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

Munkhaugen, John; Ruddox, Vidar; Halvorsen, Sigrun; Dammen, Toril; Fagerland, Morten W; Hernæs, Kjersti H; Vethe, Nils Tore; Prescott, Eva; Jensen, Svend Eggert; Rødevand, Olaf; Jortveit, Jarle; Bendz, Bjørn; Schirmer, Henrik; Køber, Lars; Bøtker, Hans Erik; Larsen, Alf Inge; Vikenes, Kjell; Steigen, Terje; Wiseth, Rune; Pedersen, Terje; Edvardsen, Thor; Otterstad, Jan Erik; Atar, Dan

Published in:
American Heart Journal

DOI (link to publication from Publisher):
10.1016/j.ahj.2018.10.005

Publication date:
2019

Document Version
Accepted author manuscript, peer reviewed version

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

J Munkhaugen, V Ruddox, S Halvorsen, T Dammen, MW Fagerland, KH Hernæs, NT Vethe, EIB Prescott, SE Jensen, O Rødevand, J Jortveit, B Bendz, H Schirmer, L Køber, HE Bøtker, AI Larsen, K Vikenes, T Steigen, R Wiseth, T Pedersen, T Edvardsen, JE Otterstad, D Atar

PII: S0002-8703(18)30301-6
DOI: https://doi.org/10.1016/j.ahj.2018.10.005
Reference: YMHJ 5793

To appear in: *American Heart Journal*

Received date: 14 May 2018
Accepted date: 20 October 2018

Please cite this article as: J Munkhaugen, V Ruddox, S Halvorsen, T Dammen, MW Fagerland, KH Hernæs, NT Vethe, EIB Prescott, SE Jensen, O Rødevand, J Jortveit, B Bendz, H Schirmer, L Køber, HE Bøtker, AI Larsen, K Vikenes, T Steigen, R Wiseth, T Pedersen, T Edvardsen, JE Otterstad, D Atar , 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. Ymhj (2018), https://doi.org/10.1016/j.ahj.2018.10.005

Trial Designs

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

RCT# 2018-000590-75

Munkhaugen J, MD, PhD[a,b], Ruddox V, MD, PhD[c], Halvorsen S, MD, PhD[d], Dammen T, MD, PhD[b], Fagerland MW, PhD[e], Hernæs KH, Cand. Econ[f], Vethe NT, PhD[g], Prescott EIB, MD, DMSc[h] , Jensen SE, MD, PhD[i], Rødevand O, MD, PhD[j], Jortveit J, MD, PhD[k], Bendz B, MD, PhD[l], Schirmer H, MD, PhD[m], Køber L, MD, PhD[n], Bøtker HE, MD, PhD[o] , Larsen AI, MD, PhD[p], Vikenes K, MD, PhD[q], Steigen T, MD, PhD[r], Wiseth R, MD, PhD[s], Pedersen T, MD, PhD[t], Edvardsen T, MD, PhD[l], Otterstad JE, MD, PhD[b], and Atar D, MD, PhD[d]

From the [a]Department of Medicine, Drammen Hospital, Vestre Viken Trust, Drammen, Norway, [b]Department of Behavioural Science in Medicine, Faculty of Medicine, University of Oslo, Norway, [c]Department for Cardiology, Vestfold Hospital Trust, Norway, [d]Department of Cardiology, Oslo University Hospital, Ullevaal, Oslo, Norway, [e]Oslo Centre for Biostatistics and Epidemiology, Research Support Services, Oslo University Hospital, Oslo, Norway, [f]Clinical Trial Unit Health economics, Oslo University Hospital, Oslo, Norway, [g]Department of Pharmacology, Oslo University Hospital, Oslo, Norway, [h]Department of Cardiology, Bispebjerg Hospital, University of Copenhagen, Denmark, [i]Department of Cardiology, Aalborg University Hospital, Aalborg, Denmark, [j]LHL Department of Cardiology, LHL Hospital Gardermoen, Norway, [k]Department of Cardiology, Sørlandet Hospital Arendal, Arendal, Norway, [l]Department of Cardiology, Oslo University Hospital, Rikshospitalet, Oslo, Norway, [m]Department of Cardiology, Akershus University Hospital AHUS, Lørenskog, Norway,[n]Department of Cardiology, Rigshospitalet, Copenhagen, Denmark, [o]Department of Cardiology, Aarhus University Hospital Skejby, Denmark, [p]Department of Cardiology, Stavanger University Hospital, Stavanger, Norway, [q]Department of Heart Disease, Haukeland University Hospital, Bergen, Norway, [r]Department of Cardiology, University Hospital of North Norway and the Arctic University of Norway, Tromsø, Norway, [s]Clinic of Cardiology, St. Olavs University Hospital, Trondheim, Norway, [t]Oslo University Hospital, Ullevaal and Medical Faculty, University of Oslo, Oslo, Norway.

