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

NCT01849575

Statistical Analysis Plan

Version 5.0 (10-28-2019)

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

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Statistical Analysis Plan

1-year evaluation

Version 4.0 (05-28-2018)

Evaluation after one year of follow-up, version 4.0

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1. Introduction

The purpose of this Statistical Analysis Plan (SAP) is to describe the pre-planned statistical analysis steps and data presentation for the clinical study report of the VIPVIZA trial (ClinicalTrials.gov Identifier: NCT01849575).

First patient in (FPI) was April 2013, and the last pre-FPI protocol version was submitted to ClinicalTrials.gov on 2013-05-08. Subsequent amendments in ClinicalTrials.gov were on 2017-09-25. The estimated primary complete data is June 2019. The estimated study completion date is December 2026.

2. Objectives and outcome variables

2.1. Objectives

This population-based randomized controlled trial (RCT) aims at optimizing cardiovascular disease (CVD) prevention through ensuring accurate identification of individuals at high risk of CVD through carotid ultrasonography examination, promoting accurate perception of the risk through communication of ultrasonography results, and enhancing better compliance to preventive treatments with the ultimate goal to reduce premature CVD morbidity and mortality.

The objective of this SAP is to describe evaluation the effects of the VIPVIZA intervention at one year of follow up. In this section, we describe the primary and secondary objectives and outcome variables for the 1-year evaluation.

2.1.1. Specific objectives

In this study, we test the hypothesis that adding risk communication using direct visualisation of asymptomatic atherosclerotic disease, assessed through carotid ultrasound, is superior in reducing a combined index of CVD risk factors at 1-year follow-up compared to the routine clinical guidelines followed at the primary health care setting. The combined measures of CVD risk factors are the Framingham risk score (FRS) and the SCORE.

2.2. Outcome variables

2.2.1. Primary outcome variables

The primary outcomes include:
- Framingham Risk Score
- SCORE risk

To achieve the overall aim, we will evaluate the SCORE risk and the Framingham scores between the intervention groups at baseline and 1-year.

We will generate the SCORE risk using gender-specific regression weights to estimate the risk for cardiovascular risk of men and women. The SCORE includes assessment on the levels of total cholesterol, systolic blood pressure, smoking and age.

We will also generate Framingham score using gender-specific algorithm to estimate the 10-year cardiovascular risk of men and women. The Framingham score includes assessment on the levels of total cholesterol, LDL-cholesterol, systolic blood pressure, treatment for high blood pressure, diabetes, smoking and age.

2.2.2. Secondary outcome variables

The secondary outcomes include:
- Changes in the CVD risk factors (blood pressure, serum cholesterol, LDL, HDL, triglycerides, fasting glucose, HbA1c) between the baseline and 1-year follow-up.
- Changes in the lifestyle behaviours (physical activity, tobacco use, alcohol use, eating habits) between the baseline and 1-year follow-up.

2.2.3. Variables

To test the hypothesis, we will use arrays of lifestyle behaviours, physical measurements and results from blood samples assessed in the baseline and 1-year follow-up.

Self-reported lifestyle behaviours
- Smoking behaviour
- Snus consumptions
- Use of alcohol, assessed with the AUDIT questionnaire
- Physical activity level and sedentary behaviour
- Dietary habits, indicated by daily consumption of fruits, roots, legymes and vegetables

Physical measurements
- Height measurement (in cm)
- Weight measurement (in kg)
- Waist circumference (in cm)
- Systolic blood pressure (in mmHg)
- Diastolic blood pressure (in mmHg)

Blood examinations
- Total serum cholesterol (in mmol/l)
- Serum triglyceride (in mmol/l)
- LDL-cholesterol (in mmol/l)
- HDL-cholesterol (in mmol/l)
- Fasting blood glucose (in mmol/l)
- 2-hour post-prandial blood glucose (in mmol/l)

