Visualization of asymptomatic atherosclerotic disease for optimum cardiovascular prevention (VIPVIZA): a pragmatic, open-label, randomised controlled trial

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Summary

Background Primary prevention of cardiovascular disease often fails because of poor adherence among practitioners and individuals to prevention guidelines. We aimed to investigate whether ultrasound-based pictorial information about subclinical carotid atherosclerosis, targeting both primary care physicians and individuals, improves prevention.

Methods Visualization of asymptomatic atherosclerotic disease for optimum cardiovascular prevention (VIPVIZA) is a pragmatic, open-label, randomised controlled trial that was integrated within the Västerbotten Intervention Programme, an ongoing population-based cardiovascular disease prevention programme in northern Sweden. Individuals aged 40, 50, or 60 years with one or more conventional risk factors were eligible to participate. Participants underwent clinical examination, blood sampling, and ultrasound assessment of carotid intima media wall thickness and plaque formation. Participants were randomly assigned 1:1 with a computer-generated randomisation list to an intervention group (pictorial representation of carotid ultrasound plus a nurse phone call to confirm understanding) or a control group (not informed). The primary outcomes, Framingham risk score (FRS) and European systematic coronary risk evaluation (SCORE), were assessed after 1 year among participants who were followed up. This study is registered with ClinicalTrials.gov, number NCT01849575.

Findings 3532 individuals were enrolled between April 29, 2013, and June 7, 2016, of which 1783 were randomly assigned to the control group and 1749 were assigned to the intervention group. 3175 participants completed the 1-year follow-up. At the 1-year follow-up, FRS and SCORE differed significantly between groups (FRS 1·07 [95% CI 0·11 to 2·03, p=0·0017] and SCORE 0·16 [0·02 to 0·30, p=0·0010]). FRS decreased from baseline to the 1-year follow-up in the intervention group and increased in the control group (–0·58 [95% CI –0·86 to –0·30] *vs* 0·35 [0·08 to 0·63]). SCORE increased in both groups (0·13 [95% CI 0·09 to 0·18] *vs* 0·27 [0·23 to 0·30]).

Interpretation This study provides evidence of the contributory role of pictorial presentation of silent atherosclerosis for prevention of cardiovascular disease. It supports further development of methods to reduce the major problem of low adherence to medication and lifestyle modification.

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Introduction

Smoking cessation, physical activity, statins, and antihypertensive medication to prevent cardiovascular disease are among the most evidence-based and cost-effective treatments in health care. However, in the real world, prevention fails because of low and non-sustained adherence to prevention guidelines among practitioners and individuals.[1,2] Statistical modelling based on clinical risk factors is recommended for risk assessment of cardiovascular disease, and the Framingham risk score (FRS) and the European systematic coronary risk evaluation (SCORE) are the most widely used measures.[3,4] Evidence showing that use of these scores translates into reduction of cardiovascular disease morbidity or mortality is scarce.[5] These risk scores might be too abstract and therefore fail to communicate risk in order to stimulate appropriate pharmacological prescription and enhanced motivation for a healthier lifestyle.

Information alone rarely leads to rational behavioural modification.[6] The recall of advice regarding exercise and diet is poorer than advice to take medications.[7] The risk of cardiovascular disease is usually communicated to individuals verbally;[8] visual tools are seldom used.[9,10] A more person-centred approach by adding pictorial information about the individual's atherosclerosis would increase motivation and adherence to guidelines.[11] It could be argued that this is as important as development of new treatment modalities for prevention of cardiovascular disease. Providing information to physicians concerning their patients' risk of cardiovascular disease has been

Research in context

Evidence before this study

Physical activity, smoking cessation, and treatment of hypertension and hypercholesterolaemia are among the most effective, cost-effective, and evidence-based therapies for non-communicable diseases. However, prevention of cardiovascular disease fails, largely because of low adherence to guidelines and recommendations for lifestyle change and pharmacological treatment by individuals and health-care professionals. Risk assessment, risk communication, and motivation for a change in lifestyle are all targets to improve adherence to prevention measures. Pictorial representation of the risk factor burden might improve risk perception and motivation, but few studies have investigated this hypothesis, and no systematic reviews are published. Vascular ultrasound of atherosclerotic plaques and intima media wall thickness is an established diagnostic tool to assess atherosclerosis, but the effects on adherence to healthy lifestyle and drug therapy have not previously been studied in randomised controlled trials.

Added value of this study

This pragmatic, open-label, randomised controlled trial, targeting both physicians and individuals, aimed at improved efficacy and adherence to prevention measures in an asymptomatic population, showed significant benefits with respect to lowering the risk factor burden for cardiovascular disease in participants given a pictorial representation of their atherosclerotic plaques and intima media wall thickness, presented as vascular age, compared with participants who received routine care, with no pictorial information (Framingham risk score 1·07 [95% CI 0·11 to 2·03, p=0·0017] and systematic coronary risk evaluation [SCORE] 0·16 [0·02 to 0·30, p=0·0010]).

Implications of all the available evidence

This study provides further evidence on the contributory role of pictorial representations and dialogue about silent atherosclerosis for primary prevention of cardiovascular disease, which are valid for clinical practice. Whether the results are sustainable for more than 1 year and lead to reduction of cardiovascular disease events warrant long-term follow-up.

found to increase prescription of lipid-lowering and blood pressure medication, with the greatest effect in those with the highest risk.[12,13]

However, results on the contributory impact of image-based information about silent atherosclerosis on adherence to prevention are inconsistent.[14,15] Therefore, additional large-scale randomised controlled trials are needed.[1,16,17]

The primary aim of this study was to investigate the impact of pictorial information about individuals' atherosclerosis, as demonstrated by carotid ultrasound, in comparison with traditional risk factor-based risk communication.

