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

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Study Protocol Version 5.0

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Protocoll version: Version 4.0

Principal Investigator, PI: Ulf Näslund, Department of Public Health and clinical medicine, Umeå University.

Co-PI: Margareta Norberg, Department of Public Health and clinical medicine, Umeå University.

Start of the study: 2012-08-01

End of study: 2026-12-31

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PROTOCOL AGREEMENT

PI and co-PI undertake to complete the study in accordance with protocols, and, referring to national and local regulations, in accordance with the Helsinki Declaration: Ethical Principles for Medical Research that Include People.

PI and co-PI agree, through written consent, to this Protocol and to fully participate and allow direct access to all documentation, including source data, for the relevant authorities.

The agreement above is signed

Signature: _____ Date: November 10 2017

Ulf Näslund, Professor

Signature: _____ Date: November 10 2017

Margareta Norberg, Associate professor

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1. Abbreviations and definitions

VIPVIZA	Visualization of asymptomatic Atherosclerotic disease for optimum cardiovascular prevention – a pragmatic randomized controlled trial nested in the Västerbotten Intervention Program. The setting is highlighted by VIP positioned first in the acronym.
BMI	Body Mass Index
BMQ	Beliefs about Medicines Questionnaire
CIMT	Carotid artery Intima-Media Thickness
CVD	Cardiovascular disease
GCP	Good Clinical Practice
HDL	High density Lipoprotein
HbA1c	Hemoglobin A1c
LDL	Low Density Lipoprotein
KFC	The clinical research center at Umeå University Hospital [Swedish: Kliniskt Forsknings Center]
PCI	Percutaneous Coronary Intervention.
PTCA	Percutaneous transluminal coronary angioplasty
RCT	Randomized Controlled Trial
SCORE	Systematic Coronary Risk Evaluation
SP	Study participant in VIPVIZA
VIP	Västerbotten Intervention PRogramme

2. Supplementary files

Appendix 1 The Informed Consent form translated from Swedish to English.

Appendix 2 VIPVIZA diagnoses clinical events and causes of death

Appendix 3 VIPIVZA Database Description

Appendix 4 Statistical analyses plan, primary outcomes at one-year evaluation

Appendix 5 Monitoring plan

All documents in Swedish are available from co-PI Margareta Norberg. This include all applications to the Regional Ethical Board and the respective decisions, written information about the study to VIP-participants, information about VIPVIZA to district nurses and family physicians, written information to VIPVIZA-participants, questionnaires used in the study, the written report on ultrasound results and forms for postal information about results on CVD risk factors.

3. Research team, contact information

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4. Summary

Scientific title:	Visualization of Asymptomatic Atherosclerotic Disease for Optimum Cardiovascular Prevention: VIPVIZA – a Population-based RCT nested in Routine Care in Sweden
Principal Investigator	Ulf Näslund
Study director	Margareta Norberg
Study period	2012-08-01–2026-12-31
Hypotheses and aims	<p>VIPVIZA has three distinct, but complementary hypotheses:</p> <p>Pictorial representation of asymptomatic atherosclerotic disease, assessed with carotid ultrasound, has the potential to identify individuals at high risk of CVD with higher precision than conventional risk factor-based statistical models.</p> <p>The clear understanding of an image of arterial disease during an early asymptomatic phase is of superior value in optimizing adherence to clinical preventive management for both physicians and patients, Literally, the English quotation is ‘A picture speaks a thousand words’.</p> <p>The resulting preventive management will improve control of premature CVD.</p> <p><i>Specific aims</i></p> <p>To assess the prevalence of asymptomatic atherosclerotic disease in men and women through identification of carotid plaques and measurement of CIMT, and to relate plaques and CIMT to clinically estimated CVD risk factors.</p> <p>To assess the impact of visualization of atherosclerosis on quality of life, preventive measures, risk factor control and progress of atherosclerotic disease over the course of three years.</p> <p>To explore the impact of visualization of atherosclerosis, as a low-intensive preventive intervention, on physicians’ and patients’ risk perception, communication and attitudes to CVD prevention.</p> <p>To evaluate how individuals’ health literacy and coping strategies relate to CVD risk at baseline, attitudes to screening, risk perception and preventive measures.</p> <p>To investigate novel biomarkers in relation to CIMT and plaques at baseline, changes in conventional CVD risk markers and lifestyle, and progression of atherosclerosis.</p> <p>To assess the impact of visualization of atherosclerosis by carotid ultrasound on premature CVD morbidity and mortality over the course of 5 and 10 years.</p>
Primary outcome	SCORE and Framingham risk scores

Secondary outcomes	CVD risk factors, lifestyle, ultrasound results (CIMT, presence of plaque, quantitative and qualitative plaque parameters, presence and degree of significant stenosis), prescriptions and purchases of medications (for the treatment of hypertension, dyslipidemia and diabetes), biochemical markers, and the clinical endpoints myocardial infarction, stroke, revascularization procedures and mortality (all-cause and CVD-specific).
Study design	A pragmatic randomized controlled trial nested within routine clinical care
Study population	Subjects aged 40, 50 or 60 years, invited as part of their VIP participation within Västerbotten primary healthcare. No:3700
Follow-up period	10 years from first ultrasound examination
Inclusion criteria	<ul style="list-style-type: none"> • age=40 years and first-degree relative with history of CVD at age <60 years • age=50 years and at least one of the following: first-degree relative with history of CVD at age <60 years, smoking, diabetes, hypertension, S-LDL cholesterol ≥ 4.5 mmol/L, abdominal obesity • age=60 years <p>Individuals are included in the study only once, at whichever qualifying age point is achieved first.</p>
Statistical methods	<p>The differences in primary outcomes (SCORE risk and Framingham Risk Score) at one year between the treatment groups will be measured and analyzed using t-test. Differences in changes of SCORE and FRS from baseline to 1-year follow-up will be analyzed with regression methods to identify predictors of the changes in the scores.</p> <p>Survival curves will be established using Kaplan-Meier curves for CVD mortality and morbidity at 5 and 10 years of follow up comparing the intervention to the control group. Predictive Cox Proportional Hazard models will be developed to estimate the overall predictive ability of CIMT, plaque and risk factors on CVD morbidity and mortality at 5 and 10 years.</p> <p>Health economic modelling studies will be performed for evaluation of cost-effectiveness. Interviews with participants and physicians will be analyzed using qualitative content analysis.</p>
Evaluation criteria	Primary and secondary outcomes will be evaluated according to Intention-to-treat methodology

5. Background

5.1 Survey of the field and rationale for the trial

Primary prevention of cardiovascular disease (CVD) often fails due to the low precision of the conventional risk scores, and poor adherence among practitioners and patients to evidence-based prevention guidelines. Moreover, these risk scores focus on high-risk individuals only, despite 60-70% of all CVD events occurring among individuals at low or intermediate risk for CVD (1). VIPVIZA takes a different approach from current practice for the prevention of CVD. Instead of being based solely on indirect risk factors, this project evaluates the atherosclerotic disease itself while it still is silent, providing improved assessment, communication and perception of the CVD risk and higher motivation for prevention.

The evidence for effective modification of risk factors by lifestyle change and pharmacological treatment is well established. Despite this, suboptimal adherence to CVD prevention guidelines among practitioners and patients leads to poor risk factor control in both primary and secondary prevention (2-4). Contributory factors include poor communication about the CVD risk by the physician, inaccurate risk perception and lack of awareness of the weak association between the actual estimated and perceived CVD risk among patients (5, 6). The risk message is usually communicated verbally or numerically (7), while potentially more effective visual tools are seldom used. In addition to the format and framing of the message, the perceived risk also depends on social and cultural factors (8).

Moreover, for the success of risk management, the extent of the patient's behavioral change is crucially dependent on their psychological characteristics. The individual's ability to cope with stressful situations (coping strategy) (9), trust in their own capability to change behaviour (self-efficacy) (10), level of positive expectations in life (dispositional optimism) (11), and health literacy (capacity to understand health information and make appropriate related health decisions) (12) are important. Rational choices due to increased risk awareness often fail, and knowledge about a risk, on its own is rarely enough for sustainable behavioural change. These aspects are usually ignored in the field of primary prevention (13). For CVD prevention programs to be effective, a more person-centred approach towards the individual's clinical and behavioural change may need to be implemented (14), and in order to make use of existing evidence-based methods to the fullest extent, both the physicians' and individuals' adherence to existing CVD prevention guidelines should be targeted.

