PONTIAC II

NT-proBNP Selected PreventiOn of cardiac eveNts in a populaTion of dIabetic patients without A history of Cardiac disease;
a prospective randomized trial

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Protocol Synopsis

Title of the study

NT-proBNP Selected Prevention of cardiac events in a population of diabetic patients without A history of Cardiac disease (PONTIAC II); a prospective randomized trial

Purpose and rationale

The purpose of this study is to evaluate the effect of high dose Renin-Angiotensin System (RAS)-antagonists and beta-blocker treatment for the primary prevention of cardiac events in a population of patients with Type 2 diabetes mellitus (T2DM) with no evidence of a preexisting cardiac disease. An additional aim is to demonstrate an interaction between concentrations of amino-terminal pro-B type natriuretic peptide (NT-proBNP as a surrogate of imminent cardiac risk) and treatment effects and the economic impact of the intervention overall and in the biomarker stratified subgroups.

Primary objective

Superiority of high dose treatment with RAS-antagonists and beta-blockers compared to conventional therapy regarding the reduction of unplanned hospitalization or death due to a cardiac event in T2DM patients with a NT-proBNP > 125pg/ml.

Co-primary objective

Superiority of high dose treatment with RAS-antagonists and beta-blockers compared to conventional therapy regarding the reduction of unplanned hospitalization or death due to a cardiac event in T2DM patients in the whole population

Secondary objective

Dependency of treatment efficacy (reduction of unplanned hospitalization or death due to a cardiac event in T2DM patients) on the NT-proBNP concentration (interaction effect between NT-proBNP concentrations and treatment).

Population

The study population will consist of patients with T2DM without any history or signs of cardiac disease. Patients from approximately 20 centers worldwide will be included into the study and randomized 1:1 to intensive or conventional therapy. It is estimated that about 3000 patients have to be screened In order to include 2400 patients. The screen failure rate is anticipated to be approximately 20%.

Inclusion/Exclusion criteria

The inclusion criteria for this study are as follows:

1) Type-2 diabetes mellitus for at least six months,
2) ≥ 18 years of age, men or female,
3) Written informed consent to participate in the study and ability to comply with all requirements.

Patients with any of the following will be excluded from participation in the study:

1) History of hypersensitivity to any of the drugs investigated as well as known or suspected contraindications to the study drugs or previous history of intolerance to high dose of RAAS-antagonists or beta-blocker in the absence of any other blood pressure lowering drugs.
2) Patients already receiving a maximum dose of RAAS-antagonists or beta-blocker.
3) Creatinine > 2.5mg/dl.
4) Symptomatic hypotension and/or systolic blood pressure (SBP) < 100mmHg at visit 1.
5) Symptomatic bradycardia and/or heart rate (HR) < 60bpm at visit 1.
6) Signs of cardiac disease in the electrocardiogram such as atrial fibrillation; ST-T abnormalities or a bundle branch block/ higher degree AV block.

7) Abnormal echocardiography, defined as low ejection fraction < 50%; wall motion abnormalities suggesting coronary artery disease (CAD), significant valve dysfunction > grades I.
8) Coronary artery disease, defined by a history of myocardial infarction, known coronary stenosis > 70% detected either by angiography or by CT-scan, significant defects in myocardial scintigraphy or positive stress-test echocardiography.
9) A disease other than diabetes lowering the patient's life expectancy to less than two years.
10) Chronic infections or malignancies.
11) Systemic treatment with corticosteroids.
12) Renal replacement therapy.
13) Women of child-bearing potential (WOCBP), defined as all women physiologically capable of becoming pregnant, including women whose career, lifestyle, or sexual orientation precludes intercourse with a male partner and women whose partners have been sterilized by vasectomy or other means, UNLESS they meet the following definition of post-menopausal: 12 months of natural (spontaneous) amenorrhea or 6 months of spontaneous amenorrhea with serum Follicle Stimulating Hormone (FSH) levels > 40mIU/m or 6 weeks post surgical bilateral oophorectomy with or without hysterectomy OR are using one or more of the following acceptable methods of contraception: surgical sterilization (e.g., bilateral tubal ligation), hormonal contraception (implantable, patch, and oral), and double-barrier methods (if accepted by local regulatory authority and ethics committee). Reliable contraception should be maintained throughout the study and for 7 days after study drug discontinuation.
14) Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive Human Chorionic Gonadotropin (hCG) laboratory test (> 5mIU/ml).
15) History of noncompliance to medical regimes and patients who are considered potentially unreliable.

16) Current double blind treatment in diabetic trials.
17) Participation in an investigational drug study at the time of enrollment or within the past 90 days.

