

## The Impact of CAROTid plaque Screening on Smoking (CAROSS) cessation and control of other cardiovascular risk factors: Rationale and design of a randomized controlled trial

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### ARTICLE INFO

#### Article history:

Received 19 December 2007

Accepted 3 March 2008

#### Keywords:

Atherosclerosis  
Smoking cessation  
Diagnostic techniques  
Cardiovascular  
Ultrasonography  
Health behavior  
Clinical trial

### ABSTRACT

**Background:** Screening tests for subclinical cardiovascular disease, such as markers of atherosclerosis, are increasingly used in clinical prevention to identify individuals at high cardiovascular risk. Being aware of these test results might also enhance patient motivation to change unhealthy behaviors but the effectiveness of such a screening strategy has been poorly studied.

**Methods:** The CAROTid plaque Screening trial on Smoking cessation (CAROSS) is a randomized controlled trial in 530 regular smokers aged 40–70 years to test the hypothesis that carotid plaque screening will influence smokers' behavior with an increased rate of smoking cessation (primary outcome) and an improved control of other cardiovascular risk factors (secondary outcomes) after 1-year follow-up. All smokers will receive a brief advice for smoking cessation, and will subsequently be randomly assigned to either the intervention group (with plaque screening) or the control group (without plaque screening). Carotid ultrasound will be conducted with a standard protocol. Smokers with at least one carotid plaque will receive pictures of their own plaques with a structured explanation on the general significance of plaques. To ensure equal contact conditions, smokers not undergoing ultrasound and those without plaque will receive a relevant explanation on the risks associated with tobacco smoking. Study outcomes will be compared between smokers randomized to plaque screening and smokers not submitted to plaque screening.

**Summary:** This will be the first trial to assess the impact of carotid plaque screening on 1-year smoking cessation rates and levels of control of other cardiovascular risk factors.

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In recent years, several tests for subclinical – asymptomatic – cardiovascular disease (CVD), ranging from serum and urinary markers to direct vascular imaging of atherosclerosis, have been proposed for improving the prevention of CVD [1–4]. Several of these interventions are widely used in clinical prevention [3], but their impact on improving cardiovascular risk factor control and other health outcomes has been poorly studied [1,3,5]. Further-

more, recommendations for the use of several of these markers in clinical practice are still controversial [5–7].

Being aware of test results of atherosclerosis might also enhance patients' motivation to change unhealthy behaviors [1] and subsequent risk factor levels, but this strategy has been poorly studied so far [5]. As smokers are known to underestimate their personal risks of smoking-related diseases [8], showing them evidence of their own atherosclerosis might be an efficacious strategy to enhance both their motivation for smoking cessation and control of other cardiovascular risk factors. A recent systematic review of biomedical risk assessment as an aid for smoking cessation (such as exhaled CO) [9]

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has shown that the only strategy with promising results was showing smokers pictures of their own atherosclerosis in one study [10] that was performed in smokers with low nicotine dependence. However, the authors of this review concluded that current evidence did not support the use of biomedical risk assessment for smoking cessation, as available data of sufficient quality were limited. Other studies using the presence of atherosclerosis as a motivational tool yielded conflicting results on smoking cessation and improvement of control of other cardiovascular risk factors [11,12].

To assess whether pictures of subclinical CVD, as measured by atherosclerotic plaques, has an effect on patients' behavior, we propose a randomized controlled trial to test the hypotheses that carotid plaque screening will i) improve rate of smoking cessation and ii) improve the control of other cardiovascular risk factors after 1-year follow-up. Our intent is to capture the “teachable moment” in those with plaques [12]. Similarly, acute events, such as acute myocardial infarction or coronary artery bypass surgery, have been shown to be very effective “teachable moments”, when smoking habits are particularly susceptible to intervention for smoking cessation [13,14]. This report describes the rationale and study design and baseline characteristics of the CAROSS trial.