An alternative strategy to evaluate and improve CVD risk communication would be to directly view in pictorial form the degree of atherosclerotic disease before symptoms develop, rather than to indirectly evaluate risk factors of atherosclerosis (15-17). This is achieved with ultrasonography of medium sized arteries with assessment of carotid artery intima-media thickness (CIMT) and existing atherosclerotic plaques, which have a clearly higher predictive power for plaques. Pharmacological

and lifestyle interventions have the potential to slow down or even reverse the progress of ultrasound-assessed atherosclerosis (18, 19), but results on the contributory impact from image-based information on adherence to prevention are inconsistent (20, 21).

Therefore, large-scale randomized controlled trials (RCTs) targeting low and intermediate-risk adults with a focus on assessing the impact of viewing an image of existing silent disease on the stratification and communication of CVD risk to physicians and patients, as well as on major clinical outcomes, should be prioritized (1, 2, 21).

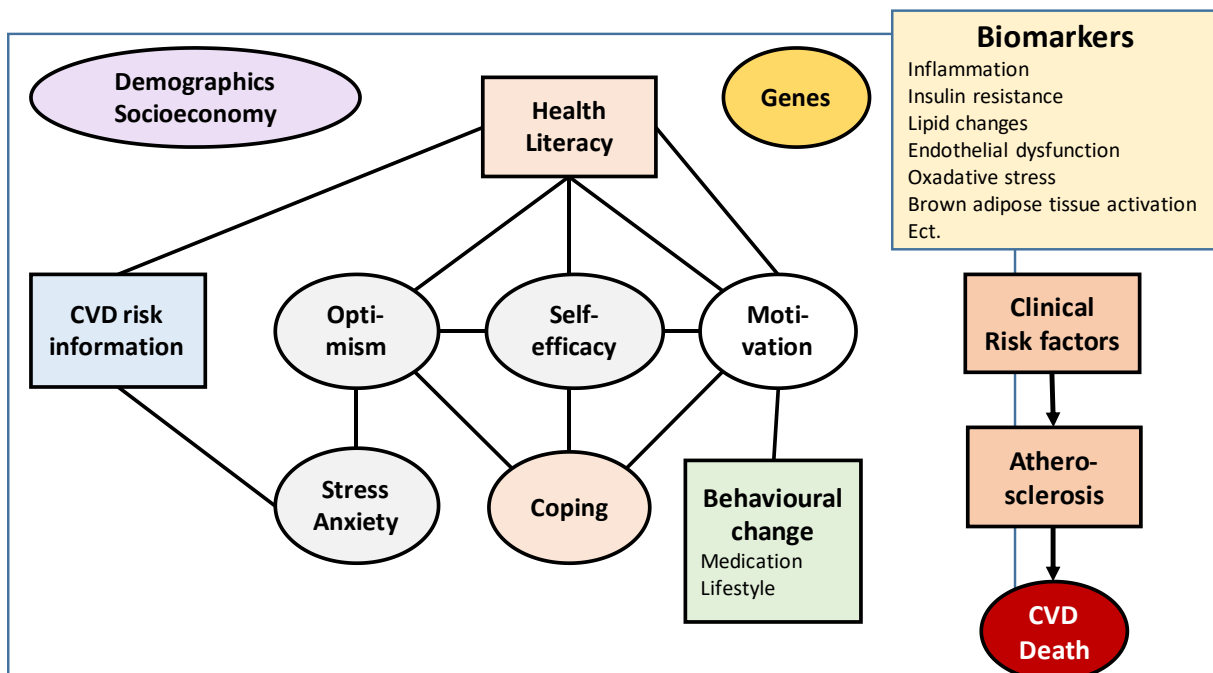
5.2 Hypotheses

VIPVIZA has three distinct, but complementary hypotheses:

- Direct viewing of a pictorial representation of asymptomatic atherosclerotic disease, assessed with carotid ultrasound, has the potential to identify individuals at high risk of CVD with higher precision than conventional risk factor-based statistical models.
- The clear understanding of an image of arterial disease during an early asymptomatic phase is of superior value in optimizing adherence to clinical preventive management for both physicians and patients: "A picture speaks a thousand words".
- The resulting preventive management will improve the control of premature CVD.

5.3 Theoretical model

Social, genetic, psychological and behavioral mechanisms impact the subclinical molecular processes that manifest as clinical risk factors and the subclinical morphologic atherosclerotic process, and eventually in clinical cardiovascular disease events or death.



6. Objective and aims

6.1 Objective

To assess the impact of a visual image and pictorial report, seen and discussed by both physician and patient, for improving guideline adherence and patient perception and understanding of the CVD risk and consequent motivation for prevention. The extent of the impact is assessed by differences between randomization groups in Framingham Risk Score and SCORE as well as changes in these scores after one and three years. Differences between groups will also be evaluated by risk factor assessment and a further scan after three years to determine disease progression, and a comparison of the prevalence of acute events and mortality at five and 10 years.

6.2 Specific aims

1. To assess the prevalence of asymptomatic atherosclerotic disease in men and women through identification of carotid plaques and measurement of CIMT, and to relate plaques and CIMT to clinically estimated CVD risk factors.
2. To assess the impact of pictorial representations of atherosclerosis on quality of life, preventive measures, risk factor control and progress of atherosclerotic disease over the course of three years.
3. To explore the impact of pictorial representations of atherosclerosis, as a low-intensive preventive intervention, on physicians' and patients' risk perception, communication and attitudes to CVD prevention.
4. To evaluate how individuals' health literacy and coping strategies relate to CVD risk at baseline, attitudes to screening, risk perception and preventive measures.
5. To investigate biomarkers in relation to CIMT and plaques at baseline, changes in conventional CVD risk markers and lifestyle, and progression of atherosclerosis.
6. To assess the impact of the pictorial representation of atherosclerosis by carotid ultrasound on premature CVD morbidity and mortality over the course of 5 and 10 years.

7. Endpoints

7.1 Primary endpoints:

- 7.1.1 SCORE (22)
- 7.1.2 Framingham risk score (23)

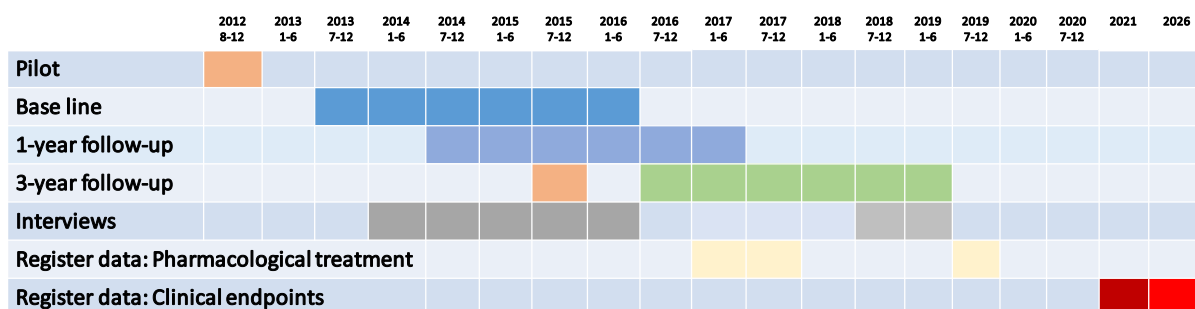
7.2 Secondary endpoints

- 7.2.1 CVD risk factors (blood pressure, serum cholesterol, LDL, HDL, triglycerides, fasting glucose, HbA1c)
- 7.2.2 Lifestyle (physical activity, tobacco use, alcohol use, eating habits)
- 7.2.3 Ultrasound results (CIMT, presence of plaque, quantitative and qualitative plaque parameters, presence and degree of significant stenosis)
- 7.2.4 Pharmacological treatments of hypertension, dyslipidemia and diabetes, prescriptions and purchases
- 7.2.5 Biochemical biomarkers
- 7.2.6 Clinical endpoints: Hospitalizations due to CVD, diagnostic and therapeutic revascularization procedures (PTCA, PCI, stent) regarding atherosclerotic disease and deaths (all-cause and CVD-specific), as specified in Appendix 2: VIPVIZA diagnoses clinical events and causes of deaths
- 7.2.7 Quality of life.

8 Project description

8.1 Study design The design is a pragmatic randomized controlled trial (24, 25).

8.2 Time plan A summary of the time plan for participants' visits in the study as well as for interviews and acquisition of register data from the National Board of Health and Welfare is shown in the figure below.