Reprint requests: John Munkhaugen, MD, PhD, Department of Medicine, Drammen Hospital, Vestre Viken Trust, Dronninggata 41, 3004 Drammen, Norway. E-mail: johmun@vestreviken.no

Short title: β-blockers after myocardial infarction

Manuscript word count (without references): 4616

Keywords: β-blockers, myocardial infarction, left ventricular ejection fraction, randomized controlled trial

Abstract

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 (PROBE) multi-center 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 ≥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 non-fatal 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 endpoints include recurrent MI, heart failure, cardiovascular and all-cause mortality, and clinical outcomes linked to β-blocker therapy including drug adherence, side-effects, cardiovascular risk factors, psychosocial factors, and health economy. Statistical analyses will be conducted according to the intention-to-treat principle. A pre-specified 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. **EudraCT number** 2018-000590-75.

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 treatments[4] 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 (ESC) 2017 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 ESC 2015 guidelines for 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 contraindication,[11] 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] two large meta-analyses of randomized, controlled trials,[13,14] and a large US registry study using propensity score analysis[15] 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 LVEF, we found that β-blocker treatment was associated with a 26% reduction in all-cause mortality a after 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 practice[19,20,21] are lower than used in the landmark trials.[1-3] Unfortunately, information about β-blocker types, doses, persistence and new prescriptions are lacking in most prospective cohort studies conducted in the post-revascularization era.[16] Furthermore, studies comparing the effect of high vs. low β-blocker doses on cardiac outcomes report conflicting results.[19,20,21] 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 follow-up.[22] Similar estimates are reported internationally, but with large variations between countries.[23] Whilst β-blockers are considered relatively safe and inexpensive, they do have well-known and common side effects[1-3] 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 non-fatal 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 including outcomes in treatment subgroups (i.e. dose tertiles), LVEF subgroups (preserved LVEF: ≥50% vs. mid-range LVEF: 40-49%), drug-related side-effects, drug adherence, cardiovascular 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 non-adherence with β-blockers, statins and other cardiovascular drugs assessed by liquid chromatography-tandem mass spectrometry (LC-MS/MS) methods quantifying drug concentrations in blood. Pharmacokinetic, pharmacodynamic and pharmacogenetic markers associated with side-effects and suboptimal response to treatment with β-blockers and other cardiovascular drugs will also be explored.

Study design

This is a prospective, randomized, open, blinded end-point (PROBE) superiority multi-center study conducted in Norway. The study flow chart is shown in Figure 1. In all, 10,000 patients will be included from ten participating centers (n=8 with PCI, n=2 without PCI). Reperfusion therapy is defined as primary PCI or thrombolysis for STEMI, and "early" PCI (i.e. 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 guidelines[4] 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 number 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 Oslo Center of Biostatistics and Epidemiology (OCBE) are the responsible bodies 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. 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 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 ≥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 sub-group 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 1.

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 centre 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 200mg daily, bisoprolol up to a total dose of 10mg daily or carvedilol up to a total dose of 50mg daily. In general, doses ≥100mg OD of metoprolol ret/equivalence dose of the other three 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 information to the local Primary investigator (PI) and study nurse in addition 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 2. Baseline data will be obtained from hospital records and discharge letters (medication, comorbidity, cardiac rehabilitation, and blood pressure, weight and height measurements) echocardiographic examinations, and a self-report questionnaire about lifestyle behavior, psychosocial factors and quality of life. Relevant standard blood samples (i.e. hematology, clinical chemistry and lipids) will be analyzed at community site hospitals. In addition, blood samples from a random subsample of 2500 patients will be sent to the central laboratory for inter-laboratory validation, analyses of cardiovascular biomarkers and pharmacokinetic, pharmacodynamic and pharmacogenetic markers, as well as biobanking for future research. The echocardiographic records will be analysed for a variety of functional and prognostic parameters.