Methods

Study design and participants

Visualization of asymptomatic atherosclerotic disease for optimum cardiovascular prevention (VIPVIZA) is a pragmatic, open-label, randomised controlled trial with masked evaluators (PROBE) integrated in the Västerbotten Intervention Programme (VIP), a population-based cardiovascular disease screening and prevention programme in Sweden. VIP was initiated in the 1990s and has been described in detail.[18] In VIP, an invitation is sent to all Västerbotten County inhabitants at the of age 40, 50, or 60 years to complete a primary care health survey, which includes cardiovascular disease risk factor screening and an individual motivational interview to promote a healthy lifestyle, and pharmacological cardiovascular disease prevention according to clinical guidelines. 6500–7000 people complete the survey per year. Participation rates during 2007–16 were 68%, with only small social selection bias.[19]

Individuals were invited to the VIPVIZA trial at the individual interview when participating in VIP. Participants underwent ultrasound examinations at the hospitals in three urban centres (Umeå, Skellefteå, and Lycksele) in Västerbotten County, Sweden, and in remote rural areas at primary health-care centres. Risk factor measurements and questionnaires at the 1-year follow-up were 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 centre.

To be eligible for participation, individuals had to be aged 40 years and have a first-degree relative with a history of cardiovascular disease at an age of younger than 60 years; aged 50 years and at least one cardiovascular disease risk factor (smoking, diabetes, hypertension, serum LDL cholesterol of ≥4·5 mmol/L, abdominal obesity defined as a waist circumference of ≥102 cm for men and ≥88 cm for women, or a first-degree relative with a history of cardiovascular disease at an age of younger than 60 years); or aged 60 years.

Exclusion criteria were significant stenosis, as defined by more than 50% luminal narrowing of the investigated carotid arteries according to vascular ultrasound; violation of study protocol; and participation in other clinical studies during the study follow-up. Individuals with severe carotid stenosis were referred directly to specialised care. A detailed study protocol is presented in the appendix. VIPVIZA was approved by the Regional Ethical

See Online for appendix

Review Board, Umeå University (Dnr 2011-445-31M, 2012-463-32M, 2013-373-32M). All study participants provided written informed consent.

Randomisation and masking

Participants were randomly assigned to two groups (intervention and control group) by use of a randomisation list, which was generated by a computer before enrolment, and with consecutive allocation to the two groups by the research nurse. Outcomes were assessed by masked evaluators.

Procedures

Each participant and their primary care physician in the intervention group received pictorial presentation of the carotid ultrasound results (figure 1), including presentations of atherosclerosis as vascular age, with a gauge ranging from green to yellow, orange, and red to illustrate the individual's biological age compared with chronological age. Plaque formation was shown as a traffic light for each carotid artery, with a red circle for a detected plaque or a green circle for no plaque detected. A stylised picture of the participant's ultrasound image was included, as well as brief written information about atherosclerosis as a dynamic process that is modifiable by a healthy lifestyle and pharmacological treatment. Interpretation of the result and general advice on prevention of cardiovascular disease were also provided. After 2–4 weeks, participants received a follow-up phone call by a research nurse to reassure participants and give additional information as needed. The same pictorial information was repeated to participants after 6 months. Both groups received normal care within VIP. No pictorial information was given to the participant or their family physician about the baseline carotid ultrasound result in the control group.

Both groups were managed throughout the study according to clinical guidelines on cardiovascular disease risk factor control by nurses and physicians at health-care centres (not by the study team). Thus, the VIPVIZA intervention was added to the regular VIP prevention programme.[18] Both the intervention and control groups were informed about their 1-year follow-up results.

Risk factors for cardiovascular disease were measured at the baseline VIP health survey with standardised measurements of waist circumference, height, weight, and systolic and diastolic blood pressure. Blood samples for analyses of total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides were taken after overnight fasting, and participants had an oral glucose tolerance test. Participants answered a questionnaire on health, medication, family history of cardiovascular disease and diabetes, highest attained education, and lifestyle habits. Methods and definitions of variables are shown in the appendix.

All carotid ultrasound examinations were done according to a standardised protocol[20] by sonographers specifically trained in carotid ultrasound techniques (biomedical scientists). Portable carotid ultrasound equipment with real-time automatic carotid intima media wall thickness measurements was used (CardioHealth Station, Panasonic Healthcare Corporation of North America, Newark, NJ, USA).[21] The angle of insonation was automatically provided and recorded. The carotid intima media wall thickness (mean of a 1 cm wide segment[22]) was automatically measured in the left and right common carotid arteries at insonation angles 120, 150, 210, and 240 degrees. For each participant, the maximum of all projections' mean carotid intima media wall thickness value was used to estimate vascular age (figure 1) using the Atherosclerosis Risk In Communities study population as the reference population because of the similarity with the VIP population regarding age and risk factor profiles.[23] The presence of an atherosclerotic plaque was recorded on both sides according to the Mannheim consensus.[24]

The same clinical cardiovascular disease risk factors that were assessed at baseline were assessed at the 1-year follow-up, except fasting glucose was measured instead of an oral glucose tolerance test. The same questionnaires covering lifestyle habits and pharmacological treatments were re-administered.

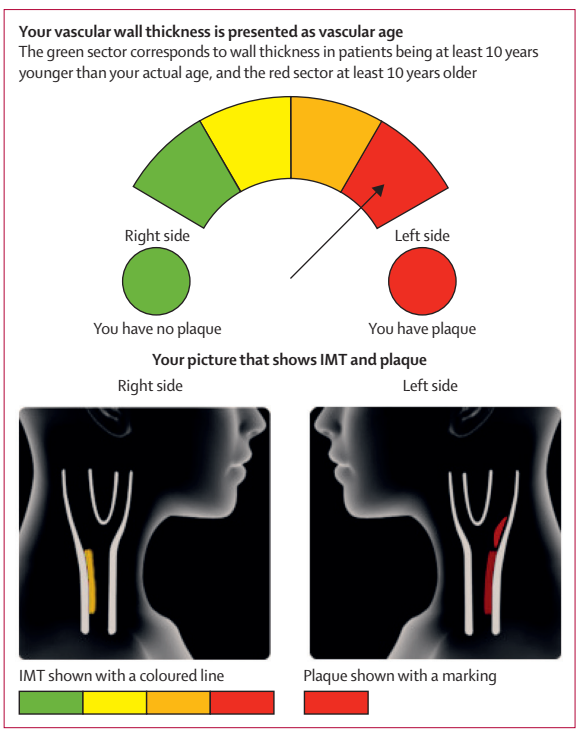

Figure 1: **Pictorial information about ultrasound results**
IMT=intima media thickness. Translated from Swedish.