8.3 Setting and research environment

VIPVIZA is integrated in the Västerbotten Intervention Program (VIP) (26), which is a population-based CVD screening and prevention program in the County of Västerbotten, Sweden (population 265,000). Since the 1990s, VIP has provided health surveys for all county inhabitants during the year in which they turn 40, 50 and 60 years (n=6500-7000/year), comprising CVD risk factor screening and individual promotion of healthy lifestyle and pharmacological CVD prevention.

To date, over 170,000 health surveys have been performed. Participation rates during recent years were around 60-70% with only small social selection bias (27). VIP is one of the largest long-term CVD prevention programs in the world. It provides a unique arena for pragmatic studies of population-based CVD risk intervention

The ultrasound examinations in VIPVIZA are performed at the hospitals in three cities/towns (Umeå, Skellefteå, Lycksele), and in remote rural areas at primary health care centres. Risk factor measurements and questionnaires at follow-up are carried out for participants in Umeå at the Clinical Research Centre at Umeå University Hospital, and for participants in the rest of the county at their local primary health care center.

8.4 Risk-benefit evaluation for the individual

The intervention in VIPVIZA is the provision of pictorial information about the presence and extent of the individual's atherosclerosis from their ultrasound results. 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 which targets a healthy population, it is a dilemma whether or not to inform asymptomatic individuals of silent disease, in this case an ongoing atherosclerotic process with increased risk of future CVD. The presence of atherosclerosis can be perceived by the subject as more serious than just an increased level of risk markers, and may therefore result in anxiety. In order to avoid unjustified concerns, all persons in the intervention group receive a telephone call from a research nurse and, if necessary, a doctor in charge, to give in-depth and balanced information about the ultrasound results. This conversation is conducted according to the methodology of motivational interviewing and also aims to increase awareness of the possibility of reducing the individual's risk by means of their 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 and a more healthy lifestyle is also expected to bring benefits through increased well-being and quality of life. Similarly, subjects without ongoing atherosclerotic disease will be able to avoid unjustified concerns that their risk factors, if any, may be contributing to an active disease process.

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

8.5 Discontinuation of the study

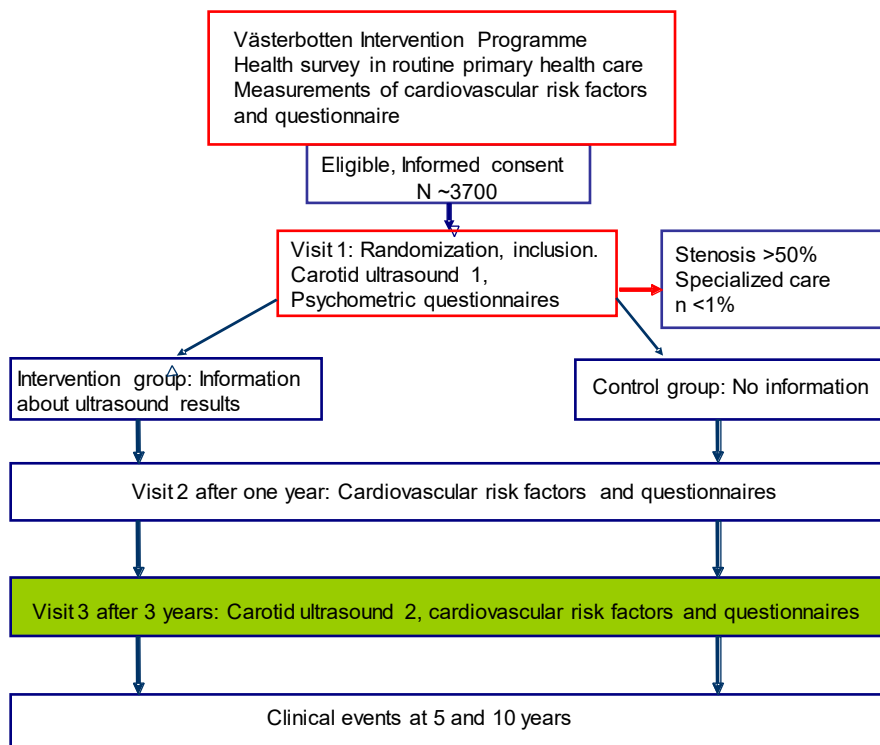
Individuals at high risk of stroke, defined as severe carotid stenosis, i.e. stenosis >50% of the lumen, are excluded from the study, informed of the results and referred to the Stroke Center, University Hospital, Umeå, with treatment in accordance with current guidelines for this group.

8.6 Pilot study

A pilot study with 95 participants was performed September-October 2012. The study organisation worked well and protocols and procedures were further developed and showed good feasibility, although randomization to intervention and control groups was not carried out. In order to optimize understanding of atherosclerosis as a process and the accurate perception of the ultrasound result, the information was calibrated according to participants' experiences and suggestions, collected through questionnaires and interviews. After 3 years, complete data on risk factors from 81 pilot participants was collected, and favorable changes regarding LDL-cholesterol, triglycerides and fasting glucose were observed, with the addition of favorable weight changes among women only.

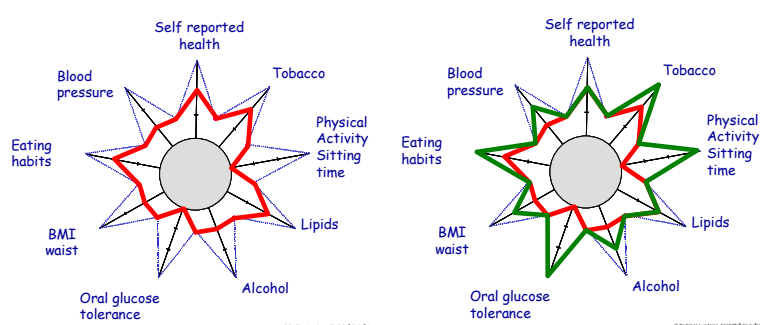
9. Study plan, the main study

9.1 Flow chart



9.2 Visits

9.2.1 Baseline visit, participation in VIP. Data collection: demographic, socio-economic, clinical risk factors for CVD, and lifestyle. This data is used in an individual health dialogue with a trained district nurse at the primary health care center. Applying the methodology of Motivational Interviewing, this session aims at health promotion and CVD prevention. A pictorial tool, the “Star profile” (Figure below), is used to facilitate the individual’s understanding of how his/her lifestyle is linked to CVD risk factors.



When requested, VIP-participants are also recommended follow-up visits or referrals to the family physician for pharmacological treatment according to guidelines. Samples of blood are frozen and stored at the Biobank, Umeå University Hospital.

VIP participants who are eligible for participation in VIPVIZA are given written and verbal information about the VIPVIZA study and are invited to the study at the occasion of their participation in VIP at their primary health care centre. The district nurses who conduct the health dialogues also sign that the study information is given and collect the informed consent forms and send them to research nurses at KFC. The research nurses register all forms. Appendix 1: The Informed Consent form translated from Swedish to English

9.2.2 Baseline visit with ultrasound examination. Study participants are randomized into two equal groups, intervention and control, following a computer-generated randomization list. They then complete psychometric questionnaires, questions about self-rated risk of CVD and health-specific self-efficacy, and undergo the first ultrasound examination of both carotids. Written information about results are sent to those in the intervention group and their respective family physician in primary care.

9.2.3 Follow-up one year after the ultrasound examination. Measurement of clinical risk factors for CVD, lifestyle, self-reported pharmacological treatment, self-rated health, risk of CVD and health-specific self-efficacy. Framingham Risk Score and Score are estimated.

9.2.4 Follow-up three years after the ultrasound examination Data collection: clinical risk factors for CVD, completion of lifestyle questionnaire, psychometric questionnaires, questions about self-rated risk of CVD and health-specific self-efficacy. Participants also undergo the second ultrasound examination of both carotids. Samples of blood are drawn, frozen and stored at the

Medical Biobank, Umeå University Hospital. Written information about ultrasound results are sent to all SPs and their respective family physicians in primary care.

