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

NCT01849575

Amendment 1 to the Statistical Analyses Plan

Evaluation after 3, 6 and 10 years
A Regarding Intention to treat analyses
B Regarding CVD risk scores, single CVD risk factors, and life style
C Regarding ultrasound data

Version 1.0

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A. Regarding Intention to treat analyses at 1, 3, 6 and 10 years:
The VIPVIZA study protocol does mention that the data will be analyzed using the intention to treat principle (ITT) which could sometimes be considered different from a pragmatic RCT. The ITT mention was considering handling of crossover individuals from the intervention to the control group, or vice versa. However, the VIPVIZA intervention study did not include any crossovers between the groups. Everyone in the intervention group was treated. The treatment was risk communication by being informed about their ultrasound result in person, and a follow up phone call. No risk communication with an ultrasound report was given to participants in the control group, or to their primary care health provider. The ultrasound results generated by the ultrasound machine were not available in the computerized medical records system. Overall, there were no defiers, and no participants refuting being randomized to the control or intervention group. There was no alternative to treatment, the intervention group received intervention in the form of pictorial ultrasound based risk communication in addition to standard risk information based on clinical risk factors, and the control group received standard risk information based on clinical risk factors only, and treatment to both groups followed the guidelines in Sweden. In the VIPVIZA study in contrast to other pharmacological or surgical trials, there were no or negligible adverse events due to the intervention per se, in the intervention group, that caused drop outs. The preventive actions (life style modification and pharmacological treatments), were totally in the hands of both intervention and control participants and their physicians without any involvement from the VIPVIZA study team.

The primary outcome was FRS and SCORE risk estimates, and there was a low number of missing data for the primary outcome. The VIPVIZA study thus made the decision not to impute for missing data. The primary outcome FRS and SCORE (unlike hard end clinical events like death) cannot be measured without the participant to show up for the follow-up, which is a normal clinical routine after a baseline measurement. Due to the pragmatic design we had no interim analyses prior the first year follow up.

As discussed by Hernan & Robins in their recent paper on per-protocol analyses in pragmatic trials in the New England Journal of Medicine (1), based on the above situation, we consider the pragmatic evaluation of measured outcomes and the intention to treat analysis using added imputed data equal in the VIPVIZA study. To cite Hernan & Robins:
“Some pragmatic trials compare treatment strategies that consist of a single intervention at baseline. For example, in a study designed to compare two different types of hernia operation, patients would be randomly assigned to undergo one of the two interventions immediately. In this research setting, an intention-to-treat analysis would provide valid estimates of both the intention-to-treat effect and the per-protocol effect because nearly all patients undergo the assigned intervention.“

For our primary outcome (in contrast to death, MI or stroke, which easily had been measured without participants coming in person for the one-year FU) in a "pure" ITT we would have to make multiple imputations for the 9-10% participants not showing up. But then we feared that we would not present real world results from the ordinary health care, which is

fundamental for a pragmatic RCT – and would face criticism for that. The pragmatic design is fundamental for our study, and we will consider the VIPVIZA study a pragmatic design study hereon, considering the equality of the ITT and the pragmatic study in this specific case. This means that for the 3 and subsequent 6 and 10 year evaluations we will perform in addition to ITT analyses (with imputations of missing data) also analysis of real world data as participants show up for follow-up according to the pragmatic design (2).

References:

1. Hernan MA, Robins JM. Per-Protocol Analyses of Pragmatic Trials. N Engl J Med 2017; 377: 1391-1398
2. Hernan MA, Hernandez-Diaz S. Beyond the intention-to-treat in comparative effectiveness research. Clin Trials 2012; 9: 48-55.

B. Evaluation of VIPVIZA intervention effects on cardiovascular risk, single risk factors and health behaviours after1 , 3 and 6 year of follow-up

Research questions:

- Do the intervention effects regarding cardiovascular risk (measured by Framingham Risk Score and SCORE) and individual risk factors differ between the intervention and the control group at 1-year, 3-year and 6-year follow-up?
- Does VIPVIZA intervention has any effect on health behaviours such as, smoking, tobacco and physical activity level at 1-year, 3-year and 6-year follow-up?
- Were the intervention effects on CVD risk score, risk factors and health behaviours observed at 1-year follow-up sustained or attenuated at the 3-year and 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 3-year follow-up measurements. The main outcome variables in this analysis are Framingham Risk Score (FRS) and SCORE. In addition, we will also assess several health behavior variables, including smoking, tobacco and physical activity level. We will also adjust for potential confounders that are related to the outcome variables.

Analyses: We will estimate the effect of VIPVIZA intervention on the outcome variables measured at 1-year, 3-year and 6-year of follow-up adjusted for the baseline value of the outcome variables using two methods, including (i) longitudinal analysis of covariance, and (ii) repeated measure analysis. The results of the two methods will be evaluated and discussed. For the longitudinal analysis of covariance, we will include outcome variable at baseline, as well as time and interaction between the treatment variable and time to the regression model and control for other confounders. For the repeated measure analysis, we will include time and the interaction between treatment variable and time in the model, but not the treatment variable. But we will control for other confounders in the regression.

We will analysis the overall treatment effects in a pooled analysis. In addition, we will conduct stratified analyses and evaluate VIPVIZA treatment effects by:

- Gender (men/women)
- Age
- Socioeconomic status using highest educational level as a proxy and, after register-data are made available from Statistics Sweden, also income (Not yet available October 2019)
- Baseline information about ultrasound results (to the intervention group)
- Time for inclusion in the study during the inclusion phase (May 2013-June 2016)

C. Ultrasound data

Research questions:

- Are there differences (or differences-in-difference) in ultrasound risk markers (cIMT, plaque presence, and plaque area/score) between intervention and control groups measured at baseline and 3-year follow-up?
- Are there differences in plaque and/or intima media risk markers related to composition (e.g., Gray scale median, coarseness, etc) between intervention and control group measured at baseline and 3-y follow-up?
- Are there differences in intra-subject ultrasound measurements (different projections and sides) between intervention and control groups measured at baseline and 3-y follow-up?

Analyses:

In the analyses, the main outcome variables are cIMT (intima media thickness), plaque presence, and plaque area (score). The main focus is to analyse the differences in the ultrasound variables from baseline to 3-year follow-up, and differences between the intervention and control group.

We will also conduct stratified analyses and evaluate intervention effects by
• Gender (woman/man)
• Age
• Socioeconomic status
• Baseline information about ultrasound results
• Baseline CVD risk scores and traditional risk factors

Univariate analysis (on outcome variables) will be used to evaluate the overall effect of intervention and differences between groups, effect size quantification for the differences, and significance level correction to adjust for multiple testing. In addition, we will use Generalized Linear Modelling or similar to determine predictors of differences. Adjustment of

covariates (e.g. age and sex) will be carried out before comparisons in ultrasound variables and their differences.

In a second step we will evaluate changes of ultrasound markers in relation to changes in CVD risk scores as well as changes of single risk factors.
Hypothesis: Atherosclerosis assessed by ultrasound does not increase or decreases in participants with no change or decrease in FRS/SCORE or single risk factors.