Outcomes

Primary outcomes were FRS and SCORE at the 1-year follow-up and changes in the two variables from baseline

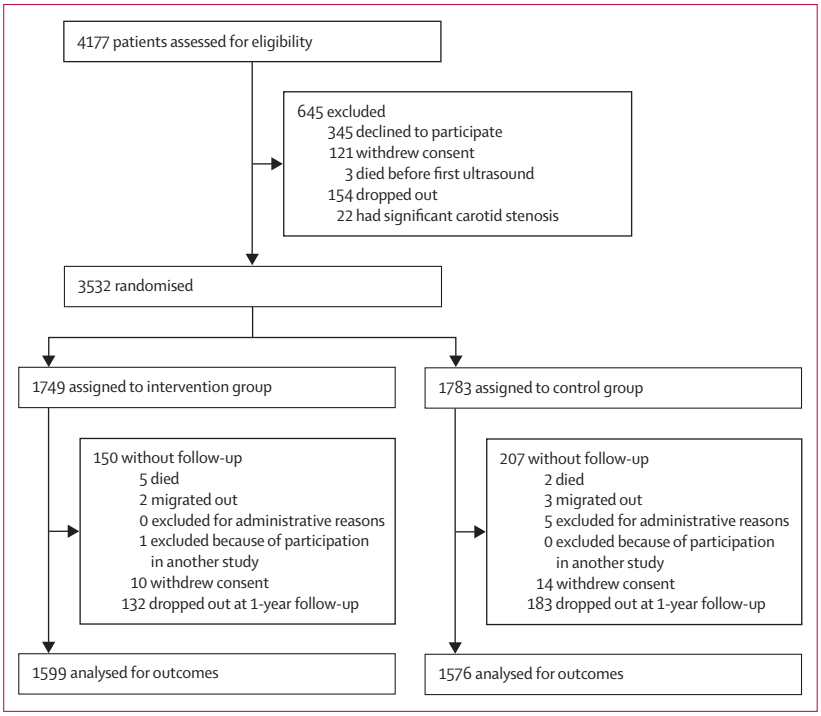

Figure 2: **Trial profile**

to the 1-year follow-up. Secondary outcomes were systolic and diastolic blood pressure, total cholesterol, LDL cholesterol, HDL cholesterol, fasting glucose, weight, waist circumference, smoking, and self-reported pharmacological treatments for hypertension and dyslipidaemia (see the appendix for the full list of secondary outcomes).

Statistical analysis

Power calculations based on data on conventional risk factors from VIP 2012, as well as on ultrasound data from the Tromsø study,[25] revealed that 3500 participants with a dropout rate of 20% 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 hypothesised effect, was carotid intima media wall thickness, since it is an important component of the intervention and will be an outcome at the 3-year follow-up (appendix).

We calculated the overall sex-stratified descriptive characteristics at baseline of the control and intervention groups. Using Student's *t* test for two independent groups, we calculated the difference between the control and intervention groups for primary and secondary outcomes among participants who were followed up. There were no crossovers between control and intervention. The primary outcome was calculated for participants with 1-year follow-up. Furthermore, we did an intention-to-treat analysis of the primary outcome after imputations for missing data by using linear regression with all baseline and available 1-year follow-up variables in the dataset. For subgroup analyses, we also estimated the intervention effect on primary outcomes for different age groups, sex, atherosclerosis severity (with regard to the presence of plaques and to intima media thickness presented as vascular age at baseline), and education level (basic to mid-level defined as compulsory 9 years of schooling or senior high school [≤12 years]; high level of education is defined as 13 years or more of schooling). To assess the intervention effect on secondary outcomes, we estimated the differences-in-differences in the outcomes between the groups from baseline to the 1-year follow-up. We calculated the differences-in-differences estimates using an interaction term between intervention groups and round in linear regression for each of the outcomes, adjusted for age, sex, and education level at baseline. We applied the Bonferroni correction to adjust for multiple comparisons. Additionally, we evaluated the intervention effect on cholesterol and LDL cholesterol with stratification for treatment with statins, and the effect on systolic and diastolic blood pressure with stratification for treatment with antihypertensive medication.

We did a dropout analysis to assess whether the baseline characteristics differed between individuals with 1-year follow-up and dropouts. We did a sensitivity analysis to confirm or exclude eventual selection bias of dropouts, in which we systematically increased the values of FRS and SCORE among individuals who dropped out by 5%, 10%, 15%, and 20%, while keeping the values among those who participated in the 1-year follow-up constant. Independent *t* tests were used to assess significant differences between groups for continuous variables and χ^2 tests for categorical variables. All the statistical analyses were done in Stata, version 15.0. A detailed statistical analysis plan is included in the appendix.

This study is registered with ClinicalTrials.gov, number NCT01849575.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

3532 participants were enrolled between April 29, 2013, and June 7, 2016, of which 1783 were randomly assigned to the control group and 1749 to the intervention group. 3175 participants completed the 1-year follow-up (figure 2). The dropout analysis showed no differences between dropouts and participants in baseline FRS or SCORE in both the control and the intervention groups (appendix). For individual components of risk scores and other risk

factors, there were no differences in the control group apart from younger age among dropouts than among participants. In the intervention group, the dropouts were younger, had a lower level of education, more individuals who smoked daily or occasionally, more individuals with abdominal obesity, and higher concentration of triglycerides than participants (appendix).