At 30 days following randomization and every 6 months thereafter until the end of study, an 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 i.

status on β-blocker treatment, ii. concomitant treatment with antiplatelets, and statins, iii. lifestyle behavior, drug adherence, and perceived CV drug related side-effects, iv. participation in cardiac rehabilitation and other secondary preventive follow-up visits, v. screening questions on generic health status, depression, anxiety, muscle pains, fatigue, sexual dysfunction, and insomnia. These symptoms are known side-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 side-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 Practices 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 cardiovascular events. Hospital records will be screened for the safety end-points (i.e. 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 if patients a) report hospitalization for cardiovascular 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 follow-

up. In addition, the PIs at each participating center are responsible for reporting Serious Adverse Events (SAEs) and Suspected Unexpected Serious Adverse Reactions (SUSARs) to the DSMB according to good clinical practice and the requirements put forward by the Norwegian Medicines Agency.

A sub-sample of 2500 patients from both treatment arms will be invited to a subsequent visit at the hospital outpatient clinic after 6 months follow-up to repeat the baseline examination, the self-report questionnaire, and collect blood samples for analyses of drug-related biomarkers and concentrations of β-blockers and other cardiovascular 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 endpoints 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, healthcare 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 endpoint which is a composite of all-cause mortality or recurrent MI. Incidence rates were obtained from the NORSTENT trial[26] indicating a 3-year event rate of 11% for the primary endpoint 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 7940 patients (794 events) will provide a power of 80% to detect a relative risk reduction of approximately 20% (11% primary endpoints with no β-blocker treatment vs 9% primary endpoints with β-blocker treatment; hazard ratio of 1.22). Based upon estimated drop-out 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 (5000 per treatment group).

Statistical analyses

The primary statistical analyses will be conducted according to the intention-to-treat (ITT) principle. A secondary/sensitivity analysis will be performed on the per protocol (PP) set of patients (patients truly on β-blockers or not). OCBE will be responsible for the statistical quality of the trial. The primary endpoint is time to all-cause mortality or non-fatal MI, assessed after all patients have completed a minimum of 2 years 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 (two-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 since these factors were used to stratify the randomization. A hazard ratio for prescription of β-blocker vs no β-blocker 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 (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 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 detailed in the statistical analysis plan (SAP). 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 committee.

Safety analysis

After 1/3 (n=3334) and 2/3 (n=6668) of the patients, respectively, have completed 30 days follow-up, the Data and Safety Monitoring Board (DSMB) will analyze the 30-days safety endpoint. 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, triggering a recommendation from DSMB to steering committee (SC) to stop the study.

The safety endpoint of non-fatal MI and all-cause mortality, to be assessed at 6 and 18 months by the DSMB, will not be subjected to a pre-defined 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

Steering committee and data safety monitoring board

The National SC composed of the study chair (DA) and co-chair (JM), work-package leaders (TD, KHH, NTV, JM, MWF), 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 three 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 (CEC) and adjudication

Adjudication of safety-points at 30 days follow-up according to pre-specified and standardized criteria will be performed by a CEC blinded to study assignment. The CEC will not evaluate the primary study endpoints at study end since 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 were 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 complete[28] due to 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, 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 a 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 - 3-year period. The first patients will be enrolled on October 1st 2018. With an inclusion duration of three 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 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 endpoint are expected in March 2023.

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

A large number of patients is needed to identify the benefits of β-blockers in patient (i.e. 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 7000 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 pre-specified post-trial 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 facilitates clinical decision making on both primary and secondary endpoints, 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 side-effects for drug adherence, quality of life, functional status and social and economic aspects, further encourage a scientific re-evaluation of the potential benefits or risks associated with current clinical practice.