Prescriptions and purchases of medications for the treatment of:
- hypertension and/or dyslipidemia and/or diabetes

Ultrasound results

- CIMT (carotic intima-media wall thickness)
- Presence of plaque (in categories: yes or no)
- Quantitative and qualitative plaque parameters
- Presence and degree of significant stenosis

2.3. Independent and other covariates

Treatment groups
- Group: intervention or control group

Sociodemographic variables
- Birth year
- Sex
- Age groups
- Highest education level

Other variables
- History/being diagnosed of diabetes among the participant
- Family history of heart infarction before 60 years old among parents and siblings
- Family history of diabetes among parents and siblings
- Portion of potato/rice, meat/fish, and vegetable consumptions
- Date of baseline or follow-up examination

3. Study Design

3.1. Design

- A pragmatic randomised clinical trial within the entire primary health care in Västerbotten County.
- Participants were randomized to two equal groups (intervention and control group) using a randomisation list generated prior to the study using simulation from a uniform probability distribution.
- Both groups will be managed throughout the study according to clinical guidelines on CVD risk factor control within primary health care.

3.2. Population

3.2.1. Inclusion criteria

Inclusion criteria were based on 1/ the aim of targeting subjects at intermediate risk of CVD, and 2/established clinical criteria (smoking, diabetes, hypertension, abdominal obesity) or evaluation of levels and distributions of clinical CVD risk markers (S-LDL) in the 2011 VIP population. In this population, the cut-off for the 4th quartile among 50 years old men and women was 4.4 mmol/L and 4.0 mmol/L, respectively, and 9% and 12%, respectively, had S-LDL concentrations ≤2.5 mmol/L, and 81% and 88%, respectively, S-LDL ≤4.5 mmol/L.

1. age=40 and a history of CVD at age <60 years among first-degree relative(s)
2. age=50 years and at least one of the following: a history of CVD at age <60 years among first-degree relative(s), smoking, diabetes, hypertension, S-LDL-cholesterol ≥4.5 mmol/L, abdominal obesity defined by waist >88cm for women and >102 cm for men

3. age=60 years

3.2.2. Exclusion criteria

A significant stenosis as defined by >50% luminal narrowing of the investigated carotid arteries according to the first vascular ultrasound. These individuals are, irrespective of their randomisation status, informed with a phone call about results. They are therefore not included in the study population and hence not invited to the follow-up examination in the trial. We also exclude individuals who violate the study protocol during the trial as well as those who participate in another clinical trial after the baseline examination.

3.3. Treatment

- **Intervention group:**
    - Information about carotid ultrasound results were given to the participant and his/her primary care physician including graphic presentations of atherosclerosis highlighted in colour against normal vascular age patterns as a gauge going from a green sector over yellow and orange to a red sector that illustrate the percentiles, 1-25, 26–50, 51–75 and 76–100, respectively. Plaque formation was shown as a traffic light for each side, with a green circle for not detected and a red circle for detected plaque. A stylized picture of the participant's own ultrasound image showed vascular age as a coloured line and plaques as a red mark. Brief written information about atherosclerosis as a dynamic process modifiable by healthy lifestyle and pharmacological treatment was also given.
    - After 2-4 weeks, participants received a follow-up phone call by a research nurse in order to reassure and give additional information if needed.
    - The same graphic information was repeated after 6 months.
    - Treatment according to clinical guidelines.

- **Control group:**
- No information about the carotid ultrasound was given at baseline.
- Treatment according to clinical guidelines.

4. Definitions of Analysis Populations

- Intention to Treat analysis (ITT). The full analysis set will be used for all primary presentation of data and analysis. Individuals enrolled in the routinely implemented VIP screening among the population was invited to the study. Those giving their consent were randomized to join either the intervention group or the control group with equal (50%) probability. A randomization list for the treatment group was created in the R-program for statistical computing.