Missing data for the variables recorded in the database for baseline and 1-year follow-up are shown in the appendix. There were missing data for variables used in

	Men (n=1670)		Women (n=1862)		Total (n=3532)	
	Control (n=862)	Intervention (n=808)	Control (n=921)	Intervention (n=941)	Control (n=1783)	Intervention (n=1749)
Framingham risk score	17·6 (9·7)	18·2 (10·6)	8·4 (5·4)	8·3 (5·3)	12·9 (9·1)	12·9 (9·6)
Low risk (<5%)	38/859 (4%)	40/805 (5%)	272/915 (30%)	266/936 (28%)	310/1774 (17%)	306/1741 (18%)
Light risk (5–9%)	154/859 (18%)	122/805 (15%)	379/915 (41%)	420/936 (45%)	533/1774 (30%)	542/1741 (31%)
Moderate risk (10–19%)	383/859 (45%)	367/805 (46%)	225/915 (25%)	211/936 (23%)	608/1774 (34%)	578/1741 (33%)
High risk (20–39%)	258/859 (30%)	243/805 (30%)	39/915 (4%)	38/936 (4%)	297/1774 (17%)	281/1741 (16%)
Very high risk (≥40%)	26/859 (3%)	33/805 (4%)	0	1/936 (<1%)	26/1774 (1%)	34/1741 (2%)
SCORE risk estimates	1·93 (1·40)	1·97 (1·38)	0·70 (0·51)	0·68 (0·49)	1·29 (1·21)	1·27 (1·19)
Low risk (<1%)	239/860 (28%)	197/805 (24%)	741/918 (81%)	762/937 (81%)	980/1778 (55%)	959/1742 (55%)
Moderate risk (1–4%)	596/860 (69%)	579/805 (72%)	177/918 (19%)	175/937 (19%)	773/1778 (43%)	754/1742 (43%)
High risk (5–9%)	23/860 (3%)	28/805 (3%)	0	0	23/1778 (1%)	28/1742 (2%)
Very high risk (≥10%)	2/860 (<1%)	1/805 (<1%)	0	0	2/1778 (<1%)	1/1742 (<1%)
Carotid plaques (left or right)	442/862 (51%)	406/808 (50%)	370/921 (40%)	361/939 (38%)	812/1783 (46%)	767/1747 (44%)
Carotid intima media wall thickness, mm*	0·77 (0·17)	0·77 (0·16)	0·71 (0·14)	0·71 (0·14)	0·74 (0·16)	0·74 (0·15)
Intima media thickness as vascular age†						
Quartile 1 (green)	97/862 (11%)	86/808 (11%)	56/921 (6%)	53/941 (6%)	153/1783 (9%)	139/1749 (8%)
Quartile 2 (yellow)	152/862 (18%)	150/808 (19%)	186/921 (20%)	183/941 (19%)	338/1783 (19%)	333/1749 (19%)
Quartile 3 (orange)	236/862 (27%)	212/808 (26%)	281/921 (31%)	313/941 (33%)	517/1783 (29%)	525/1749 (30%)
Quartile 4 (red)	377/862 (44%)	360/808 (45%)	398/921 (43%)	392/941 (42%)	775/1783 (43%)	752/1749 (43%)
Age group						
40 years	73/862 (8%)	61/808 (8%)	69/921 (7%)	73/941 (8%)	142/1783 (8%)	134/1749 (8%)
50 years	248/862 (29%)	226/808 (28%)	244/921 (26%)	260/941 (28%)	492/1783 (28%)	486/1749 (28%)
60 years	541/862 (63%)	521/808 (64%)	608/921 (66%)	608/941 (65%)	1149/1783 (64%)	1129/1749 (65%)
Sex						
Men	862/1670 (52%)	808/1670 (48%)	NA	NA	862/1783 (48%)	808/1749 (46%)
Women	NA	NA	921/1862 (49%)	941/1862 (51%)	921/1783 (52%)	941/1749 (54%)
Education‡§						
Basic to mid-level	611/857 (71%)	581/802 (72%)	526/905 (58%)	562/933 (60%)	1137/1762 (65%)	1143/1735 (66%)
High	246/857 (29%)	221/802 (28%)	379/905 (42%)	371/933 (40%)	625/1762 (35%)	592/1735 (34%)
Waist circumference, cm	101·2 (11·3)	101·2 (11·7)	92·7 (13·6)	91·9 (12·8)	96·8 (13·2)	96·2 (13·1)
Abdominal obesity (≥102 cm waist circumference for men, ≥88 cm waist circumference for women)	378/851 (44%)	353/803 (44%)	566/899 (63%)	554/929 (60%)	944/1750 (54%)	907/1732 (52%)
Fasting glucose, mmol/L	5·53 (1·52)	5·45 (1·37)	5·34 (1·08)	5·30 (1·06)	5·44 (1·31)	5·37 (1·21)
Diabetes¶	48/861 (6%)	61/808 (8%)	44/918 (5%)	33/940 (4%)	92/1779 (5%)	94/1748 (5%)
Blood pressure						
Systolic blood pressure, mm Hg	131·9 (15·2)	132·3 (16·5)	126·8 (16·1)	127·2 (16·3)	129·3 (15·9)	129·6 (16·6)
Diastolic blood pressure, mm Hg	84·6 (10·3)	85·0 (10·9)	80·9 (9·8)	80·8 (10·1)	82·7 (10·2)	82·8 (10·7)
Use of antihypertensives‡	262/862 (30%)	267/808 (33%)	259/921 (28%)	268/941 (28%)	521/1783 (29%)	535/1749 (31%)
Hypertension‖	483/862 (56%)	478/806 (59%)	427/917 (47%)	440/938 (47%)	910/1779 (51%)	918/1744 (53%)
Plasma lipids						
Total cholesterol, mmol/L	5·51 (1·11)	5·51 (1·13)	5·70 (1·04)	5·69 (1·04)	5·61 (1·08)	5·61 (1·08)
HDL cholesterol, mmol/L	1·23 (0·34)	1·25 (0·38)	1·54 (0·44)	1·51 (0·42)	1·39 (0·42)	1·39 (0·42)
LDL cholesterol, mmol/L	3·56 (1·00)	3·55 (0·99)	3·55 (0·94)	3·58 (0·95)	3·55 (0·97)	3·57 (0·96)
Triglycerides, mmol/L	1·66 (1·12)	1·66 (1·13)	1·34 (0·75)	1·33 (0·74)	1·50 (0·96)	1·48 (0·95)
Use of lipid-lowering medication‡	118/862 (14%)	118/808 (15%)	73/921 (8%)	81/941 (9%)	191/1783 (11%)	199/1749 (11%)
Dyslipidaemia**	799/861 (93%)	751/803 (94%)	862/920 (94%)	862/939 (92%)	1661/1781 (93%)	1613/1742 (93%)