9.3 Activity scheme

	Base line		Follow-up			Action defined
	Visit 1 VIP exam	Visit 2 Ultrasound	Visit 3 1 year	Visit 4 3 years	5 and 10 years	
Informed consent	X					9.2.1, 11.1, 12.1, 14.1
Clinical risk markers	X		X	X		9.2.1, 9.2.3, 9.2.4, 11.3, 12.2, 12.3
Lifestyle habits	X		X	X		9.2.1, 9.2.3, 9.2.4, 11.2, 12.2.1, 12.3
Demographic socioeconomic and psychosocial factors						9.2.1, 11.1, 11.8.2
Ultrasound examination		X		X		9.2.2, 9.2.4, 11.5, 12.2.1, 12.2.2, 12.3
Psychometric questionnaires		X		X		9.2.2, 9.2.4, 11.4, 11.8.3
Self-rated health, risk of CVD and health-specific self-efficacy		X	X	X		9.2.1, 9.2.2, 9.2.3, 9.2.4, 11.4, 12.2.1
Interviews with GPs		X				11.6, 12.2.1
Interviews with study participants		X		X		11.6, 12.2.1
Pharmacological treatment	X		X	X		9.2.1, 9.2.3, 9.2.4, 11.2, 11.8.1
Biomarkers	X			X		9.2.1, 9.2.4, 11.7
Hospitalizations registry data					X	11.8.2, 11.8.4
Deaths registry data					X	11.8.2, 11.8.4

10 Study population

10.1 Target group and invitation

The study focuses on subjects at intermediate risk of CVD. Based on VIP data from 2012, around 60% of all VIP participants of 40, 50 and 60 years of age, i.e. n= 4000/year, was estimated to be at moderate risk of CVD due to having at least one conventional CVD risk factor (see below for inclusion criteria). Since VIP is on-going continuously in primary care, inclusion can continue until the desired number of SPs is reached.

VIP participants who are eligible for participation in VIPVIZA are given written and verbal information about the VIPVIZA study and are invited to the study at the occasion of their participation in VIP at their primary health care centre. The district nurses who conduct the health dialogues also sign that the study information is given and collect the informed consent forms and send them to research nurses at KFC. The research nurses register all forms (baseline visit performed in the VIP).

10.2 Selection criteria

10.2.1 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 distribution 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, while 9% and 12% respectively had S-LDL concentrations ≤ 2.5 mmol/L, and 81% and 88% respectively had S-LDL concentrations ≤ 4.5 mmol/L.

- age=40 and a history of CVD at age <60 years among first-degree relative(s)
- 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
- age=60 years

Individuals are included in the study only once, at whichever qualifying age point is achieved first.

10.2.2 Exclusion criteria

Significant stenosis as defined as >50% luminal narrowing of the investigated carotid arteries according to vascular ultrasound. These individuals are informed about results irrespective of randomization

status, are excluded from the study and referred to the Stroke Center, Umeå University Hospital, for further evaluations and treatment.

11 Examinations and measurements

11.1 Demography, socio-economic and psychosocial data

From the baseline VIP questionnaire: Age, sex, civil status, education, family history of premature CVD and diabetes, social network and support according to the International schedule on social interaction (Swedish version) (28) and work stress (according to the Karasek-Theorell demand/control model) (29).

11.2 Lifestyle and health status

From VIP data at base line and at 1- and 3-year follow-up visits: Questionnaire data including self-reported physical activity, sitting time, tobacco habits, alcohol (AUDIT questionnaire), diet (food-frequency questionnaire, except at the 1-year visit), self-rated health, self-reported (known) diabetes as well as blood pressure and lipid-lowering pharmacological treatment. At 3-year follow-up, the Swedish version of the Beliefs about Medicines Questionnaire (BMQ) (30, 31) was also added from March 2017.

11.3 Clinical risk factors

At baseline, 1- and 3-years. Measurements:

- Anthropometrics: Waist is measured on the skin at the point mid-way between the last palpable rib and the iliac crest, using a non-elastic measuring tape; height and weight are measured in light clothing without shoes using calibrated scales and stadiometers.
- Systolic and diastolic blood pressure is measured twice with a calibrated digital blood pressure gauge at the precision of 2 mm after 5 minutes rest with the subject in a sitting position. The mean value of the two systolic and diastolic measurements are recorded.
- Lipids: Blood samples for serum-cholesterol, serum-LDL, serum-HDL, serum-triglycerides are drawn after an overnight fast and sent to the department of Clinical Chemistry at the nearest local hospital and analyzed with standard clinical biochemical methods. The three hospital labs in the county are all quality assured.
- Glucose status: Within the VIP (26), at baseline after an overnight fast, an oral glucose tolerance test is carried out according to WHO standards, with measurements of capillary fasting plasma glucose and 2-hour plasma glucose (32). At 1- and 3-year follow-up, capillary fasting plasma glucose is measured using HemoCue® Glucose analyzer (HemoCue AB, Ängelholm, Sweden).

11.4 Psychometric data

Psychometric data will be utilized as moderators and/or mediators of the intervention effect on primary and secondary outcomes, and also as outcomes at 3-year examination. At baseline and 3-year examination: Health literacy (33), Coping strategies (Brief Cope) (34), General Self-Efficacy (35), Anxiety and Depression (HAD) (36), Optimism/Pessimism (LOT-R) (37). At base-line, 1- and 3-year follow-up there are also questions about self-rated health (5 alternatives) (38), self-rated risk of CVD and health-specific self-efficacy (ability to reduce the CVD risk through preventive actions) using a

VAS scale 0-10. In a subset of the study population, the Newest Vital Sign test on health literacy (39) was added to the questionnaire at 1-year follow-up from January 2017 until completion of 1-year visits in August 2017.

11.5 Ultrasound data

IMT variables measured at specific positions and angles on both sides of the arteria carotis. Since there is no international consensus on which specific IMT measurement to use optimally, in particular in early stage atherosclerosis, a separate explorative analyses will be performed on this issue. Vascular age is calculated based on IMT and related to IMT values among subjects matched for sex and age in the Atherosclerosis Risk In Communities study population (ARIC) (40). This reference study was selected due to similarity with risk factor patterns in the VIP population. Plaque is defined according to the Mannheim Consensus (41). The presence of plaque on both sides of the carotid artery, plaque area and plaque texture are recorded.

11.6 Qualitative data

Telephone interviews with around 25 purposively sampled participants from the intervention group (based on age, sex, ultrasonography results) are conducted within four weeks of receiving the baseline ultrasound information, as well as at 3-year follow-up. Interviews will also be performed with practitioners, who have received at least five different patients' ultrasound results, to explore how viewing the ultrasound results affects physicians' perceptions of their patients' risk, the communication with patients and attitudes to treatment of CVD risk factors.

11.7 Biomarkers

Plasma samples are collected at baseline for the entire study population and in a subsample of SPs living in Umeå and surrounding municipalities. These samples are centrifuged and stored at -80° C at the Medical Biobank, Umeå University Hospital, to be analyzed at the 3-year follow-up for hypothesized CVD biomarker. Examples are:

- The end product of oxidized LDL detected via autoantibodies against distinct apoB peptides and its prospective correlation to current atherosclerotic burden (42, 43).
- Bile acid receptors: the farsenoid xenobiotic receptor (FXR) and the G-protein coupled receptor TGR5 (44) and their longitudinal role related to CVD.
- Lipoprotein lipase (LPL) activity (45) to assess whether substrate differences for LPL translates into predictive risk changes (Lookene et al. in preparation).
- Metabolomics, particularly lipidomics: (Umeå Plant Science Centre, SciLifeLab, and Uppsala Clinical Research Centre, Sweden)

11.8 Registry data

11.8.1 Pharmacological treatment: At baseline, 1 and 3 years: Prescriptions retrieved from medical records in the Västerbotten County Council digital system registries. At 1 and 3 years: purchases of pharmacological products from the Statistics on Pharmaceuticals at the National Board of Health and Welfare.

11.8.2 Socio-economic status: Income and highest attained educational level from Statistics Sweden.

11.8.3 Cognitive characteristics at age 18 (males only): The Conscripts register at the National Archives Database.

11.8.4 Clinical events: From data retrieved from registers at the National Board of Health and Welfare at 5 and 10 years after the last ultrasound examination: Hospitalizations due to cardiovascular morbidity and diagnostic and therapeutic procedures and mortality (all-cause and CVD-specific), according to the International Classification of Diagnoses ICD10, as specified in Appendix 2 VIPVIZA diagnoses clinical events.

12 Intervention and control

12.1 Randomization and invitations to visit.

VIP participants who are eligible for participation in VIPVIZA are given written and verbal information about the VIPVIZA study and are invited to the study at the occasion of their participation in VIP at their primary health care centre. The district nurses who conduct the health dialogues also sign that the study information is given and collect the informed consent forms and send them to research nurses at KFC. The research nurses register all forms.

SPs are then randomized to two equal groups (intervention and control group) before the first ultrasound examination. The randomization list is generated prior to the study through simulation from a uniform probability distribution. At this stage a unique identification code is assigned to each SP. Invitation with appointment times for the baseline visit is sent by mail to both groups by the research nurses who manage the study at KFC.

