Visualization of Asymptomatic Atherosclerotic Disease for Optimum Cardiovascular Prevention: VIPVIZA – a Population-based RCT nested in Routine Care in Sweden

NCT01849575

Amendment 2 to the Statistical Analyses Plan

Evaluation after 6 years
CVD risk scores, CVD risk factors, and ultrasound data

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VIPVIZA Amendment 2 to the Statistical Analyses Plan

The present amendment to the VIPVIZA statistical analysis plan includes details on planned analyses of the VIPVIZA intervention after 6-year follow-up, to be presented in two publications: one evaluating the CVD risk (study A) and one evaluating cIMT and atherosclerotic plaque progression (study B). For the analysis of the 6-year follow-up of VIPVIZA, the description of outcome variables and study populations of the original VIPVIZA statistical plan is still valid, unless otherwise noted in this amendment.

The 3-year follow-up examinations were performed from September 5 2016 to May 28 2019 and all participants from both groups, as well as their respective family physicians in primary care, received the pictorial and written result of the ultrasound examination. Thus, directly after the VIPVIZA 3-year follow-up, all participants in the initial control group (IC) underwent the intervention for the first time and the initial intervention group (II) underwent a second (repeated) intervention. This means that the arms of the trials are no longer parallel and that studies following the progression of the groups after the 3-year follow-up will be post-trial evaluations that no longer allow for estimation of the VIPVIZA intervention effect through direct comparisons of IC and II. Even so, it is still of interest to evaluate the long-term development of the two arms, and to investigate if there still exist group differences in CVD risk and severity of atherosclerosis, e.g. due to the different lag times from when the intervention was given. Furthermore, there are few studies about the development over time of riskfactors and atherosclerosis (assessed by imaging, ultrasonography). Therefore, we will investigate development (regression-progression) of risk factors for CVD and atherosclerosis as assessed by carotid ultrasonography in the complete study population and subdivided in combinations of subgroups, and in particular on age groups (40-, 50- and 60 year old), sex, educational level, severity of ultrasound result. We will also separately analyze scenarios with worst vs best development (e.g. groups of individuals with severe progression vs groups with regression).

The VIPVIZA 6-year collection of data on cardiovascular risk factors, health behaviors and other questionnaires were conducted between December 1st 2019 and March 17th 2023, and the carotid ultrasound examinations were performed between January 13th 2020 and May 13th 2023.

Study A: Evaluation of cardiovascular risk, single risk factors and health behaviors at 6-year follow-up examination at the 6-year follow up examination of VIPVIZA

Research question:

- What is the development of cardiovascular risk and cardiovascular risk factors within the VIPVIZA treatment arms up to the 6-years follow-up?
- Is there a difference in cardiovascular risk and cardiovascular risk factors between the treatment arms at the 6-year follow up?

Data and variables: The analysis will utilize the VIPVIZA panel data, which consists of the baseline, 1-year, 3-year and 6-year follow-up measurements. During the period between 3-year and 6 follow-up of VIPVIZA, SCORE2 was introduced in the ESC guidelines(1). SCORE2 will replace SCORE as, along with Framingham risk score (FRS), one of two primary outcomes in the 6-year follow-up study of study A. Secondary outcomes are systolic and diastolic blood pressure, serum triglycerides, LDL cholesterol, HDL cholesterol, waist circumference and current smoking.

Analyses:
We will graphically visualize mean trajectories of outcomes, measured from baseline over 1-year, 3-year and 6-year of follow-up for the two arms and when stratifying the two arms by baseline age groups. Development of continuous outcomes will be analyzed using mixed effects repeated measures with group (II or IC), time point (baseline, 1, 3 or 6 years) and group*times interaction as fixed factors, assuming an unstructured covariance matrix. Corresponding analysis of smoking will be performed using a generalized linear mixed effects model with a logistic link function, with group, time points and group*time point as fixed effects and a random effect for participant.
As group differences at 1 and 3 years of are already published on all outcomes except SCORE2(2,3), only group differences in outcomes at 6 years will be statistically tested and presented with 95% confidence intervals. They will be estimated using ANCOVA for continuous outcomes, adjusted for corresponding baseline value. Serum triglycerides will be transformed using the natural logarithm before analysis, and group differences on logarithmic scale will be re-transformed back to a ratio of geometric means in the original scale. Prevalence ratio of smoking will be estimated from Poisson regression with robust Huber-White sandwich estimator of standard errors, adjusting for baseline smoking status. All ANCOVA/Poisson models will be fitted with and without adjustments for sex and educational level.

