BETAMI Study

BEta-Blocker **T**reatment after
Acute **M**yocardial **I**nfarction

PROTOCOL SYNOPSIS

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

Sponsor	Oslo University Hospital
Phase and study type	Prospective, randomized, open, blinded end-point (PROBE) study.
Investigational Medical Product (IMP) (including active comparator and placebo):	The study aims to investigate whether oral betablocker (BB) therapy is superior to no such treatment following an acute myocardial infarction (AMI).
Centers:	Approx. 15 hospitals in Norway
Study Period:	Estimated date of first patient enrolled: 3-SEP-2018 Anticipated recruitment period: 2.5-3 years Estimated date of last patient completed: 1-SEP-2023
Treatment Duration:	Estimated (non) treatment duration per patient: range 2 – 4 years
Follow-up:	Subjects will be followed up for at least 2 years for the primary and secondary endpoints .
Objectives	The primary objective is to test whether oral BB therapy reduces the risk of all-cause death or non-fatal MI compared to no such therapy, in post-AMI patients treated with PCI or thrombolysis without reduced LVEF. The key secondary objectives are: • To study whether oral BB therapy reduces the risk of each of the components of the primary end-point separately, compared to no such therapy • To study whether oral BB therapy reduces the risk of hospitalization

for ventricular arrhythmias or heart failure compared to no such therapy
- To study whether oral BB therapy reduces the risk of cardiovascular death compared to no such therapy
- To assess clinical outcomes linked BB therapy including outcomes in treatment subgroups (i.e. doses), 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
- To study sociodemographic, clinical, and psychosocial characteristics (PROMS and clinical data) between the two study arms and in the total sample
- To conduct a cost-utility analysis in relation to quality of life and a health economic evaluation including drug use, health care utilization, employment, income, and benefit take-up
- To assess study safety

Exploratory biobanking objectives:

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

Post-trial objective:
- To perform a joint analysis of the data from this study with that of the REDUCE study (Sweden). This analysis will comprise 17000 patients, giving increased power and precision for clinical decisions on both primary and secondary endpoints.

Endpoints:

Primary endpoint:

- Time to all-cause mortality or non-fatal MI since randomization.

Secondary endpoints:

- Time to non-fatal MI, all-cause mortality, ventricular arrhythmias, hospitalization for heart failure, cardiovascular death since randomization.Costs and benefits from a societal perspective, and net gain for public budgets at study end.

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Safety endpoint:

- Rate of ventricular arrhythmias, heart failure, new MI or all-cause death 30 days after randomization and rate of new MI or all-cause death after 6 and 18 months

	Exploratory biobank end-points • Traditional cardiovascular risk factors, drug adherence, and self-reported side-effects
Assessment of primary study end points	The primary study end-points will be obtained through linkage to the Norwegian Cardiovascular Disease Registry and The Norwegian Population Registry (Folkeregisteret)
Assessment of safety end points	Safety endpoints will be under the responsibility of the primary investigators at all participating centers and collected by: - 30 days: direct telephone contact with the patient and from hospital medical records - At 6 and 18 months:, safety assessments at the study visitsin addition to linkage to the Norwegian Cardiovascular Disease Registry and The Norwegian Population Registry - Continuous surveillance of serious adverse events (SAEs)
Assessment of secondary registry-based study end points	In addition to SAE reporting, data will be collected through linkage to the following national registries: The Norwegian Population Registry (Folkeregisteret), the Cause of Death Registry, the Norwegian Patient Registry, the Norwegian Cardiovascular Disease Registry, the Norwegian Prescription Database, the Norwegian registry for income, the FD-Trygd database (social security micro data for research) and the Control and payment of reimbursements to health service providers (KUHR) database
Study Design:	This is a **prospective, randomized, open blinded end-point (PROBE)** study. Patients with AMI will be randomized 1-8 days following PCI or thrombolysis, and allocated to either prescription of a BB or to no such prescription
Main Inclusion Criteria:	• An AMI diagnosis verified according to the "Universal Definition of AMI" and treatment with PCI and/or thrombolysis during the AMI hospitalization
Main Exclusion Criteria	• No clinical diagnosis of heart failure. • LVEF < 40% or significant LV akinesia in ≥ 3 segments regardless of LVEF by visual assessment • Conditions requiring BB therapy • Contraindications to BB treatment • End-stage somatic disease, dementia, psychosis and other conditions could put the subject at significant risk, confound the study results, interfere significantly with the subject participation in the study, or rendering informed consent unfeasible • Women of childbearing potential

Sample Size:	10 000 patients in Norway
Power Calculation	The overall 3-years event rate for the primary endpoint is estimated to be 10%. To detect a difference between the two study groups of 2 percentage points, which corresponds to an HR = 1.22 in a Cox regression model, 7940 patients (794 events) are needed to achieve 80% power. To account for a possible lower event rate (9%) and information loss due to drop-outs and cross-overs, 10 000 patients will be included
Efficacy Assessments:	Not applicable
Safety Assessments:	Subjects will be interviewed by phone after a standardized protocol by a specially trained study nurse after 30 days for the assessment of safety endpoints. A safety analysis will be performed as soon as data from 3334 patients (1/3 of the population) and 6668 (2/3 of the population) at 30 days are available
Type and Dosage of BB Treatment	Information will be collected from a telephone interview with the patients at day 30, from the Norwegian Prescription Registry at study end
Statistical Analysis	Statistical analyses will be conducted according to the intention-to-treat principle. A separate pre-specified analysis will also be conducted as per-protocol analysis (i.e., for patients truly on BBs or not). Clinical endpoints will be assessed by using Cox-regression and Kaplan-Meier curves Oslo Centre for Biostatistics and Epidemiology (OCBE) is responsible for all statistics. A statistical analysis plan (SAP) describing all details in this respect will be produced
Clinical Endpoint Committee (CEC)	Adjudication of all end-points according to pre-specified and standardized criteria will be performed by a CEC blinded to study assignment
Data Safety Monitoring Board	This committee consisting of two senior cardiologists and one trial-science statistician will overview safety and will have access to unblinded data