12.2 Intervention group

12.2.1 Procedures

- Baseline: Research nurses send invitation letters with an appointment time for the baseline ultrasound examination by mail to those who gave informed consent to participation in VIPVIZA. One reminder letter with a new appointment time is sent to non-attenders. At this visit, participants answer the psychometric questionnaires and undergo the baseline ultrasound examination. Ultrasound examinations are performed by sonographers specifically trained in carotid ultrasound techniques (Biomedical Scientists) from the Department of Clinical Physiology, Heart Centre, Umeå University Hospital. Examinations are undertaken in hospitals in three towns in Västerbotten county (Umeå, Skellefteå and Lycksele), and at the local primary healthcare centres in rural areas. A portable automatic carotid ultrasound equipment (CardioHealth Station®, Panasonic Healthcare Corporation of North America, Newark, NJ, USA) is used. A standardized protocol according to current guidelines is applied for the examinations (46, 47). The angle of insonation is automatically provided by the system and is recorded. Measurements of CIMT (max, min and mean values)

are automatically obtained (41). The same ultrasound machine is used during the entire study period.

Within two weeks of the ultrasound examination, information about the carotid ultrasound results are sent by post to the participant, see 12.2.2. At the same time, exactly the same information is sent to their respective primary care physician. After an additional 2-4 weeks participants receive a follow-up phone call by a research nurse in order to ascertain whether the information was accurately understood and to reassure the participant and give additional information if needed.

- Qualitative interviews with a subgroup of around 20 SPs within the intervention group concerning their experiences and reactions to the information about the ultrasound results.
- Qualitative interviews with General Practitioners who have received at least five written reports from VIPVIZA regarding their patients.
- At 6 months, participants receive a reminder in the form of a letter with the identical information about the ultrasound results and very brief reminder about possible preventive measures.
- At 9 months, participants receive a letter with information about proceedings in the study and reminder about the 1-year follow-up.
- At 1 year, participants receive an invitation to the follow-up visit, with an appointment time at KFC. This is sent by research nurses to participants living in Umeå and surrounding municipalities. The information is also sent to the health care centers outside the Umeå area, where VIPVIZA participants are eligible for the 1-year follow-up. Nurses at these health care centers conduct the 1-year visits for their VIPVIZA participants. This visit includes measurement of risk factors and a questionnaire including self-rated health, health-related quality of life (RAND 36), prescribed medication for hypertension and dyslipidemia, tobacco and alcohol use, physical activity, usual portion sizes as an indicator of possible changes of eating habits, and self-rated risk of CVD as well as possibilities to reduce this risk, i.e. health-specific self-efficacy.

The results regarding risk factor measurements are provided on a form that has been approved by the Steering Group and also includes recommendations for preventive measures depending on the levels of risk factors. This form is sent by post by the research nurses at KFC and district nurses at health care centers.

In the intervention group, the questionnaire which was sent during the spring semester 2017 to the last 500 participants before completion of the 1-year visits, includes questions concerning how participants perceived and recalled the pictorial ultrasound information and the phone call received at baseline

- At 2 years, a letter is sent with information about proceedings in the study and a reminder about the 3-year follow-up.
- At 2.5 years, a letter is sent with repeated information about the atherosclerotic process, as well as general information regarding healthy eating.

- At the 3-year follow-up: Invitations and appointment time for the ultrasound examination, risk factor measurement and questionnaire completion is sent by post to participants living in Umea and surrounding municipalities by research nurses at KFC; all examinations are conducted at KFC. Participants outside this area are also invited for ultrasound examinations undertaken in hospitals in the three towns in Västerbotten County (Umeå, Skellefteå and Lycksele), and at the local primary health care centres in rural areas. Invitations are sent only once, with no reminder following non-attendance. . Research nurses also inform the health care centers outside the Umeå area when it is time to invite participants to the 3-year visit, although this visit is managed by the health care centers, including risk factor measurements and questionnaire completion. At this time point, the intervention group also answer questions about how they perceived the pictorial information and phone call received at baseline concerning the ultrasound results.

Results of clinical risk factor measurements and the completed questionnaires are sent to KFC and the research nurses give feedback to participants using a predefined form similar to the form used at the 1-year follow-up.

Within two weeks of the carotid ultrasound examination, information about the results are sent by post to the participant, see 12.2.2. At the same time, exactly the same information is sent to their respective primary care physician. After an additional 2-6 weeks, participants whose ultrasound results indicated CIMT values higher than expected according to age and sex (red gauge) or with plaques (red), receive a follow-up phone call by a research nurse in order to ascertain whether the information is accurately understood and to reassure the participant and give additional information if needed. Participants without plaques (green) or vascular age similar or lower than expected (green or yellow/orange gauge) are informed by a standard letter including the contact information for research nurses, in case of questions or concerns.

Qualitative interviews are conducted with a few SPs, regarding their experience of receiving the second ultrasound report and how they interpreted this in relation to any life style modification carried out, including taking prescribed medications, following the first ultrasound examination.

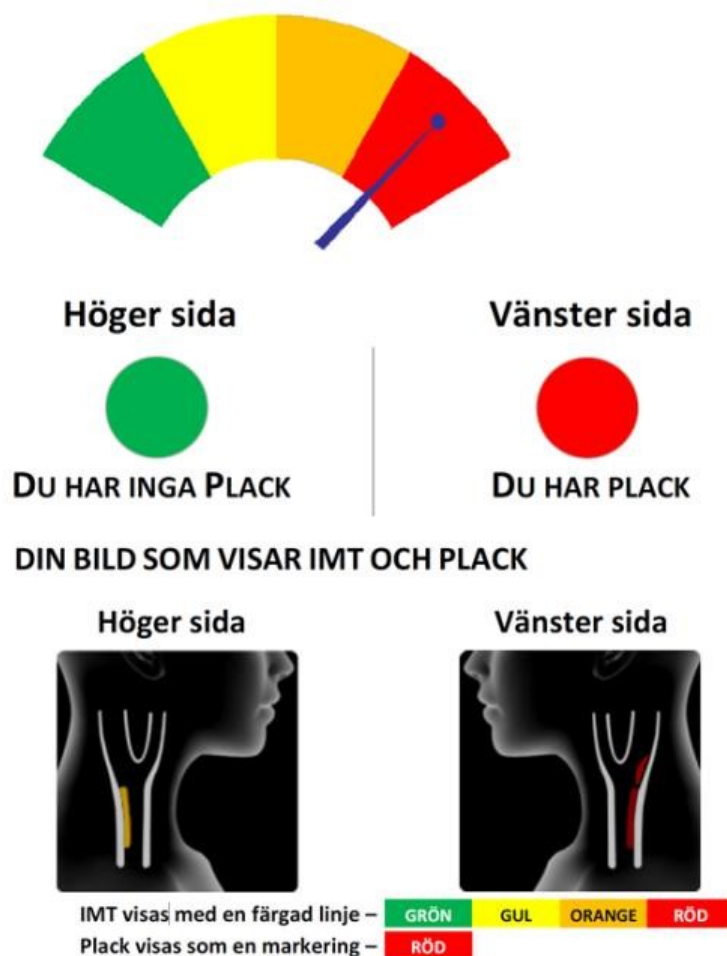
12.2.2 Image-based pictorial information

This information was developed during the pilot phase. The original report from the CardioHealth station was tested and refined in communication with VIPVIZA pilot participants, with patients at the clinic of Behavioral Medicine, who had a different educational status and who had lifestyle related metabolic diseases. The research nurses' experiences from discussions of the results with participants were also considered. The team of researchers compiled the collected impressions and developed the written information, aiming to provide easy and accurate understanding of the scanning result and concerning atherosclerosis as a dynamic process that can be modified by lifestyle changes and pharmacological treatment. A

technician adjusted the print scripts accordingly, so that the approved information is automatically generated by the CardioHealth station, including both graphics and text.

The information includes the following:

- The carotid intima media thickness is presented as vascular age with graphic presentations of atherosclerosis highlighted in color against normal vascular age patterns as a gauge, proceeding from a green sector, through yellow and orange to a red sector to illustrate the percentiles 1-25, 26–50, 51–75 and 76–100, respectively. Since no data are available from VIPVIZA's source population, the Atherosclerosis Risk In Communities study population (ARIC) (40) was selected as the reference population for calculation of vascular age by sex and age due to the similarity with the VIP population of risk factor patterns.
- Plaque formation shown as a traffic light for each side of the carotid artery, with a green circle for 'no plaque detected' and a red circle for 'plaque detected'.
- A stylized picture of the participant's own ultrasound image showing vascular age as a colored line and plaques as a red mark.
- Brief written information about atherosclerosis as a dynamic process, which is modifiable by a healthy lifestyle and pharmacological treatments for hypertension, dyslipidemia and diabetes.