(Table continues on next page)

	Men (n=1670)		Women (n=1862)		Total (n=3532)	
	Control (n=862)	Intervention (n=808)	Control (n=921)	Intervention (n=941)	Control (n=1783)	Intervention (n=1749)
(Continued from previous page)						
Family history of cardiovascular disease or diabetes	402/834 (48%)	341/760 (45%)	468/890 (53%)	510/901 (57%)	870/1724 (50%)	851/1661 (51%)
Smoking daily or occasionally	111/860 (13%)	92/807 (11%)	128/918 (14%)	115/939 (12%)	239/1778 (13%)	207/1746 (12%)

Data are mean (SD) or n/N (%). SCORE=systematic coronary risk evaluation. NA=not applicable. VIPVIZA=visualization of asymptomatic atherosclerotic disease for optimum cardiovascular prevention. *Maximum mean value independent of side and angle. †Vascular age in comparison with individuals of same age and sex in a reference population (Atherosclerosis Risk In Communities study population). Quartile 1 is comparable to being 10 years younger, quartile 2 is comparable to being 5 years younger, quartile 3 is comparable to being 5 years older, and quartile 4 is comparable to being 10 years older. ‡Self-reported. §Basic to mid-level of education is defined as compulsory 9 years of schooling or senior high school (≤12 years). High level of education is defined as 13 years or more of schooling. ¶Self-reported known diabetes or fasting glucose ≥7·0 mmol/L. ||Self-reported use of antihypertensive medication or systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg. **Self-reported use of lipid-lowering medication or serum cholesterol ≥5 mmol/L or serum LDL cholesterol ≥2·5 mmol/L.

Table: **Baseline characteristics of the VIPVIZA study population**

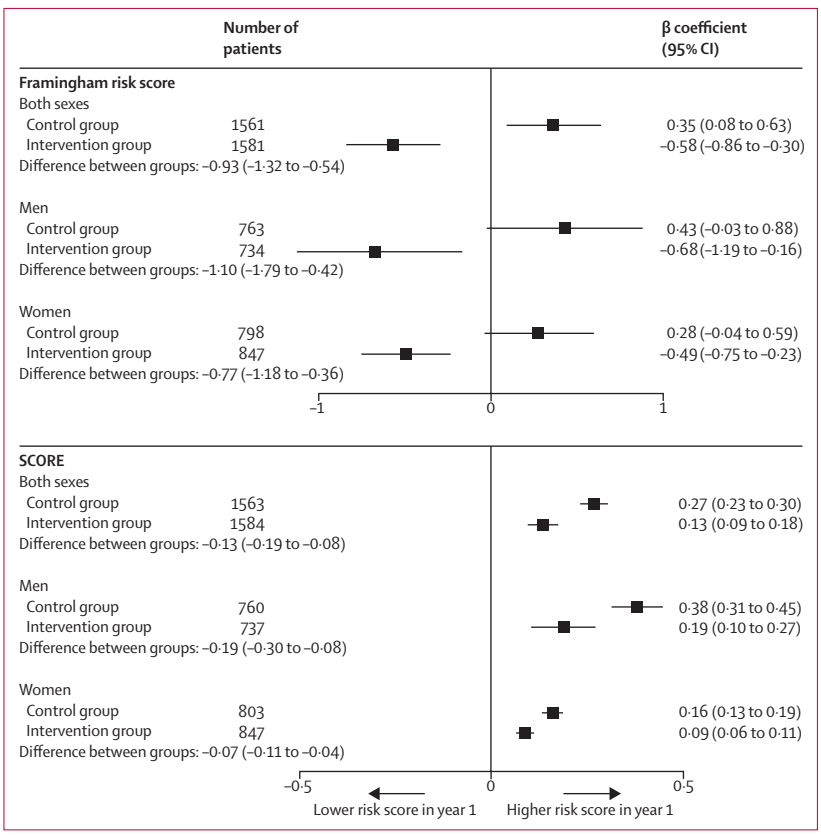

Figure 3: **Changes in Framingham risk score and SCORE in the intervention and control groups between baseline and 1-year follow-up**

SCORE=systematic coronary risk evaluation. Difference between groups is given with 95% CI.

the equations for FRS in 17 participants and for SCORE in 12 participants at baseline, and for 26 and 25 participants, respectively, at the 1-year follow-up.

The mean FRS was 12·9 (SD 9·1) in the control group and 12·9 (9·6) in the intervention group, and the mean SCORE was 1·29 (1·21) in the control group and 1·27 (1·19) in the intervention group (table). The distributions of FRS and SCORE are given in the appendix.

There were significant differences between the intervention and control groups in primary outcomes at the 1-year follow-up in favour of the intervention, with FRS 12·24 in the intervention group *vs* 13·31 in the control group (difference 1·07 [95% CI 0·11 to 2·03], p=0·0017) and SCORE 1·42 in the intervention group *vs* 1·58 in the control group (difference 0·16 [0·02 to 0·30], p=0·0010). Changes in the whole study population over 1 year were small but statistically significant, with a decrease in FRS by –0·58 (95% CI –0·86 to –0·30) in the intervention group (relative change –5%), in contrast with an increase in the control group by 0·35 (0·08 to 0·63; relative change +3%; figure 3). SCORE increased slightly in both groups albeit significantly less in the intervention group (0·13 [95% CI 0·09 to 0·18] in the intervention group *vs* 0·27 [0·23 to 0·30] in the control group; figure 3).