The three 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 re-infarctions, respectively. Only the BHAT trial evaluated the incidence of a new diagnosis of heart failure and could not show any difference between propranolol and placbo.[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 over-estimation of β-blocker`s effect on the patient reported outcomes during follow-up, since 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 (i.e. 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 25-100 mg (mean 60mg) 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 post-revascularization period.[12-15,16] The impact of β-blocker doses on cardiac outcomes has recently been addressed in several observational studies.[19,20,21] Whereas lower one-year in-hospital mortality following MI was observed in patients treated with ≥50% vs. <50% of the β-blocker target doses in one study,[19] two 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. Since 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 ≥100mg 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 cut-off value introduced for LVEF has been a matter of debate; especially since the ongoing REDUCE trial will only include patients with LVEF ≥50%. Such a high level will inevitably reduce inclusion rates but concerns of safety have been raised for selecting the lower level of ≥40%. In a recent meta-analysis of PCI-treated patients with STEMI and preserved LVEF, however, Misumida et al[31] 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 ≥50% versus all patients who had LVEF measured, with a cut-off level of ≥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 mid-range LVEF (40-49%), but this finding was based on only 570 randomized patients as opposed to a highly significant mortality benefit among 13355 patients with reduced LVEF (< 40%).[14] By introducing a cut-off value of ≥40%, the BETAMI study gives a valuable opportunity to evaluate patients without reduced LVEF and stratify patients with mid-range (i.e. LVEF 40-49%) vs. preserved LVEF (i.e. LVEF ≥ 50%) for clinical outcome in post-MI patients without clinical evidence of

heart failure. It is well known that a left ventricular ejection fraction (EF) below 35-40% is an 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 (GLS) has superior accuracy for prognostic information compared to traditional measures when LVEF is above 40%.[33] A BETAMI sub-study including traditional and modern echocardiographic methods will be analysed for myocardial function and prognostic information.

The use of β-blockers is associated with well-known potentially serious side-effects such as hypotension, and bradyarrhythmia's.[1-3] The potential risk of participating in BETAMI is therefore related to the risk of adverse cardiovascular 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 al[34] 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 one year was not associated with different five-year survival. In a large recent registry study of post-MI patients without heart failure, Dondo et al[15] did not observe any mortality benefit from β-blocker versus non- β-blocker after 30 days, 6 or 12 months in a propensity analysis comprising 16 683 patients. The strict study inclusion and exclusion criteria, the planned safety analyses based on a careful adverse event monitoring after 30 days follow-up and after 6 and 18 months in addition to the predefined termination criteria are pursued in order to mitigate the risk of study participation.

Other side-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 side-effects are supported by evidence from randomized trials, e.g. 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 reduce or increase the concentrations (and thus the effects) of β-blockers in blood leading to side-effects or poor treatment response[35]. Altogether, the evidence from the cardiovascular, pharmacological, genetic, biomarker, and psychosocial sub-studies may be useful in personalizing secondary prevention and modelling effective and sustained interventions[36] that may potentially reduce the burden of side-effects,[37] 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, healthcare 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.

Acknowledgments

The study idea originates from the Department for Cardiology, Hospital of Vestfold, the Department of Medicine, Drammen Hospital Trust and Oslo University Hospital Ullevaal. The concept is developed by the project in collaboration with communities at the University of Oslo. The authors thank Martin Sending, Ellen Johnsen and Martha Colban, at OUH CRRS for their invaluable contribution to the planning phase of the study.

Author contribution

JEO, JM, VR, MWF, SH, KHH, TD, TP, and DA contributed to the design of the work. JM 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.

Declaration of conflicting interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

References

1. Beta-Blocker Heart Attack (BHAT) Trial. **A randomized trial of propranolol in patients with acute myocardial infarction. Mortality results.** *JAMA.* 1982;247:1707-1714.
2. Pedersen, T. **The Norwegian Multicenter Study on timolol after myocardial infarction--design, management and results on mortality**. *Acta Med Scand Suppl.* 1981;651:235-241.
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;297:1892-1900.
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;316:1073-1082.
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;39:119-177.
8. Roffi, M, Patrono, C, Collet, JP, et al. 2**015 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:e78-140.

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;366:1622-1632.

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;127:939-953.

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;69:2710-2720.

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 Sep 6 2018 Sep 6. doi: 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;37:2129-2200.

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;36:2793-2867.

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. J. **Effect of Beta-Blocker Dose on Survival After Acute Myocardial Infarction**. *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.

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;70:1543-1554.

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;140:152-154

26. Bonaa, KH, Mannsverk, J, Wiseth, R, et al. **Drug-Eluting or Bare-Metal Stents for Coronary Artery Disease.** *N Engl J Med.* 2016;375:1242-1252.

27. Govatsmark, RE, Sneeggen, S, Karlsaune, H, et.al. **Interrater reliability of a national acute myocardial infarction register.** *Clin Epidemiol.* 2016;8:305-312.