12.3 Control group procedures

- Baseline: Identical to procedures for the intervention group, except that no information about ultrasound results are sent to SPs and their respective GPs, and there are no qualitative interviews.
- At 1-year: Identical to follow-up procedure for the intervention group, except that there is no sub-study regarding perceptions about the baseline ultrasound report.
- At 3-years: Identical to follow-up procedures for the intervention group, except that there are no questions regarding perceptions about the baseline ultrasound report and the phone call and no qualitative interviews.

13 Statistical analyses and considerations

13.1 Power and number of study participants

Calculations were performed to estimate the sample size needed to detect a clinically significant difference between the control group and the intervention group with sufficient power regarding change from baseline to 1-year follow-up in the primary clinical outcome variables, Framingham Risk Score and SCORE, as well as for S-LDL and total cholesterol, systolic blood pressure. Regarding possible detectable change of CIMT from baseline to 3-year follow-up, the available literature reported a mean change of 0.010 ± 0.005 mm/year from the MESA study (48) and in a meta-analysis the progression was 0.000-0.023/year for mean maximal IMT of the common carotid artery (49). For evaluating the effects of the various CIMT variables on the sample-size calculation for a trial, we used a pooled common CIMT progression rate of 0.0147 mm/y (0.044 mm/3 y) with the corresponding SD. For the mean maximum progression rates, we used an estimate of 0.0176 mm/y (50).

Since no data was available from the current population, we hypothesized that a change of CIMT of 0.02 mm would be theoretically possible to detect having standardized protocols for IMT assessment including multiple angles of insonation, anatomic landmarks and automated edge detection software technology as was also recommended in a state of the art paper (15). As the design utilizes randomization, the groups were assumed comparable at baseline, thus no further adjustment for background factors was considered. As a lower limit for power we used a threshold of 0.8, and for significance level we used 0.05. These calculations were based on standard deviations on conventional risk factors derived from VIP 2012 and on CIMT from the Tromsø study (51). The power calculations revealed that an initial total number of 3500 participants with a drop-out rate of 15 % during the study would be sufficient. The limiting factor demanding the largest group size to show a hypothesized detectable effect was CIMT. Thus, the sample size was decided based on that.

Variabel	Precision	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

13.2 Statistical analyses

13.2.1 Dataset and study population

All subjects participating in the study will be included in the analyses. For the drop-out analyses, non-participants (those who did not consent to participation or failed to attend the first ultrasound examination) will be included in the analyses of selection bias for participation, but this evaluation will be based on only a restricted number of variables (sex, age, education, clinical CVD risk factors and lifestyle).

13.2.2 Interim analyses

No interim analysis is planned. Any eventual differences in deaths and clinical events such as myocardial infarction, stroke and revascularisation procedures cannot be expected to be identified and analyzed statistically before three years of follow-up in this middle-aged, low/intermediate risk population. Furthermore, since they participate in the VIP, the control population (not informed) receives primary prevention actions according to guidelines and to a relatively high extent in comparison with most other counties in Sweden and most other countries globally.

13.2.3 Summary of planned analyses

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-test, for a detailed statistical analyses plan see Appendix 4. 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. A two-sided p-value <0.05 will be regarded as statistically significant. Complementary to the absolute difference in the Score and the statistical testing of hypotheses, 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.

In sensitivity analyses, we will conduct a linear regression covariate-adjusted analysis. 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 measures. As many of the baseline co-variates (including sex and age) are related to the prognosis of outcomes, adjustment of pre-defined covariates in the regression analysis might yield in adjusted coefficients which are slightly further from 1.

We will also analyze the changes of SCORE and FRS from baseline to 1-year follow-up and use regression methods to identify predictors of the changes in the scores.

Since patients are recruited into the study during 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 medication to participants recruited during the first, second and third years.

Similar statistical methods will be applied for evaluation of the three-year results. At that time point also changes in plaque distributions and IMT variables including differences between intervention and control group will be evaluated.

In long-term, adding risk communication using visualisation of carotid ultrasound results will be compared to routine CVD risk assessment and control within the primary health care setting in hospitalisation due to stroke, myocardial infarctions and revascularisations (at 5-year and 10-year) and reducing overall mortality and cause-specific mortality due to myocardial infarctions and stroke (at 5-year and 10-year) compared to.

Simple survival curves will be established using Kaplan-Meier curves for CVD mortality and morbidity at 5 and 10 years of follow up comparing the intervention to the control group. Thereafter, predictive Cox Proportional Hazard models will be developed to estimate the overall predictive ability of CIMT, plaque and risk factors on CVD morbidity and mortality at 5 and 10 years in the control group and in the intervention group, taking into account time at risk for disease and deaths. Receiver Operating Characteristic Curves (ROC) will be calculated by estimating the Area Under the Curve (AUC) to ensure the highest possible sensitivity and specificity of the predictions. Confirmatory and exploratory statistical modelling will establish relationships between the intervention and intermediate and mediating factors and variables' relative contribution to explain changes in the outcome variables.

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 among participants recruited during the first, second and third years.

As a basis for how to build regression models Causal diagrams (directed acyclic graphs - DAGs) will be established and causal mediation analysis will be undertaken to illustrate the impact of social, gender, psychological and environmental factors by biomedical risk indices on CVD morbidity and mortality.

Health economic modelling studies will be performed for evaluation of cost-effectiveness. Interviews with participants and physicians will be transcribed verbatim and analyzed using Qualitative Content Analysis (52).

13.3 Planned drop-out analyses

13.3.1 Non-participants vs participants

This category includes all individuals who were informed about VIPVIZA at the occasion of participation in the VIP and who did not consent (ticked 'NO' on the form) to participation in VIPVIZA, as well as subjects who initially consented to participate but withdrew their consent, either actively by phone or mail to the research nurses, or passively, through failing to attend the baseline ultrasound examination. One reminder to those who fail to attend is sent with a new appointment time for the baseline ultrasound examination but if they still fail to attend, they are categorized as a non-participant. Aggregated data on the group of non-participants will be compared with the included study participants regarding CVD risk markers and lifestyle as well as educational level and civil status. In this analysis, published data on participation and selection to the VIP will also be considered (27).

13.3.2 Drop-outs at the 1-year evaluation

At one year, the study population will be further reduced as a result of exclusions due to significant carotid stenosis (10.2.2), deaths and migration out from the county. Drop-outs will be defined as active withdrawal of consent to participation or failure to attend the 1-year follow-up evaluation after postal invitation and one reminder. Drop-outs will be compared to the other participants regarding risk factors, lifestyle, level of education, and intervention group status at baseline.

13.3.3 Drop-outs at the 3-year evaluation:

SPs will be invited to the 3-year examination irrespective of participation status at the 1-year follow-up, provided they were not excluded according to 10.2.2 or have withdrawn their consent). Therefore, drop-outs at Year 3 will be defined as active withdrawal following the 1 year examination or failure to attend the 3-year follow-up after postal invitation and one reminder. Drop-outs will be compared to the other participants regarding risk factors, lifestyle and educational level as well as intervention group status at baseline.

14 Study administration

14.1 Procedures for collection of informed consent

At the occasion of participation in the VIP, subjects are given written information about VIPVIZA, including the form for informed consent. Those who fulfill the inclusion criteria are informed verbally by the VIP nurse, who also collects the forms, both from those who consent to and those who decline to participate in the study. These forms are sent to the research nurses at KFC, who insert the data from those who consent into the electronic CRF document. Subjects who do not consent to participation in the study are listed separately for analysis of selection bias using aggregated data and a restricted number of variables.

14.2 Definition of source data

There are several different sources of data in VIPVIZA. See also below section Data Management.