Investigational and reference therapy

All eligible patients will be randomized to receive either a high dose of RAS-antagonists and beta-blockers (as defined in the section investigational drugs) on top of standard diabetes therapy or solely standard diabetes therapy. The use of RAS-antagonist and beta-blocker therapy at randomization is allowed in the control group (with the exception of maximal dosage), but prescription or titration during the study period is not encouraged. However, if the investigators feel that further prescription or up-titration is required a thorough justification is mandatory. Every attempt should be made to use other blood pressure lowering drugs than RAS-antagonists or beta-blockers in the control group.

Study design

This study is a randomized open-label, parallel group, active-controlled, two-arm, long-term morbidity and mortality trial to evaluate the efficacy and safety of high dose RAS-antagonist and beta-blocker therapy (as defined in the section investigational drugs) compared to standard diabetes therapy in patients with diabetes without any history or sign of a cardiac disease.

The goal is to include 2400 patients. The observation period is planned to last for two years. However, the trial is event driven and will continue until predefined event rate is reached. The total trial duration is expected to last for four years (two years of recruitment and a two year observation period after last patient in). Every patient will remain in the study for two years after randomization.

Visit 1 Screening

At the first visit eligibility to enter the study will be assessed by the investigator. All inclusion/exclusion criteria will be evaluated. Informed consent will be obtained. Demographic data (see section Demographic data) and drug prescription will be assessed. Blood will be obtained (see section Blood sampling). Blood chemistry will be assessed locally. NT-proBNP will be determined by a point of care system locally. The investigator will be blinded to the result, which will be sent to the central computer. Blood will be obtained for the core lab (see section Core Lab), centrifuged and stored at -80C° at the local unit. Vital signs will be obtained (see section Vital signs). Randomization will be performed electronically, this way randomization can be performed immediately.

Visit 2 (3 months)

At visit 2 vital signs will be obtained. Blood will be drawn. Blood chemistry parameters will be assessed locally for safety reason. Drug prescription will be documented.

Visit 3 (12 months)

At visit 3 vital signs will be obtained. Blood will be drawn. Blood chemistry parameters will be assessed locally for safety reason. Drug prescription will be documented.

Visit 4 EOS (24 months)

At visit 4 vital signs will be obtained. Blood will be drawn. Blood chemistry parameters will be assessed locally for safety reason. Additional blood samples will be sent to the core laboratory. Drug prescription will be documented.

Visit 1-4 is mandatory for all patients.

Long-term follow-up

Patients with be further followed by population register or telephone contact respectively until completion of the study to determine long-term mortality and hospitalizations.

Unscheduled visits for the treatment group

The treatment group will have additional visits for up-titration of RAS-antagonists and beta-blocker between visit 1 and visit 2. The frequency is up to the treating physician and dependent on the titration steps. A visit is not mandatory for each titration step. Patients will receive a logbook by the investigator (see section Patients diary), with weekly up-titration steps of the drugs. Additionally, patients will receive a diary for daily documentation of blood pressure, heart rate and symptoms if measurement is technically feasible for the patient. (see section Patients diary). Based on own measurements, these data and laboratory results the investigator will decide if further up-titration of medication is possible. Systolic blood pressure should not decrease permanently below 100mmHg and heart not below 60bpm permanently. Recommended drugs and recommended dosages are outlined in the section "Treatment". At each visit, blood chemistry for eGFR, creatinine, BUN, sodium and potassium will be obtained for safety reason.

Efficacy assessment

Primary efficacy variable

Combined endpoint based on the first occurrence of cardiac death and cardiac hospitalization.

Secondary efficacy variables

1) All cardiac hospitalization
2) Heart failure hospitalization
3) All cause hospitalization
4) NT-proBNP
5) Other predefined (see section plasma and serum biomarkers) biomarkers

6) Health economic analysis (cost-effectiveness of intervention considering both life-years and quality of life adjusted life years)

Safety assessment

1) Systolic and diastolic BP
2) HR
3) Laboratory values
4) Electrocardiography (ECG)
5) Echocardiography
6) eGFR
7) Adverse events profile

Data analysis

Sample Size Calculation

Sample size calculation is based on the whole study population, assuming a 6.5% event rate (primary efficacy variable) in the control and a 40% relative risk reduction in the treatment group, alpha = 5% (two-sided), beta ≥ 20%, Log-Rank-Test. Additionally, for the secondary objective a Monte Carlo Simulation was used for sample size calculation.

Assuming a 4-5% rate of loss to follow-up, 2400 patients will be randomized (1200 in each arm). The trial is event-driven based on the control arm and will continue till at least 75 events (primary efficacy variable) have been recorded.

Main Analyses

Main analyses will be performed on the intention to treat population (ITT).

All hypotheses will be tested at a two-sided significance level of 5%.

Primary and Co-primary objectives will be tested using Log-Rank-Tests and Cox proportional hazard models. Graphical representation will be done with Kaplan-Meier-Curves.

Secondary objective will be assessed with a Cox regression with three explaining variables (randomized treatment, NT-proBNP-Level, and interaction between both).