Analyses by sex and age showed that FRS decreased in the intervention group and increased in the control group to a similar extent in both men and women (figure 3; appendix). SCORE increased more in the control group than in the intervention group, and this increase was greater among participants aged 60 years than those aged 40 or 50 years (appendix), and among men than women (figure 3). The pattern was similar among men and women overall (figure 3), as well as in the groups of participants aged 50 years and 60 years (appendix).

Evaluation by baseline risk category showed a beneficial effect in the intervention group in all FRS risk categories, with the greatest effect in the group at high risk of cardiovascular disease, in which FRS decreased by –3·42 (95% CI –4·57 to –2·27) in the intervention group and by –1·26 (–2·39 to –0·14) in the control group (figure 4). The same pattern was seen in the high-risk group according to SCORE, which decreased in the intervention group but increased in the control group (figure 4). An intention-to-treat analysis, after imputations of missing data at 1-year follow-up, showed similar results for the primary outcome (appendix).

Because of the result of the dropout analysis, the analysis of the intervention effect by risk group was repeated stratified by educational level (figure 5). The patterns were the same in both the high and basic to mid-level education groups, with the greatest reduction of scores in the group

with basic to mid-level education and high risk of cardiovascular disease. This pattern was also seen in all educational categories when divided into the three levels; low, mid-level, and high (data not shown). Furthermore, a sensitivity analysis showed that the dropouts in the intervention group would have to increase at least 15% in FRS and more than 20% in SCORE (in relative change) to change the conclusions of the effect of the intervention on the primary outcome.

Total and LDL cholesterol decreased in both groups, but the reduction was greater in the intervention group than in the control group, resulting in a significant difference between groups at the 1-year follow-up (appendix). Moreover, the differences-in-differences (at baseline and at 1-year follow-up) estimates were statistically significant, and adjustment for age, sex, and education did not change this result (appendix). There was a significant increase in use of lipid-lowering medication in the intervention group compared with the control group (appendix). The differences between groups regarding other components of FRS and SCORE, as well as other relevant clinical risk indicators, did not reach statistical significance (appendix). A slight increase in weight was observed in the control group and a slight decrease in the intervention group, and systolic blood pressure increased by 1·6 mm Hg in the control group and was stable (–0·2 mm Hg) in the intervention group; the only exception from this pattern was seen in fasting glucose (appendix).

In a post-hoc analysis, in patients with lipid-lowering treatment, the reduction in total and LDL cholesterol was around double in the intervention compared with the control group (figure 6). A similar result regarding systolic blood pressure was observed for antihypertensive medication, for which the reduction was threefold in the intervention group compared with controls.

The effect of the intervention on FRS and SCORE was greatest for participants in the intervention group with the most advanced atherosclerosis with regard to presence of plaque and intima media thickness as vascular age at the carotid ultrasound examination (appendix).

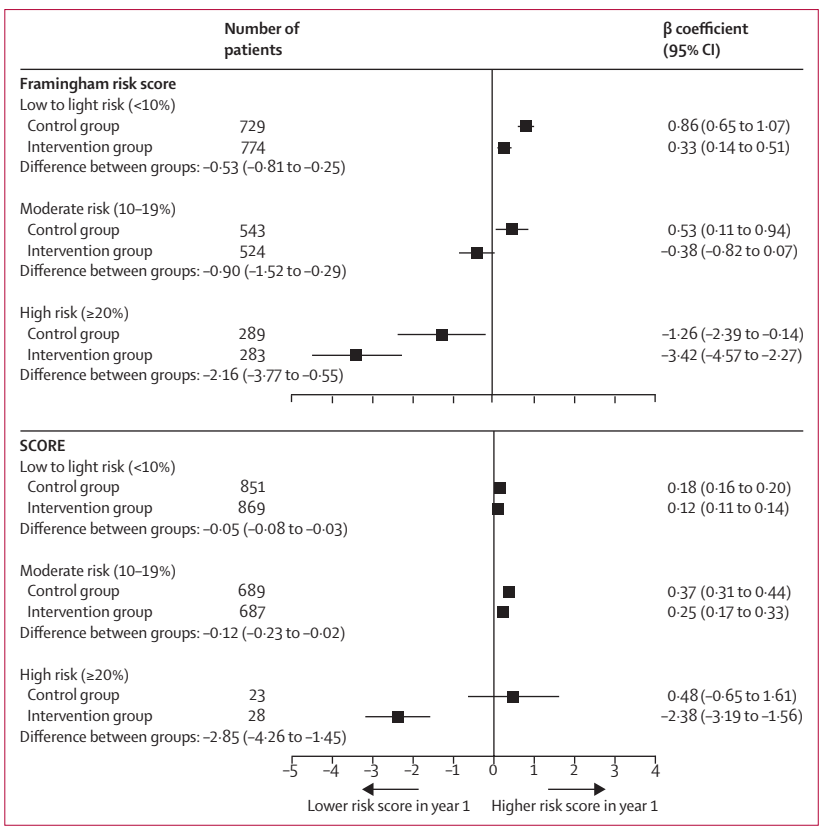

Figure 4: **Changes in Framingham risk score and SCORE by baseline risk categories in the intervention and control group between baseline and 1-year follow-up**
SCORE=systematic coronary risk evaluation. Difference between groups is given with 95% CI.

Discussion

In this pragmatic, open-label, randomised controlled trial, the most important result was that a low-intensity intervention with pictorial information of atherosclerosis followed by a nurse-led telephone call reduced the cardiovascular disease risk factor burden at the 1-year follow-up. This intervention was given in addition to an effective prevention programme managed by local health-care centres.[19,26] Of note, these results were obtained in a middle-aged population with low to moderate cardiovascular disease risk and thus overall with limited potential for improvements.