Sources for VIPVIZA data comprise:

- VIP data: The VIP questionnaires are sent from healthcare centers to the Medical Biobank, Umeå University Hospital, where they are registered and optically read by ITS, Umeå University. The electronic data are sent to the VIP database at the Unit of Epidemiology and Global Health, Umeå University. The questionnaires are stored at the Medical Biobank, Umeå University Hospital.
- The Case Report Form (CRF) contains information about randomization, as well as administrative information about visits, exclusions and drop-outs. The CRF is electronic and managed by the research nurses and located within the Västerbotten County Council's computer system.
- All questionnaires answered by participants at base line, 1-year and 3-year visits are kept in files at the Clinical Research Center under a code for each participant. After completion of all visits in the study (June 2019) they will be stored at the Unit of Epidemiology and Global Health during the entire study period in a safe archive.
- Clinical risk markers at 1- and 3-year visits are written on the front page of the lifestyle questionnaire.
- Ultrasound data are registered and stored in the CardioHealth Station.
- Pharmacological prescriptions: Stored in the electronic medical records at the participants' respective primary health care centers within the Västerbotten County Council.
- Interviews: Audiotapes taken at the occasion for interviews [should we say something about secure storage?]
- Register data: The pharmaceutical register, the Statistics on inpatient diseases in Sweden, and the Statistics on causes of death are stored at the National Board of Health and Welfare. The Conscripts register is stored at the National Archives Database. Statistics Sweden (Educational attainment and income) [are we missing something here?]

14.3 Quality control

The study is quality-controlled based on protocols and data collection on site to verify that:

- That data is reliable, accurate and complete
- That the safety and rights of all involved in the study are protected
- That the study has been conducted in accordance with current protocols and study agreements as well as GCP and all applicable government requirements.

An external monitor is selected at the Clinical Trial Unit at Västerbotten County Council. The monitor is not involved in the study.

The monitor has the necessary education, and the scientific and/or clinical knowledge necessary to monitor the trial adequately.

The Principal Investigator approves that the monitor has direct access to all relevant documentation.

Monitoring takes place in accordance with current GCP during and after the study. If any violation or negligence is discovered, the Principal Investigator shall be notified of corrective and/or preventive measures. See Appendix 5 Monitoring plan.

14.4 Quality assessment

It is the responsibility of the principal Investigator to ensure that a) collected data is checked, complete, signed and dated, b) that the study is conducted according to the protocol, to study agreements, to GCP and obligations from authorities, bearing in mind and that regulatory control/audits/inspections could be made at any time during or after closure of the study c) ensure that co-investigators and departments participating in the study approve and assist in any kind of inspection.

14.5 End of the study

The study will be formally closed on Dec 31 2026. Study visits and data collection from participants will be finalized in June 2019 or when all 3-year visits are completed. From that time point, SPs will be followed through registers for an additional 10 years. Since there is no intervention other than providing information about silent atherosclerosis to all participants at baseline and at 3-year follow-up, which qualifies as clinical prevention according to guidelines for CVD preventions, any premature termination before Dec 31 2026 will not be applicable.

14.6 The VIPVIZA research database and its management

All data will be entered into the VIPVIZA research database, which is managed by a trained database manager. The database and the database management is described in detail in Appendix 3: VIPVIZA Database Description. This document describes the original data, source files and the structured data and their content, purpose and physical storage including hardware encryption and back-up. It also

describes the variable catalogue and proposal application system. The pass word is only known by the data manager and the data can only be accessed by the data manager. The pass word is kept in a sealed envelope in a safe at the Department of Public health and clinical medicine. In order to link data from external sources to the VIPVIZA database repeatedly and during the whole study period, personal identification numbers are retained in the data base.

The key code will be retained for 10 years until register data on clinical events are retrieved and then destroyed, or if the follow-up is terminated earlier, the key code will be destroyed in the same way. All personal data will be processed in accordance with the Personal Data Act (1998: 204) and the study participants are entitled to receive information on the data recorded in the study annually free of charge and to have any errors corrected. The exception to this is base-line ultrasound results for individuals in the control group.

The files containing consent forms, questionnaires, as well as copies of the ultrasound report for the intervention group, will be archived at the Department of Public Health and Clinical Medicine.

14.7 Import of questionnaire data, risk factor data, CRF and ultrasound data to the database

Questionnaire data and risk factor data are entered into an access file on two laptops that are used for this sole purpose. The database manager creates the access file and also imports the data from the access files, as well as data from the CRFs and the ultrasound data on IMT and plaque to the VIPVIZA database.

14.8 Proposal application system and data handling

Researchers do not have access to the database. Researchers who are affiliated to VIPVIZA have access to an internal webpage for VIPVIZA. On this page, available data sets and variables are listed, including aggregated information, but no individual data. The web page also offers functionality for developing and sharing research proposals. Every authorized researcher can create and upload a proposal using a standardized form. External researchers may also apply for data if they collaborate with at least one member of the steering group. In such cases, external researchers will get access to the internal web page to follow the proposal routines regarding applications and approvals. Data without personal identification numbers will be exported to the researcher by the data manager after approval from the VIPVIZA steering group. and results will be reported only at an aggregated level. No researcher will be able to identify any participant, and therefore publications based on the study do not cause any ethical dilemma.

15 Ethical and legal aspects of the study

15.1 Ethical considerations

The study will be conducted according to the ethical principles based on the Helsinki Declaration, GCP, national regulatory mandatory instructions and this study protocol.

Both written and oral information to all participants in the study declares that participation in the study is voluntary and can be withdrawn at any time without any consequences for their ordinary health care.

Study participants will be carefully informed in a standardized way to ensure full and adequate communication, including information about randomization to an intervention or control group and treatments within primary care, prescribed according to guidelines about cardiovascular risk factors and preventive treatments, irrespective of whether information about the vascular ultrasound is provided or not. The signed consent from participants also includes information about the monitoring of the study and access to their confidential medical records at the County Council of Västerbotten, as well as, when appropriate, medical records from private primary health care centers, and register data from national registers. Specific written consent applies to storage of data and blood samples at the Biobank. The participants can at any time communicate questions to research nurses and can, without any payment, obtain information about their individual data in the study and to revise any incorrect data.

The issue of not providing information about silent atherosclerosis to half of the study population was thoroughly discussed with the Regional Ethical Board. It was judged to be acceptable, because 1/ individuals with severe carotid stenosis (<1% in the pilot study) are excluded and promptly referred for expert care (through potentially life- or function-saving measures), and 2/ there are no specific treatments for mild-moderate atherosclerotic disease other than risk factor control, according to guidelines. Risk factor control will be given irrespective of whether or not the ultrasound results are disclosed to participants.

The ultrasound message was extensively tested during the pilot study 2012 to ensure that easily understandable information is reported, that is accurately interpreted. This was carried out among out-patients with intermediate risk of CVD at the clinic of Behavioural Medicine, among patients with history of a CVD event at Heart Centre, as well as among the pilot participants.

During the study, any negative reaction, such as anxiety due to image results, is balanced through the provision of additional information and supportive counselling by research nurses in a phone call to each participant. This issue is also specifically in focus in the qualitative sub-studies and its investigation is included in the objectives of the study.

It is possible and hypothesized that the compliance to guidelines for prevention of CVD among physicians at health care centers will increase as a result of the information about ultrasound results in the intervention group. This is not considered an ethical problem, since there are no studies

demonstrating improved prognosis by using imaging techniques among subjects without signs of high-degree flow-limiting stenosis of the carotid arteries, and no study participants are excluded from prevention measures according to the current CVD prevention guidelines for health care. Previous studies of imaging techniques in health screening for cardiovascular disease suggest improved risk stratification. Therefore, from an ethical perspective it is important to investigate new pathways towards improved prevention and to discard old inefficient methods.

The study is integrated into an environment with direct links to ordinary health care, with its routines for follow up and prevention, including rapid direct referrals if pathological conditions (requiring further diagnostic or therapeutic interventions) are detected. The study is performed with stable research conditions for all study participants

There is no selection of participants in the VIP. All citizens in the county have the same opportunity to be invited the year they are 40, 50 and 60 years old. The study has no negative effects for the health care of any citizen or group of citizens. Once invited to VIP, clear information is given that the health screening is combined with advice, motivational information and measures to improve long-term health. VIPVIZA adheres fully to all the intentions of VIP.

Altogether, the eventual improved risk stratification and risk communication to physicians and study participants outweighs any potential negative effect of the study. There is no risk for harm with the direct procedure for vascular ultrasound.