5. Descriptions of Statistical Analysis

5.1. Study conduct and subject disposition

- Descriptive statistics of inclusion and follow-up will be given by randomised treatment for ITT. First and last inclusion time will be tabulated, and inclusion plotted as a cumulative plot.
- Patients with non-completion time to withdrawal or loss to follow-up, and time to last follow-up date, will be summarized in tables summarised using min, median and max, will be tabulated as number and percentage, place and individual characteristics.

5.2. Baseline characteristics and treatment group comparability

- Categorical variables will be described as number and percentage by randomized groups.
- Numerical variables will be presented as mean, median, standard deviation and range.
- The frequency of missing data will be presented in a separate column for all the variables.
- No statistical tests (p-value) will be estimated in the baseline table.

5.3. Primary efficacy analyses

5.3.1. Primary analysis

The differences in primary outcomes (SCORE risk and Framingham Risk Score) at one year between the treatment groups will be measured and analysed using t-tests. As the group sizes are large (more than thousand), it is valid to assume normal distribution of the error around the mean value estimates in both the intervention and the control group. Complementary to the absolute difference in the Score, Cohen´s effect size will be derived for the difference in mean outcome values divided by a pooled standard deviation of the Score between the 2 groups. A two-sided p-value <0.05 will be regarded as statistically significant.

5.3.2. Sensitivity analyses

Adjusted analysis will be conducted using linear regression with covariates. This is because many of the covariates are related to the prognosis of outcome (including sex and age) are related to the prognosis of outcomes, and in such situations, adjustments can yield coefficients slightly further from 0. We will use the continuous form of the primary outcomes (SCORE risk and Framingham Risk Score) as outcome in the regression analysis. We will assess the effects of the intervention independently for each of the outcome measure.
We will also conduct unadjusted linear regression as sensitivity analysis. Comparing the unadjusted and adjusted results provides assurance of the robustness of the results, especially when one of the results achieves only borderline significance.

We will conduct sub-groups analyses to compare the effects of the intervention among different population groups. More details about the sub-group analyses are presented in Section 5.4.1.

5.3.3. Effects in groups defined by their vascular ultrasound result

- Pairwise t-test will be used to assess the intervention effect in groups stratified by the vascular ultrasound result at baseline. The vascular ultrasound measurements includes information of the plaque presence and the age and sex standardized vascular age of the subject.

For this test, the vascular age groups will be created according to the age standardized quartiles: green (young vascular compared to actual age), yellow (intermediate towards young), orange (intermediate towards red), red (old vascular compared to actual age). The t-test analysis will compare red to red, orange to orange, yellow to yellow, green to green of the intervention and control group, respectively. The t-test will be adjusted for multiple testing using the Bonferroni method.

5.3.4. Checking of assumptions

Only assumption is normal distribution which can be assumed for mean values estimates if groups are larger than 30. Since our groups is much larger than 30 we see not need to assess this assumption. We will calculate the t-test using the group specific standard deviations, to relax the assumption of equal variances.

5.4. Secondary outcome analyses

5.4.1. Sub-group analyses

In the analysis, we will compare the primary and secondary outcome variables' mean value between the intervention and the control in pre-specified sub-groups.

The sub-groups are:
- Abdominal obesity based on waist circumference measurement to compare the non-obese and obese groups, using the cut-off of waist circumference ≥102 cm for men and ≥88 cm for women according to the WHO definition.
- General obesity based on the body mass index measurement to compare the underweight, normal weight, overweight and obese groups, using the cut-off points of 18.5, 25, and 30, respectively.
- Physical activity level to compare respondents with low and high-level of physical activity
- Sex to compare men and women
- Age group to compare respondents at age 40, 50 and 60 years old
- Education level to compare respondents with low, medium and high education level as defined earlier.
- Since participants are recruited into the study during the three years from mid-2013 to mid-2016, any change in physicians' prescribing behaviour over the course of the study will be evaluated by comparing prescriptions issued for lipid-lowering and anti-hypertensive medications during the first year after the baseline ultrasound examination as well as primary outcome among participants recruited during the first, second and third years

5.5. Data handling and analytical steps

The data is entered using Microsoft SQL and is stored in common database file formats including SPSS and Stata. We will follow the following steps in handling the data to ensure its validity and make an analytical dataset for the analysis of this paper.