This beneficial effect was demonstrated for both FRS and SCORE and for total and LDL cholesterol. Improvements, although not significant, were also seen in systolic blood pressure, HDL cholesterol, weight, waist circumference, and smoking, reflecting both more effective pharmacological treatment and lifestyle modification in the intervention group than in the control group. We also recorded stronger reductions of total and LDL cholesterol among participants receiving statins and of systolic blood pressure among participants on blood pressure-lowering medication in the intervention group than in the control group, which also support this. Previous research shows low awareness of the links between lifestyle habits and cardiovascular disease, in particular among people with a low level of education.[27] Notably, the intervention effect was most pronounced among participants with a high risk of cardiovascular disease, and we did not find any differential responses for education level. Therefore, our results imply that this type of risk communication might contribute to reduction of the social gap in health. An intention-to-treat analysis of the primary outcome with imputed values for missing values based on baseline and available 1-year follow-up variables showed similar results (appendix). Furthermore, a sensitivity analysis revealed that any bias in our results due to dropouts can be rejected.

A graded effect in relation to the severity of demonstrated atherosclerosis was observed. The strongest

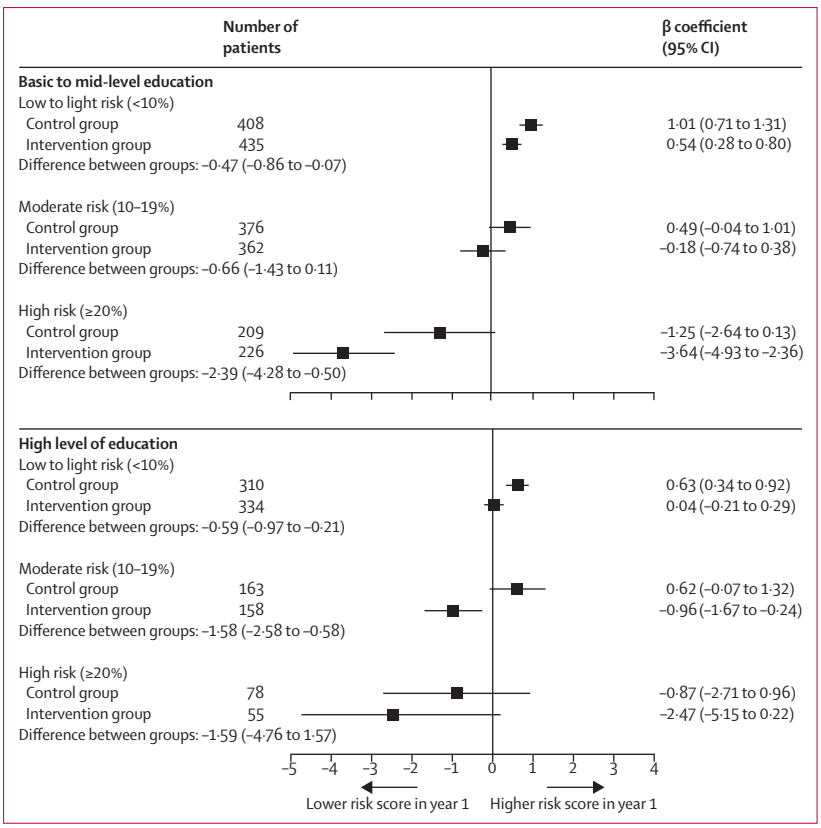

Figure 5: **Changes in Framingham risk score by baseline risk categories in the intervention and control group between baseline and 1-year follow-up stratified by education level**
Difference between groups is given with 95% CI.

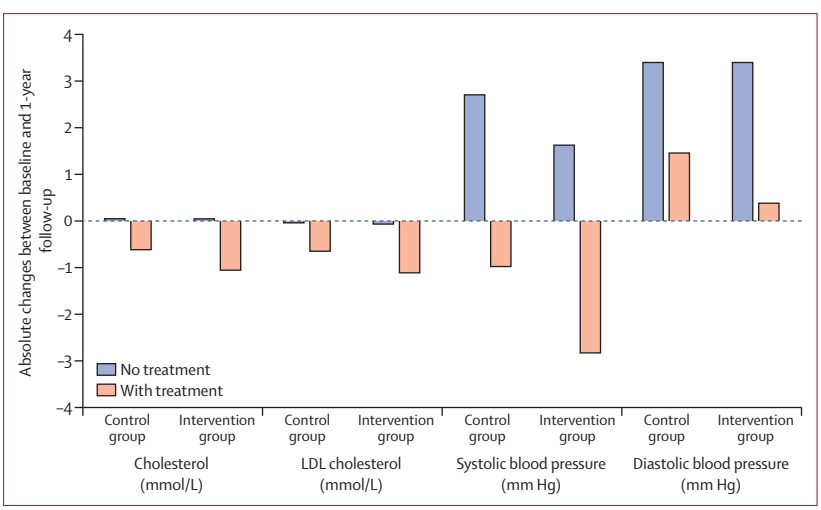

Figure 6: **Changes in the level of cholesterol, LDL cholesterol, and systolic and diastolic blood pressure between baseline and 1-year follow-up based on statin or antihypertensive treatment, stratified by treatment group**

message from the pictorial information was associated with the greatest effect. This finding supports our hypotheses regarding the use of image-based information as an effective tool in prevention to be investigated in the context of personalised medicine.

The overall effect size in FRS and SCORE after 1 year of this multimodal intervention might appear modest. Pictorial representation of the ultrasound results combined with telephone contact by a nurse is a low-intensity intervention compared with provision of new potent pharmacological treatments or surgical or catheter-based treatments. The effect was largest in the group at high risk of cardiovascular disease and with more advanced atherosclerosis, indicating the potential of a clinically relevant effect. Even small reductions in cholesterol and blood pressure levels are shown to have long-term benefit on cardiovascular events at a population level.[28,29] Furthermore, effects from lifestyle modification might add benefits beyond what is captured in FRS and SCORE—eg, reduction in inflammatory parameters, improved insulin sensitivity, weight loss or maintenance, a healthier diet, and increased fitness. A recent study[30] demonstrated a decrease in FRS from 15·6 to 13·3 by an intense multidisciplinary lifestyle programme in a population with considerably higher risk at baseline than our study population and two-thirds of the study population were women. In our population, an overall absolute difference in FRS of 1% in 10-year risk of cardiovascular disease between the intervention and control groups (12·24 *vs* 13·31) after 1 year might be relevant provided sustained lifestyle change and medication. During 1 year of follow-up, FRS and SCORE are expected to rise by adding 1 year of age to the equation. VIPVIZA recruited mainly individuals at low or intermediate risk for cardiovascular disease and with early atherosclerosis, thus offering the potential for real impact on the population burden of cardiovascular disease. This risk group contributes 60–70% of all cardiovascular disease events but has been poorly represented in published randomised controlled trials in primary prevention.[31]