15.2 Approval of the study

The application was submitted to the Regional Ethics Examination Board in Umeå, December 13 2011 and was approved February 7 2012. Documented approval to participate in study activities according to the study protocol and informed consent forms was obtained from authorities of the County Council of Västerbotten, representing the participating primary health care centers and hospital clinics, as well as from managers of private primary health care centers. These documents were attached to the application to the Regional Ethical Board (Appendix 1). Applications for amendment concerning all significant changes to the protocol thereafter have been approved by the Regional Ethics Committee. The significant amendments are:

15.3 Major amendments

- Repeated risk factor measurements and questionnaires about lifestyle at a one-year follow-up (added visit) as well as at the 3-year follow-up.
- A questionnaire to all SPs concerning important determinants of perceived risk of CVD and performance of preventive lifestyle modifications.
- Interviews with primary care physicians concerning their perceptions and reactions to the baseline ultrasound information.
- Repeated ultrasound information to the intervention group 6 months after the baseline examination.
- The psychometric questionnaires added to the 3-year follow-up.
- Qualitative interviews at 3 years among SPs in the intervention group.
- Collection of samples of blood to be frozen and stored in the Medical Biobank, Umeå University Hospital at the 3-year visit.
- To keep the personal identification number in the database to allow for linkage with register data from different sources at different time points during the whole study period until collection of data on clinical events and deaths after 10 years. The personal ID is not available to researchers, only to the database manager.
- The Beliefs about Medicines Questionnaire added to the 3-year questionnaire.
- Extended ultrasound examinations, that are necessary in cases where the CardioHealth station does not provide sufficient technological quality to allow a definite evaluation of potential significant stenosis information. This includes contrast enhancement and advanced ultrasound imaging to evaluate plaque texture.
- Psychometric data from the Conscripts register and income and education from Statistics Sweden as well as data on air-borne pollutants.

16 Funding of the study and insurances

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The Patient Injury Act applies to all patients and subjects participating in research treated in Swedish health care. The Patient Insurance as well as the Pharmaceutical Insurance also applies to the study participants in this study.

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

NCT01849575

Amendment to Study Protocol version 4.0

Additional major amendments

- A Discrepancy between first date registered on clinclatrilas.gov and first ultrasound examination in VIPVIZA Page 42
- B Data on health and physical testing from the Conscripts registry and data for the baseline drop-out analyses from Västerbotten Intervention Programme regarding eligible non-responders and drop-outs. Page 42
- C Follow-up six years after Base line Page 43

Version 1.

26/11/2019

A Discrepancy between first date registered on clinicaltrials.gov and first ultrasound examination in VIPVIZA

The VIPVIZA trial was approved by the Regional Ethical Review Board at Umeå University February 7th 2012, Dnr 2011-445-31M. A pilot study was performed September-October 2012, Study Protocol . page17 section 8.6.

The first date regarding VIPVIZA in clinicaltrials.gov was May 8th 2013, while the first baseline ultrasound examination in the main study was performed April 29th 2013. This delay is completely explained by the administrative issues that occurred during registration of the VIPVIZA record at clinicaltrials.gov. Thus, it is documented in mail conversations that the record holder (Margareta Norberg) at April 29th 2013 filled in the form for registration of VIPVIZA at clinicaltrials.gov, but it was not possible for the record holder to determine how to register members of the Steering Committee and the International Advisory Board. This had nothing to do with study procedures, inclusion of study subjects or the conducted examinations. This issue regarding registration of VIPVIZA's administrative and leadership structure was solved on May 2nd 2013, but on the same day the response message by mail from clinicaltrials.gov was that "PRS Administrator for Umeå University must Approve and Release this record". (Moreover April 30th and May 1st are normally out-of-office-days in Sweden). Furthermore, the central administrator for clinicaltrials.gov for Umeå University had only recently been appointed. This delayed the actual registration date further until May 8th 2013.

We therefore claim that the discrepancy of nine days between the date registered at clinicaltrials.gov and the first day for any baseline examination is entirely due to administrative reasons and should not prohibit publication of manuscripts based on the VIPVIZA trial in journals requiring registration before the first examination.

Through documentation in our encrypted database, which is available only to a database manager, it can be demonstrated that the very few subjects, out of the total of 3532 participants included up until June 2016, who were examined during this 9-day period were informed about the trial according to regulations, and had given their written informed consent before being included, thereby ensuring the safety of participants in advance of any treatment or intervention commencing.

B Data from the Swedish Conscripts registry regarding health information and physical testing and data from the Västerbotten Intervention Programme on eligible non-responders and drop-outs at the baseline examination in VIPVIZA

This was approved by the Regional Ethical Review Board Umeå University at December 27th 2018, Dnr 2018-482-32M

C Follow-up six years after baseline

This amendment to the VIPVIZA Study protocol Version 4.0, regards continued follow-up with data collection and examination six years after inclusion in the study using the same research questions as originally and the supplementary changes that have already been made (See Study protocol version 4.0, Major amendments section 15.3 page 36).

Study progress: The three-year follow-up: data collection was completed on June 16 2016. VIPIVZA has followed the study plan. The evaluation of the primary endpoint was completed published in Lancet (Publication 4). Additional publications up to November 30 2019 are listed in the Publications list. The two publications by Vanoli et al concern the preparatory evaluations of the ultrasound examination methodology; these evaluations were performed before the study start and did not use data from any VIPIVZA participants. All other publications are based on data collected within the main trial. To date, several substudies are ongoing. The project includes one completed PhD project and three on-going PhD projects, and a two-year post-doctoral study period that was finalised in June 2019.

The 6-year follow-up includes the following additions, removals or changes.

1. Added measurement or clinical data
 - a. Objective measurement of physical activity with accelerometer
 - b. Dental health: Two questions in the questionnaire to participants regarding dental health and retrieval of clinical data on dental health and dental radiological examinations from Dental Care.
2. Changes in the questionnaire to participants regarding psychological and social determinants of health behaviours in particular with respect to cardiovascular disease (CVD). Overall, the questionnaires were reduced in scope.
 - a. Deleted: the Three-item Brief Health Literacy Screen (BHLS), Questions on anxiety deleted from HADS (Hospital Anxiety and Depression Scale), Brief Cope on coping strategies, LOT-R on optimistic/pessimistic disposition, the 66 item Food Frequency questionnaire that is used in the Västerbotten Intervention Programme (VIP), BMSQ Beliefs about Medicines Questionnaire,
 - b. Additions: International Schedule of Social Interaction (ISSI), the Karasek Demand /Control model questionnaire (ISSI and Karasek D/C were included in the baseline VIP questionnaire), questions regarding reactions to the 3-year ultrasound information based on qualitative interviews with participants, SOM/5-HTT a validated questionnaire about personality. Questions to women about pregnancy complications and menopause and reproductive hormonal therapy.
3. New data from registries
 - a. Blood group
 - b. Data from VIPVIZA participants' previous VIP-examinations before entry to VIPIVZA 10, 20 or even 30 years earlier. Example: A person who was included in VPVIZA in

relation to participating in VIP at the age of 60 years, could have participated in VIP also at ages 50 years, 40 years and even 30 years.

4. Electronic questionnaire: A possibility to answer the questionnaires electronically. The Umeå University data collection platform is used to guarantee confidentiality and secure data handling according to GDPR.

Motivation for the extension of the trial with a 6-year follow-up: The three measurement points of ultrasound data on subclinical atherosclerosis provide a much greater statistical certainty in assessing trends, notably the effect of the intervention, as compared to only two measuring points. The problem of mis-classification "towards the null" decreases. Moreover, the atherosclerotic process is so slow that a long follow-up period is necessary and also, for CVD prevention measures to be effective with regard to affect hard endpoints, they have to be sustainable over long periods.

Ethical considerations regarding risk vs benefit: As previously during the VIPVIZA trial, there is a risk of potentially strong emotional reactions in connection with obtaining ultrasound results. However, this risk is considered to be small as the entire study population was informed about their personal ultrasound result at the 3-year follow-up and very large individual changes to the 6-year follow-up cannot be expected. This risk is also balanced by the possibility of feedback regarding implemented prevention efforts, both by the individual and provided by health professionals in terms of pharmacological treatment. As before, subjects with severe ultrasound results will also be followed up by research nurses. If strong emotional reactions nevertheless occur, the study team is prepared to take care of these cases.

There is a risk that some parts of the questionnaires, as well as collection of health data from Dental Care, may be perceived as violating privacy. This is balanced by the fact that all data is handled with complete confidentiality and that only aggregated data will be reported, and also that the results may be the basis for development of personalized CVD prevention methods.

As in previous follow-up, as well as at baseline, sampling of blood to the local Medical Biobank for future analyses of novel biomarkers carries only a minor risk of transient tenderness and bruising. The study projects do not have any direct benefit from these changes of the project. However, even if the usage of an Accelerometer does not entail any direct risk or benefit to participants, the research group's experience from previous projects is that this measurement is appreciated by participants when they get a brief feedback on their own results.

This amendment was approved by the Swedish Ethical Review Authority at September 24th 2019, Dnr 2019-04691.