Step 1: We will conduct **quality check** on the baseline and 1-year follow-up data. Information from baseline and 1-year follow-up will be merged using the unique study number allocated for each

individual (the VIPVIZAID). Individuals who did not participate in the 1-year follow-up will be noted and reasons for not participating will be identified and listed in the dataset. The completeness of all variables will be checked through, and if needed, the research nurse will double check any missing values in the dataset against the individual's responses in the paper questionnaire.

Step 2: We will check the dataset for **outliers and illogical values**. For categorical variables, responses outside the possible response categories will be coded as missing. For continuous variables, values outside the plausible ranges will be coded as missing also.

For biological markers, we will use the following cut-off points to define outliers. Any values outside these ranges will be coded as missing.

Variables	Plausible values
Fasting blood glucose (mmol/L)	2.0 – 25.0
Serum cholesterol (mmol/L)	2.0 – 18.0
LDL cholesterol (mmol/L)	1.2 – 15.0
HDL cholesterol (mmol/L)	0.4 – 6.0
Serum triglycerides (mmol/L)	0.4 – 20.0
Systolic blood pressure (mmHg)	80 – 240
Diastolic blood pressue (mmHg)	55* – 150 *unless if systolic blood pressure below 90
Pulse pressure (mmHg)	15-100
Height (cm)	110 – 210
Change in height from baseline to 1-yr exam (cm)	>4
Weight (kg)	40 – 200
Waist (cm)	50 - 170
Change waist from baseline to 1-yr exam > 5cm	Change weight >15 kg
Change weight from baseline to 1-yr exam >5 kg	Change waist >15 cm

Step 3: After all the data have been cleaned, we will conduct **imputation of missing data** (see section 5.6). To the best possible, we will impute the original variables, not the derived variables. For example, instead of imputing the variable body mass index, we will impute the variable weight and height which is used to calculate body mass index. See the next section for more detailed descriptions on missing data.

Step 4: After the data have been imputed, we will generate **derived variables** based on the imputed data. For example, body mass index will be calculated from weight and height in the imputed data.

5.6. Imputation of Missing Data

Assessment of missing data will be conducted using the missing data modules in the Stata Statistical Programme. The command *misschk*, *misstable* will be used to assess the patterns of missing data among all the variables included in the analysis. To ensure reproducibility of data analysis conducted in VIPVIZA, we plan to create one imputed dataset based on assessment of all variables in the dataset and subsequently use this imputed dataset for analysis of future papers. Information about number of study participants with missing data for each variable will be presented in the description table showing the baseline characteristics of the study participants in the intervention and control groups.

We will conduct multiple imputation based on Rubin (1987) and Schafer (1997) methods using the *mi* estimate command sets in Stata. In brief, multiple imputation involves three steps: (i) imputation step: selection of imputation model to generate 10-20 imputed complete datasets to capture the uncertainty of the imputation model; (ii) estimation step (completed-data analysis): the planned analyses are conducted separately on each imputed dataset; and (3) pooling step: the results obtained from the series of completed-data analyses are combined into a single multiple-imputation result.

