, Patrono C, Collet JP, et al. 2015 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J* 2016;37:267-315.
9. Task Force, M, Montalescot G, Sechtem U, et al. 2013 ESC guidelines on the management of stable coronary artery disease. *Eur Heart J* 2013;34:2949-3003.

10. Amsterdam EA, Wenger NK, Brindis RG, et al. 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes. *J Am Coll Cardiol* 2014;64:e139-228.
11. O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction. *J Am Coll Cardiol* 2013;61:e78-e140.
12. Chen ZM, Pan HC, Chen YP, et al. Early intravenous then oral metoprolol in 45,852 patients with acute myocardial infarction: randomised placebo-controlled trial. *Lancet* 2005;366:1622-32.
13. Bangalore S, Makani H, Radford M, et al. Clinical outcomes with beta-blockers for myocardial infarction: a meta-analysis of randomized trials. *Am J Med* 2014;127:939-53.
14. Cleland JGF, Bunting KV, Flather MD, et al. Beta-blockers for heart failure with reduced, mid-range, and preserved ejection fraction: an individual patient-level analysis of double-blind randomized trials. *Eur Heart J* 2018;39:26-35.
15. Dondo TB, Hall M, West RM, et al. Beta-blockers and mortality after acute myocardial infarction in patients without heart failure or ventricular dysfunction. *J Am Coll Cardiol* 2017;69:2710-20.
16. Dahl Aarvik M, Sandven I, Dondo TB, et al. Effect of oral β -blocker treatment on mortality in contemporary post-myocardial infarction patients. *Eur Heart J Cardiovasc Pharmacother* 2018. <https://doi.org/10.1093/ehjcvp/pvy034>. [Epub ahead of print].
17. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J* 2016;37:2129-200.
18. Priori SG, Blomstrom-Lundqvist C, Mazzanti A, et al. 2015 ESC guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. *Eur Heart J* 2015;36:2793-867.
19. Grall S, Biere L, Le Nezet M, et al. Relationship between beta-blocker and angiotensin-converting enzyme inhibitor dose and clinical outcome following acute myocardial infarction. *Circ J* 2015;79:632-40.
20. Goldberger JJ, Bonow RO, Cuffe M, et al. Effect of beta-blocker dose on survival after acute myocardial infarction. *J Am Coll Cardiol* 2015;66:1431-41.
21. Allen JE, Knight S, McCubrey RO, et al. β -Blocker dosage and outcomes after acute coronary syndrome. *Am Heart J* 2016;184:26-36.
22. Halvorsen S, Jortveit J, Hasvold P, et al. Initiation of and long-term adherence to secondary preventive drugs after acute myocardial infarction. *BMC Cardiovasc Disord* 2016;16:115-26.
23. Kotseva K, Wood D, De Bacquer D, et al. EUROASPIRE IV: a European Society of Cardiology survey on the lifestyle, risk factor and therapeutic management of coronary patients from 24 European countries. *Eur J Prev Cardiol* 2016;23:636-48.
24. Korhonen MJ, Robinson JG, Annis IE, et al. Adherence trade off to multiple preventive therapies and all-cause mortality after acute myocardial infarction. *J Am Coll Cardiol* 2017;70:1543-54.
25. Ruddox V, Otterstad JE, Atar D, et al. In current clinical practice, after percutaneous coronary intervention for acute myocardial infarction, are β -blockers prescribed for heart failure or as secondary prevention? A pilot study. *Cardiology* 2018;8(140):152-4.
26. Bona KH, Mannsverk J, Wiseth R, et al. Drug-eluting or bare-metal stents for coronary artery disease. *N Engl J Med* 2016;375:1242-52.
27. Govatsmark RE, Sneeggen S, Karlsauene H, et al. Interrater reliability of a national acute myocardial infarction register. *Clin Epidemiol* 2016;8:305-12.
28. The annual report from the Norwegian Myocardial Infarction Registry. at <https://stolav.no/seksjon/Hjerteinfarktregisteret/Documents/%C3%85rsrapporter/%C3%85rsrapport%202016/%C3%85rsrapport%202016.%20Norsk%20hjerteinfarktregister%2010.2017.pdf>. Accessed March 23, 2018.
29. Murray CJ, Barber RM, Foreman KJ, et al. Global, regional, and national disability-adjusted life years (DALYs) for 306 diseases and injuries and healthy life expectancy (HALE) for 188 countries, 1990-2013: quantifying the epidemiological transition. *Lancet* 2015;386:2145-91.
30. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009;361:1139-51.
31. Misumida N, Harjai K, Kernis S, et al. Does oral beta-blocker therapy improve long-term survival in ST-segment elevation myocardial infarction with preserved systolic function? A meta-analysis. *J Cardiovasc Pharmacol Ther* 2016;21:280-5.
32. Buxton AE, Lee KL, Hafley GE, et al. Limitations of ejection fraction for prediction of sudden death risk in patients with coronary artery disease: lessons from the MUSTT study. *J Am Coll Cardiol* 2007;50:1150-7.
33. Haugaa KH, Smedsrud MK, Steen T, et al. Mechanical dispersion assessed by myocardial strain in patients after myocardial infarction for risk prediction of ventricular arrhythmia. *JACC Cardiovasc Imaging* 2010;3:247-56.
34. Puymirat E, Riant E, Aissaoui N, et al. Beta blockers and mortality after myocardial infarction in patients without heart failure: multicentre prospective cohort study. *BMJ* 2016;354:i4801.
35. Berinstein E, Levy A. Recent developments and future directions for the use of pharmacogenomics in cardiovascular disease treatments. *Expert Opin Drug Metab Toxicol* 2017;13:973-83.
36. Bueno H, Armstrong PW, Buxton MJ, et al. The future of clinical trials in secondary prevention after acute coronary syndromes. *Eur Heart J* 2011;32:1583-9.
37. Khatib R, Schwalm JD, Yusuf S, et al. Patient and healthcare provider barriers to hypertension awareness, treatment and follow up: a systematic review and meta-analysis of qualitative and quantitative studies. *PLoS One* 2014;9, e84238.
38. Nieuwlaet R, Wilczynski N, Navarro T, et al. Interventions for enhancing medication adherence. *Cochrane Database Syst Rev* 2014;11, CD000011.
39. De Smedt D, Kotseva K, De Bacquer D, et al. Cost-effectiveness of optimizing prevention in patients with coronary heart disease: the EUROASPIRE III health economics project. *Eur Heart J* 2012;33:2865-72.