28. **The annual report from the Norwegian Myocardial Infarction Registry.** Accessed 23.03.18 at https://stolav.no/seksjon/Hjerteinfarktregisteret/Documents/%C3%85rsrapporter/%C3%85rsrapport%202016/%C3%85rsrapport%202016.%20Norsk%20hjerteinfarktregister%201.10.2017.pdf.

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;361:1139-1151.

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;21:280-285.

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;50:1150-1157.

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;3:247-256.

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 and Levy, A. **Recent developments and future directions for the use of pharmacogenomics in cardiovascular disease treatments.** *Expert opinion on drug metabolism & toxicology.* 2017;13:973-983.

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;32:1583-1589.

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. Nieuwlaat, 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;33:2865-2872.

Figure 1 BETAMI Study flowchart

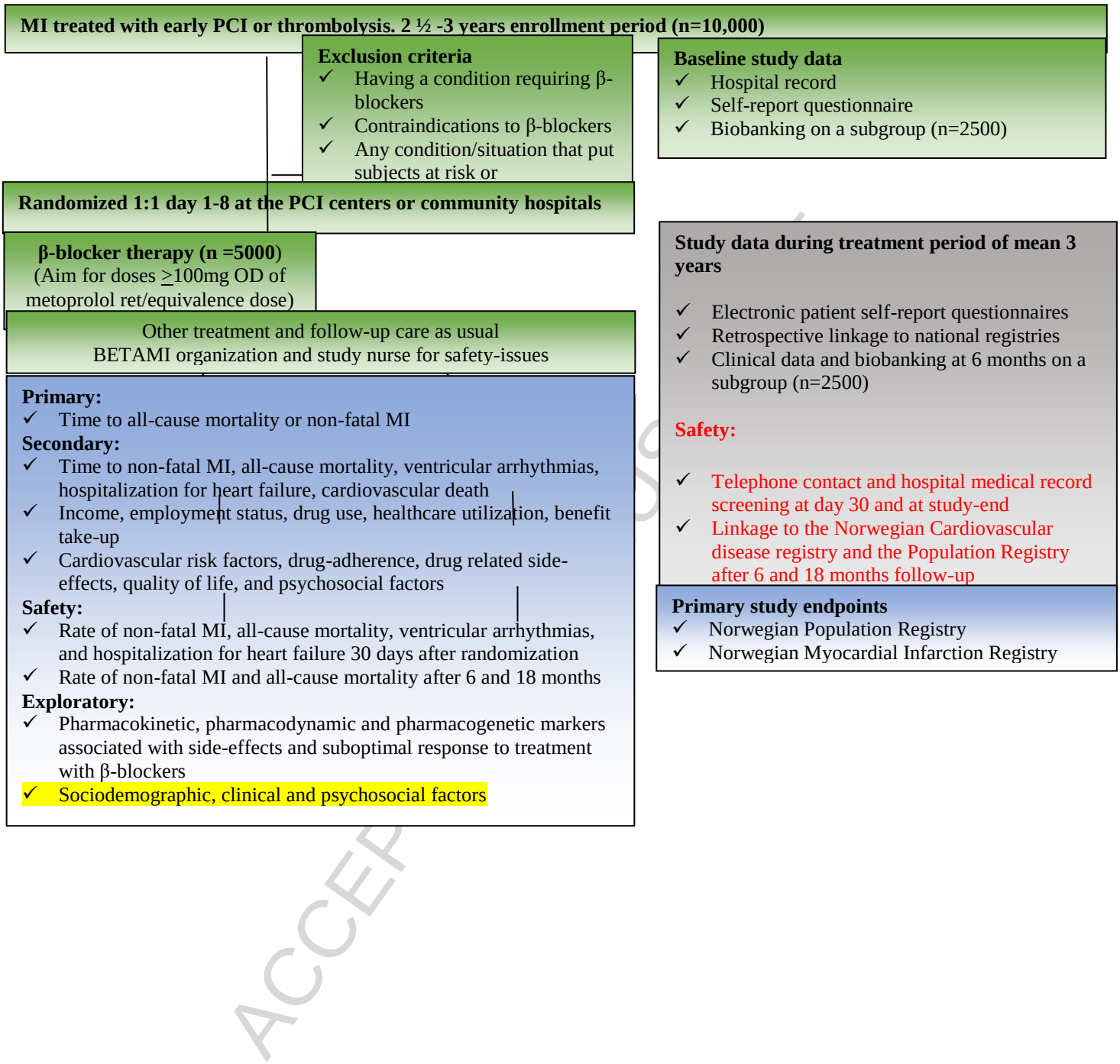

Table 1 Enrollment criteria

Inclusion criteria (all the following)