VIPVIZA is, to our knowledge, one of the largest randomised controlled trials of its kind in primary cardiovascular disease prevention, with behavioural modification as an important component. There are only a few previous full-scale randomised controlled trials of pictorial presentations based on carotid ultrasound. One study[14] was restricted to smokers recruited by an advertisement for smoking cessation, and the results were neutral. Another study[15] was restricted to patients with type 2 diabetes. One study[32] found favourable changes in risk factors and FRS in the group that received pictorial presentation from CT scans of atherosclerosis and coronary artery calcium score, which is in concert with our findings.

The pragmatic design should increase the clinical relevance and external validity of the study and reduce potential sampling selection and observational biases. Furthermore, VIPVIZA aimed to promote adherence to both lifestyle changes and medication to improve clinical outcomes.[4] The factors that mediate or modulate cardiovascular disease prevention, such as psychological and demographic factors, will be explored in future

quantitative and qualitative studies. Formal cost-effectiveness analyses will be done after 3-year follow-up. Our preliminary experience is that the method for carotid vascular ultrasound that was applied in this study is a quick and inexpensive procedure that can be decentralised.[21] The compliance to prevention guidelines by health professionals determines to a great extent the effect of prevention of cardiovascular disease and should therefore be targeted, in addition to the individual's motivation and adherence. This dual target was an essential element of VIPVIZA. Importantly, the increase in use of lipid-lowering treatment in the intervention group indicates improved adherence to guidelines among physicians as well as patients. However, the effect size could have been affected by the setting, which was ordinary health care during a period with strong pressure on health-care centres due to many vacant positions. This setting might have delayed or precluded preventive actions. Therefore, our interpretation should be considered to be conservative.

FRS and SCORE were used as outcomes, because FRS is a long-established estimate of risk factor burden in the scientific literature and incorporates both fatal and non-fatal events, and SCORE is widely used in health care, particularly in Europe, but is limited to 10-year risk for fatal outcomes. There are several other risk estimation methods with different degrees of precision and benefit. Since beneficial effects were seen in individual components of the risk scores, similar effects with alternative risk scores would be expected to occur.

Several ethical issues were discussed with the Regional Ethical Review Board before the study. It was considered acceptable that the control group was not informed about ultrasound results because all participants received risk factor screening and cardiovascular disease prevention according to clinical guidelines. In addition, on the basis of comments from participants in a pilot study, the pictorial message was modified to present balanced information to avoid both extremes of exaggerated and indifferent responses. Furthermore, the phone call with a trained research nurse close to the pictorial information aimed at reassuring and giving more information when needed.

This study has some limitations. The dropout analyses showed some baseline differences in the intervention group between dropouts and participants at the 1-year evaluation regarding metabolic risk factors, which are known to be associated with lifestyle, education level, and age. However, the intervention effect on risk factor outcomes did not change after adjustment for age, sex, and education, suggesting that these differences are of minor importance, which was also corroborated by the intention-to treat and the sensitivity analyses.

Fast-developing vascular imaging technologies, such as CT and MRI, might outdate our findings with respect to precision of risk stratification. However, these technologies have higher costs and are not available on an equitable basis for the entire population, largely due to distance from specialised health-care centres, compared with risk communication by pictorial presentation with vascular ultrasound. In addition, CT scanning can add to radiation exposure.

This study provides evidence of the contributory role of pictorial presentation of silent atherosclerosis for prevention of cardiovascular disease. Furthermore, it is a low-intensity intervention that is valid for clinical practice. However, whether the effects, mediated through relevant pharmacological treatment and healthy lifestyle habits, are sustainable and lead to reduction of cardiovascular disease events will be determined in future long-term follow-up studies. If clinical event rates are reduced in the follow-up studies, this simple intervention could easily be applied in general practice in other similar settings. Our study supports further attempts to solve the major problem of prevention failure because of low adherence, despite effective, cost-effective, and evidence-based medications and methods for a healthier lifestyle.

Contributors

UN, NN, AL, EF, CG, HJ, BerntL, KL, SKN, MNord, SN, EN, JR, DV, LW, PWen, PWes, and MNorb designed and planned the study. UN and MNorb drafted the manuscript, NN did the statistical analysis, and all authors critically revised the manuscript, provided important content, and approved the final manuscript to be published.

Declaration of interests

We declare no competing interests.

Data sharing

Study protocol and several other sets of information are available at https://clinicaltrials.gov/ct2/show/NCT01849575. Furthermore, information will be available at the VIPVIZA website from December, 2018, or January, 2019. VIPVIZA is a study programme with a steering group, principal investigator, and co-principal investigator. We are interested in research collaboration with other groups in the field of prevention of cardiovascular disease, behaviour medicine, vascular ultrasound, and biomarkers, among others. Proposals of research based on data collected in the VIPVIZA study programme will be evaluated by the steering group at regular meetings. Criteria for approval are that the proposal does not interfere with other planned or ongoing studies, does not result in double publications of data, and is covered by the ethical approval, and that there are no conflicts of interest. Co-authorship with established researchers in the VIPVIZA study team is mandatory. A prerequisite for data sharing is that the integrity of the participants is guaranteed according to the conditions specified in VIPVIZA's research ethics approval. The proposal should describe background, research question, detailed description of statistical analyses, what kind of data will be used, and information about the researchers involved. After approval for research collaboration, de-identified participant data can be made available by the VIPVIZA database manager at the earliest when the 3-year follow-up of the study is complete during the autumn, 2019. This statement might later be revised by the steering group.

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