The command ***mi estimate*** estimates model parameters from multiply imputed data and adjusts coefficients and standard errors for the variability between imputations (***the estimation step***). It runs the specified estimation command on each of the M imputed datasets to obtain the M completed-data estimates of coefficients and their variance–covariance matrix of the estimators (VCEs). It then computes MI estimates of coefficients and standard errors by applying combination rules to the M completed-data estimates (***the pooling step***). Methods and formulas for computation details are described in the Stata's Multiple Imputations' guide, available at https://www.stata.com/manuals13/mimiestimate.pdf

If data is **missing not at random**, a thorough assessment between study respondents with and without missing data on specific variables will be conducted based on the available information such as sociodemographic variables. The intention is to identify if this non-ignorable missing data might introduce any systematic bias that might influence the results of the estimation. We will employ selection models and/or pattern mixture models as multiple imputation strategies. Under the condition of MNAR, the joint density of VIPVIZA's participant responses is not the same for participants with full and partially observed data. We will perform pattern mixture models by modelling the observed data, then model the missing data as a modification of the observed data model. We will explicitly model the missing data distribution by first identifying different patterns of missing data and then including parameters in the outcomes model that capture this effect (Paddock et al. 2006).

We will also conduct sensitivity analysis by comparing the results with complete case analysis vs. results with multiple imputation with different sets of imputation.

Reference for multiple imputations:
Stata Multiple-Imputation Reference Manual Release 13, StataCorp LP, Texas: https://www.stata.com/manuals13/mi.pdf).

Paddock SM, Edelen MO, Wenzel SL, Ebener PA, Mandell W. 2006. Pattern-Mixture Models for Addressing Nonignorable Nonresponse in Longitudinal Substance Abuse Treatment Studies. RAND Health.

5.7. Safety Analysis

The intervention in VIPVIZA is pictorial information about ultrasound results on the individual's actual atherosclerosis. This is considered to be a low-intensity intervention in comparison to interventions with pharmacological drugs or surgical procedures. The ultrasound examination cannot cause any harm, physical discomfort or risk. As with all screening targeting a healthy population, it is a dilemma that asymptomatic individuals may be informed of silent disease, in this case ongoing atherosclerotic process with increased risk of future CVD. This can be perceived more serious than just an increased level of risk markers, and result in anxiety.

In order to avoid unjustified concerns, all persons in the intervention group receive a telephone call with a research nurse and, if necessary, a doctor in charge, for in-depth and balanced information about ultrasound results. This conversation is held according to the methodology of motivational interviewing and also aims at increased awareness of the possibility of reducing the individual risk by means of own preventive measures. This is expected to alleviate anxiety and increase motivation to follow the recommendations for preventive treatment.

According to the study hypotheses, this is expected to benefit the individual due to risk reduction. A healthier lifestyle is also expected to benefit the individual through increased well-being and quality of life. Similarly, subjects without ongoing atherosclerotic disease will be able to avoid unjustified concerns and informed to continue a healthy lifestyle.

All individuals with severe carotid stenosis will be excluded from the study and are referred directly to the Stroke Centre for assessment and treatment. This may potentially be life saving for these people, and may, to some extent, balance the fact that no information is given until after 3 years to half the group even if small/moderate changes are detected.

5.8. Other planned analyses

- In **medium-term**, adding risk communication using visualisation of carotid ultrasound results is more effective in reducing **hospitalisation due to stroke, myocardial infarctions and revascularisations** (at 5-year and 10-year) compared to routine CVD risk assessment and control within the primary health care setting. – Not for 1-year evaluation.

- In **long-term**, adding risk communication using visualisation of carotid ultrasound results is more effective in reducing **overall mortality and cause-specific mortality due to myocardial infarctions and stroke** (at 5-year and 10-year) compared to routine CVD risk assessment and control within the primary health care setting. – Not for 1-year evaluation.

6. Descriptions of Sample Size

Calculations based on data on conventional risk factors derived from VIP 2011, revealed that 3500 included study participants with a drop-out rate of 15 % during the study would be sufficient to assure a probability of 80% to detect a true difference between groups at a significance level of 5%. The limiting factor (demanding the largest group size to show a hypothesized effect) was CIMT.