- 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)
- 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:
  - Brady-arrhythmias
  - Hypotension
  - Severe peripheral artery disease
  - Previously known side-effects causing withdrawal
  - Severe chronic obstructive pulmonary disease
  - Others, according to the responsible investigator
- Any condition (e.g. 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 rendering 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 year) due to non-cardiac co-morbid conditions

Table 2 Study data collection

	Baseline	**Treatment period (0-2 years following randomization)**				**End-point**
Time and assessments	1-8 days following randomization	Day 30	Every 6th month	Six months	Eighteen 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*		
eCRF (patient self-report)[5)]		X	X			
Collection of fasting blood samples for analyses and biobanking[6)]	X	X*		X*		
Safety assessment obtained from medical records and linage to national health registries[7)]		X		X	X	
Assessment of primary and secondary study end-points from national registries[8)]						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 treating physician or the site-PI.
3. Relevant hospital record data at baseline and after 6 months (on a subsample of n=2500) 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 cardiovascular risk factors like blood pressure, pulse, weight, and height.
   A self-report questionnaire will be completed by all patients at baseline and on a sub-sample (n=2500) after 6 months follow-up. The questionnaire comprises lifestyle behaviour (smoking history, physical activity), muscle pains (Numeric rating scales 0-10), sexual dysfunction (Female Sexual Function Index and The International Index of Erectile Function)
4. Symptom burden (New Your 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).
5. 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 i. status on β-blocker treatment and concomitant treatment with antiplatelets, and 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, depression, anxiety, muscle pains, sexual dysfunction, fatigue and insomnia.
6. Blood sample collection at baseline and after 6 months follow-up will be performed by the local study nurse or a bioengineer. The following non-fasting blood tests will be included: HbA1c, haemoglobin, hsCRP, creatinine, cardiac biomarkers (max. Troponin-T/I,), ALT, LDL cholesterol, 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 2500 patients.

7. 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 cardiovascular events or reiteration of study proceduresThe hospital records will be reviewed by the sitePI if patients report hospitalization for subsequent cardiovascular events on the telephone interview. Satefy assessment after 6 and 18 moths follow-up include non-fatal MI and all-cause death collected from the Norwegian Cardiovascular Disease Registry and the Norwegian Population Registry.
8. 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, healthcare utilization, drug prescription) and clinical CVD (myocardial infarction, heart failure, arrhythmias, coronary angiography) registries and the Cause of Death Registry after patient enrollment is completed.