For SCORE2, group differences at 1-years and 3 years will be estimated using previously described ANCOVA model.

In addition, we will conduct stratified analyses by:

- Sex/Gender (men/women)
- Age-groups at baseline (40, 50 or 60 years).
- Baseline educational level
- Risk level at baseline
- Severity of ultrasound result

The main analysis will be performed on complete case data. Analyses using multiple imputation of missing data will be performed as secondary analyses. No correction for multiple comparisons to control the familywise error rate will be performed. This is motivated

by the fact that this is a post evaluation of the original trial and does not fall under the convention of adjusting for multiplicity within randomized trials.

B. Evaluation of subclinical atherosclerosis measured by carotid ultrasound at the 6-year follow-up of VIPVIZ, including IMT, carotid plaque prevalence and carotid plaque characteristics.

Research questions:

- What is the development of subclinical atherosclerosis measured by carotid ultrasound within the VIPVIZA treatment arms up to the 6-year follow-up?
- Is there a difference in the degree of subclinical atherosclerosis measured by carotid ultrasound between the treatment arms at the 6-year follow-up?

Data and variables: The primary outcomes are carotid IMT and carotid plaque prevalence (categorized as no plaque, unilateral plaque, and bilateral plaque), and carotid plaque area (mm^2).
Secondary outcomes are carotid plaque greyscale median (GSM) and carotid plaque thickness (mm)

Analyses:
We will graphically visualize trajectories of mean values and prevalence of outcomes, measured from baseline over 3-year and 6-year of follow-up for the two arms and when stratifying the two arms by baseline age groups.

Development of continuous outcomes (carotid IMT and plaque area) will be analyzed using mixed effects repeated measures with group (II or IC), time point (baseline, 3 or 6 years) and group*times interaction as fixed factors, assuming an unstructured covariance matrix. Corresponding analysis of plaque prevalence (one and two-sided, respectively) will be performed using a generalized linear mixed effects model with the fixed effects and a random effect for participant. As group differences at 1 and 3 years are already published(4), only group differences in outcomes at 6 years will be presented. For continuous outcomes, they will be estimated using ANCOVA, adjusted for corresponding baseline value. Group difference of plaque prevalence at 6-years will be evaluated using an ordinal proportional odds model. All ANCOVA/proportional odds models will be fitted with and without adjustments for sex and educational level.

We will also conduct stratified analyses and evaluate intervention effects by

- Sex/Gender (men/women)
- Age-groups at baseline (40, 50 or 60 years).
- Severity of ultrasound result
- Baseline educational level

The main analysis will be performed on complete case data. Analyses using multiple imputation of missing data will be performed as secondary analyses. No correction for multiple comparisons to control the familywise error rate will be performed.

References

1. SCORE2 working group and ESC Cardiovascular risk collaboration. SCORE2 risk prediction algorithms: new models to estimate 10-year risk of cardiovascular disease in Europe. Eur Heart J. 2021 Jul 1;42(25):2439–54.

2. Näslund U, Ng N, Lundgren A, Fhärm E, Grönlund C, Johansson H, et al. Visualization of asymptomatic atherosclerotic disease for optimum cardiovascular prevention (VIPVIZA): a pragmatic, open-label, randomised controlled trial. The Lancet. 2019 Jan 12;393(10167):133–42.

3. Bengtsson A, Norberg M, Ng N, Carlberg B, Grönlund C, Hultdin J, et al. The beneficial effect over 3 years by pictorial information to patients and their physician about subclinical atherosclerosis and cardiovascular risk: Results from the VIPVIZA randomized clinical trial. Am J Prev Cardiol. 2021 Sep 1;7:100199.

4. Nyman E, Grönlund C, Vanoli D, Liv P, Norberg M, Bengtsson A, et al. Reduced progression of carotid intima media thickness by personalised pictorial presentation of subclinical atherosclerosis in VIPVIZA—A randomised controlled trial. Clin Physiol Funct Imaging. 2023;43(4):232–41.