Variabel	Significance level	Power	SD	Relevant change Population level	Sample size per group	Minimum detectable change if n=1500/group
SBP (mmHg)	0.05	0.8	16	2	1500	1.7
Serum Cholesterol (mmol/L)	0.05	0.8	0.5	0.5	1500	0.05
LDL (mmol/L)	0.05	0.8	0.5	0.5	1500	0.05
CIMT (mm)	0.05	0.8	0.2	0.02	1500	0.02
SCORE	0.05	0.8	1.40	0.5	1500	0.143
Framingham Risk Score	0.05	0.8	6.60	1	1500	0.7

7. Analysis Database Definitions

Variable	Description
age_0	Age in days at VIP baseline (*Rec)
age_1	Age in days at 1 year examination (*Rec)
alder_0	Age group (*Rec)
byear_0	Year of birth
in_kon	Gender (*Rec)
in_part0	Eligible participant and participation in main study (baseline) (*Rec)
in_part1	Eligible participant and participation in 1 year follow-up (*Rec)
in_randg	Randomization group (*Rec)
in_status	Participation status
educa_0	Education status (*Rec)
health_0	Perceived health during last year
g1d_0	Travel to and from work - Winter (*Rec)
g1d_1	Travel to and from work - Winter (*Rec)
g1km_0	How many kilometers do you have to travel to commute? (One way) (*Rec)
g1km_1	How many kilometers do you have to travel to commute? (One way) (*Rec)
g3a_0	What recreational activities do you participate in - Walks (*Rec)
g3a_1	What recreational activities do you participate in - Walks
g3b_0	What recreational activities do you participate in - Bicycling (*Rec)
g3b_1	What recreational activities do you participate in - Bicycling
g6_0	How often have you worked out or exercised in your training-clothes during the last three months (*Rec)
g6_1	How often have you worked out or exercised in your training-clothes during the last three months (*Rec)
g9_0	To what extent have you been physically active during leisure time during the past 12 months? (*Rec)
g9_1	To what extent have you been physically active during leisure time during the past 12 months? (*Rec)
g10_0	During an ordinary week, how much time do you spend on moderately strenuous activities (*Rec)
g10_1	During an ordinary week, how much time do you spend on moderately strenuous activities (*Rec)
h1antal_0	Number of cigarettes / day
h1antal_1	Number of cigarettes / day
h1a_0	Do you presently smoke? No, I never have smoked
h1a_1	Do you presently smoke? No, I never have smoked
h1b_0	Do you presently smoke? Yes, I smoke cigarettes
h1b_1	Do you presently smoke? Yes, I smoke cigarettes
h1c_0	Do you presently smoke? Yes, I smoke cigars
h1c_1	Do you presently smoke? Yes, I smoke cigars
h1d_0	Do you presently smoke? Yes, I smoke a pipe
h1d_1	Do you presently smoke? Yes, I smoke a pipe