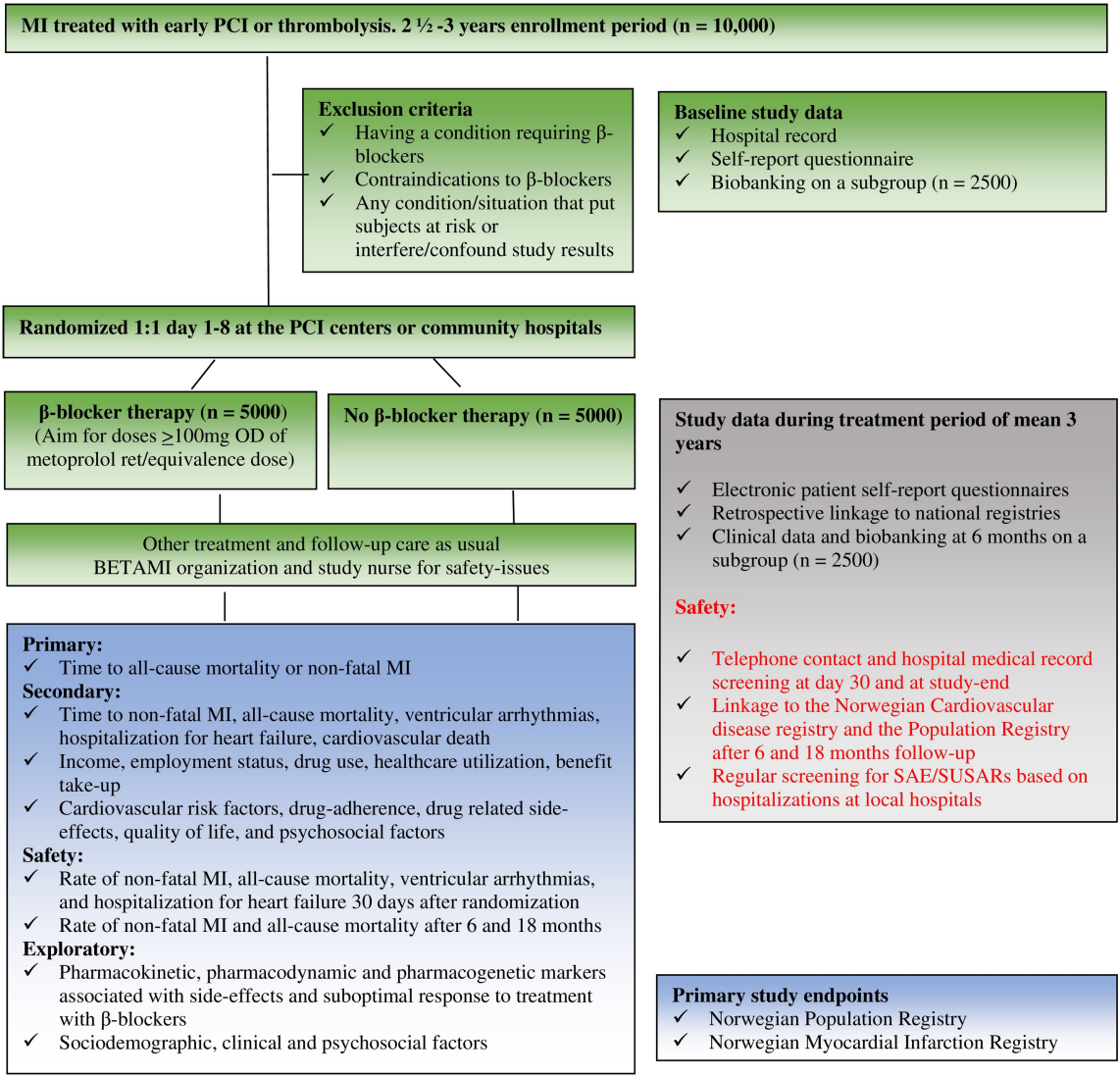
MI treated with early PCI or thrombolysis. 2 ½ -3 years enrollment period (n = 10,000)
Exclusion criteria
✓ Having a condition requiring β-blockers
✓ Contraindications to β-blockers
✓ Any condition/situation that put subjects at risk or interfere/confound study results
Baseline study data
✓ Hospital record
✓ Self-report questionnaire
✓ Biobanking on a subgroup (n = 2500)
Randomized 1:1 day 1-8 at the PCI centers or community hospitals
β-blocker therapy (n = 5000)
(Aim for doses ≥100mg OD of metoprolol ret/equivalence dose)
No β-blocker therapy (n = 5000)
Other treatment and follow-up care as usual
BETAMI organization and study nurse for safety-issues
Primary:
✓ Time to all-cause mortality or non-fatal MI
Secondary:
✓ Time to non-fatal MI, all-cause mortality, ventricular arrhythmias, hospitalization for heart failure, cardiovascular death
✓ Income, employment status, drug use, healthcare utilization, benefit take-up
✓ Cardiovascular risk factors, drug-adherence, drug related side-effects, quality of life, and psychosocial factors
Safety:
✓ Rate of non-fatal MI, all-cause mortality, ventricular arrhythmias, and hospitalization for heart failure 30 days after randomization
✓ Rate of non-fatal MI and all-cause mortality after 6 and 18 months
Exploratory:
✓ Pharmacokinetic, pharmacodynamic and pharmacogenetic markers associated with side-effects and suboptimal response to treatment with β-blockers
✓ Sociodemographic, clinical and psychosocial factors
Study data during treatment period of mean 3 years
✓ Electronic patient self-report questionnaires
✓ Retrospective linkage to national registries
✓ Clinical data and biobanking at 6 months on a subgroup (n = 2500)
Safety:
✓ Telephone contact and hospital medical record screening at day 30 and at study-end
✓ Linkage to the Norwegian Cardiovascular disease registry and the Population Registry after 6 and 18 months follow-up
✓ Regular screening for SAE/SUSARs based on hospitalizations at local hospitals
Primary study endpoints
✓ Norwegian Population Registry
✓ Norwegian Myocardial Infarction Registry

Figure 1