h1e_0	Do you presently smoke? Yes, I smoke occasionally (Not daily)
h1e_1	Do you presently smoke? Yes, I smoke occasionally (Not daily)
h1f_0	Do you presently smoke? Not now, but I used to smoke daily
h1f_1	Do you presently smoke? Not now, but I used to smoke daily
h1g_0	Do you presently smoke? Not now, but I used to smoke occasionally
h1g_1	Do you presently smoke? Not now, but I used to smoke occasionally
h4_0	Have you ever used snuff? (*Rec)
h4_1	Have you ever used snuff? (*Rec)
j01_0	How often do you have a drink containing alcohol?
j01_1	How often do you have a drink containing alcohol?
j02_0	How many drinks containing alcohol do you have on a typical day when you are drinking?
j02_1	How many drinks containing alcohol do you have on a typical day when you are drinking?
j03_0	How often do you have six or more drinks on one occasion?
j03_1	How often do you have six or more drinks on one occasion?
j04_0	How often during the last year have you found that you were not able to stop drinking once you had started?
j04_1	How often during the last year have you found that you were not able to stop drinking once you had started?
j05_0	How often during the last year have you failed to do what was normally expected of you because of drinking?
j05_1	How often during the last year have you failed to do what was normally expected of you because of drinking?
j06_0	How often during the last year have you needed a first drink in the morning to get yourself going after a heavy drinking session
j06_1	How often during the last year have you needed a first drink in the morning to get yourself going after a heavy drinking session
j07_0	How often during the last year have you had a feeling of guilt or remorse after drinking?
j07_1	How often during the last year have you had a feeling of guilt or remorse after drinking?
j08_0	How often during the last year have you been unable to remember what happened the night before because of drinking?
j08_1	How often during the last year have you been unable to remember what happened the night before because of drinking?
j09_0	Have you or someone else been injured because of your drinking?
j09_1	Have you or someone else been injured because of your drinking?
j10_0	Has a relative, friend, doctor or other health care worker been concerned about your drinking or suggested to cut down?
j10_1	Has a relative, friend, doctor or other health care worker been concerned about your drinking or suggested to cut down?
langd_0	Body height cm (*Rec)
langd_1	Body height cm (*Rec)
vikt_0	Body weight kg (*Rec)
vikt_1	Body weight kg (*Rec)
midja_0	Waist circumference cm (*Rec)
midja_1	Waist circumference cm (*Rec)

sbt_0	Systolic blood pressure mmHg (*Rec)
sbt_1	Systolic blood pressure mmHg (*Rec)
dbt_0	Diastolic blood pressure mmHg (*Rec)
dbt_1	Diastolic blood pressure mmHg (*Rec)
skol_0	Serum cholesterol mmol/l (*Rec)
skol_1	Serum cholesterol mmol/l (*Rec)
stg_0	Serum triglycerides mmol/l (*Rec)
stg_1	Serum triglycerides mmol/l (*Rec)
ldl_0	LDL-cholesterol mmol/l (*Rec)
ldl_1	LDL-cholesterol mmol/l (*Rec)
hdl_0	HDL-cholesterol mmol/l (*Rec)
hdl_1	HDL-cholesterol mmol/l (*Rec)
blods0_0	Blood sugar fasting mmol/l (*Rec)
blods0_1	Blood sugar fasting mmol/l (*Rec)
c10_1_0	Medication in the last 2 weeks - Hypertension (*Rec)
c10_1_1	Medication in the last 2 weeks - Hypertension (*Rec)
c10_5_0	Medication in the last 2 weeks - Lipid lowering drug (*Rec)
c10_5_1	Medication in the last 2 weeks - Lipid lowering drug (*Rec)
c10_8_1	Medication in the last 2 weeks - Diabetes medication (*Rec)
c2_0	Did any of your parents or siblings suffer a heart attack/myocardial infarction or stroke before age 60 years?
c3_0	Does any of your parents or siblings suffer from diabetes?
c6_0	Do you suffer from diabetes?
c7a_0	If you have answered Yes on question C6, what is your treatment? Diet and exercise
c7b_0	If you have answered Yes on question C6, what is your treatment? Tablets
c7c_0	If you have answered Yes on question C6, what is your treatment? Insulin
c7d_0	If you have answered Yes on question C6, what is your treatment? None of the above
smoking_0	Smoking
smoking_1	Smoking 1 year (*Rec)
snus_0	Use of snus
phyact_0	Physical activity (*Rec)
phyact_1	Physical activity 1 year (*Rec)
fruitandveg_0	Fruit and vegetable consumption (*Rec)
lrmx_0	IMT CCA max mean value independent of side and angle
lrplack_0	Plack left/right combined
imt_color_0	IMT color code for patient information
usage_0	Age in days at ultrasound baseline
usdat_0	Ultrasound date (*Rec)
provdat_0	Sample date on optical questionnaire
provdat_1	Sample date on optical questionnaire (*Rec)

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

Version 1.0

10-28-2019

VIPVIZA Amendment to the Statistical Analyses Plan

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.