## 1. Study objectives and design

### 1.1. Objectives

The first main objective of this trial (Clinicaltrials.gov: ID number NCT00548665) is to test the hypothesis that carotid plaque screening will improve rate of smoking cessation, as assessed by self-report and confirmed by exhaled carbon monoxide (CO) measured at each visit and cotinine concentration measured at the final visit [15]. The main outcome will be one-week point prevalence abstinence at 1 year (i.e. not having smoked and not having used other tobacco products in the preceding week of the last exam) and, as a secondary outcome, continuous abstinence from quit date to the end of the study, as described in the Russell Standard Criteria for smoking cessation trials [15]. We will also examine, as secondary endpoints, the one-week point prevalence abstinence at weeks 8 and 26 and prevalence of continuous abstinence between weeks 3 and 8 and between weeks 3 and 26, similar to a previous study [16].

The second main objective of the study is to test the hypothesis that carotid plaque screening will improve the control of the following cardiovascular risk factors: low-density lipoprotein cholesterol, hemoglobin A1C (if diabetes), high-sensitivity C-reactive protein (hs-CRP), blood pressure, and overall 10-year cardiovascular risk [12], as measured by the Framingham risk score. We hypothesize that patients' knowledge of these test results might enhance adherence to treatment [3] and enhance motivation for lifestyle change, with subsequent risk factor improvement.

### 1.2. Study design and follow-up

This study is a randomized controlled trial (RCT) of carotid plaque screening in 530 regular male and female smokers aged 40 to 70 years. Our protocol follows the revised CONSORT statement to conduct RCT [17] and Russell Standard criteria for smoking cessation trials [15]. This is a single-

centre study conducted at the Department of Ambulatory Care and Community Medicine at the University of Lausanne, Switzerland. The prevalence of smoking is high in Switzerland with one third (31%) of adults currently smoking [18], as compared to 22% in the United States, for example [19].

Smokers will be randomly assigned to either the group with carotid plaque screening or the control group without plaque screening (Fig. 1). Carotid ultrasound will be performed according to a standard protocol. Smokers with at least one plaque will receive 2 pictures of one of their plaques with a 7-min structured explanation on the general significance of plaques, as previously tested in a pilot study [20]. The tutorial informs smokers with plaques that their cardiovascular risk is increased in presence of atherosclerotic plaques. Smokers without plaques will receive a 7-min structured explanation on the risks associated with tobacco smoking. To ensure similar contact conditions, smokers randomized to the control group without ultrasound will also receive a brief advice for smoking cessation and a 7-min structured explanation on the risks associated with tobacco smoking. All tutorials highlight the benefits of smoking cessation on CVD, in particular that the risk of myocardial infarction decreases by half after 1 year of cessation and is equal to that of non-smoker 10 years after cessation [21]. Following the tutorial, patients' understanding of the significance of atherosclerosis is assessed through completion of a ten-question multiple-choice test [20]. All smokers will receive a brief advice for smoking cessation. Participants will be asked to set a quit date within the week following the ultrasound.

After the test results, participants of both groups will be followed during 1-year by a nurse trained in smoking cessation. At each visit, smokers will receive smoking cessation counseling and nicotine replacement therapy (NRT). At the 2nd visit, before randomization (Fig. 1), a resident will give results on cardiovascular risk factors, and provide recommendations based on guidelines for cardiovascular risk factor control [22–24]. Participants who have uncontrolled cardiovascular risk factors with a need for risk-reducing medications according to these guidelines will be referred to their own primary care physicians for management of these risk factors. Other participants with abnormal lipid or glucose levels according to current guidelines will receive advice for lifestyle modification. All outcomes, including smoking cessation, will be collected by a psychologist (outcome assessor). The psychologist and the nurse will be as much as possible blinded to the assigned group and ultrasound result. Study investigators will not be involved in the care of the participants. Participants will be blinded to the specific aims of the study, but will not be blinded to the assigned group and ultrasound result, as the ultrasound result is the potential motivational tool we will assess.

### 1.3. Rationale for the randomized trial

The effect of testing for subclinical CVD on patients' behavior and cardiovascular risk factor control has been poorly studied [1,5]. A previous randomized controlled trial (RCT) of our group has shown that providing smokers with pictures of their own atherosclerotic plaques improved smoking cessation in the Seychelles Islands with 17.6% in the screened group and 22.2% in smokers who had plaque vs.

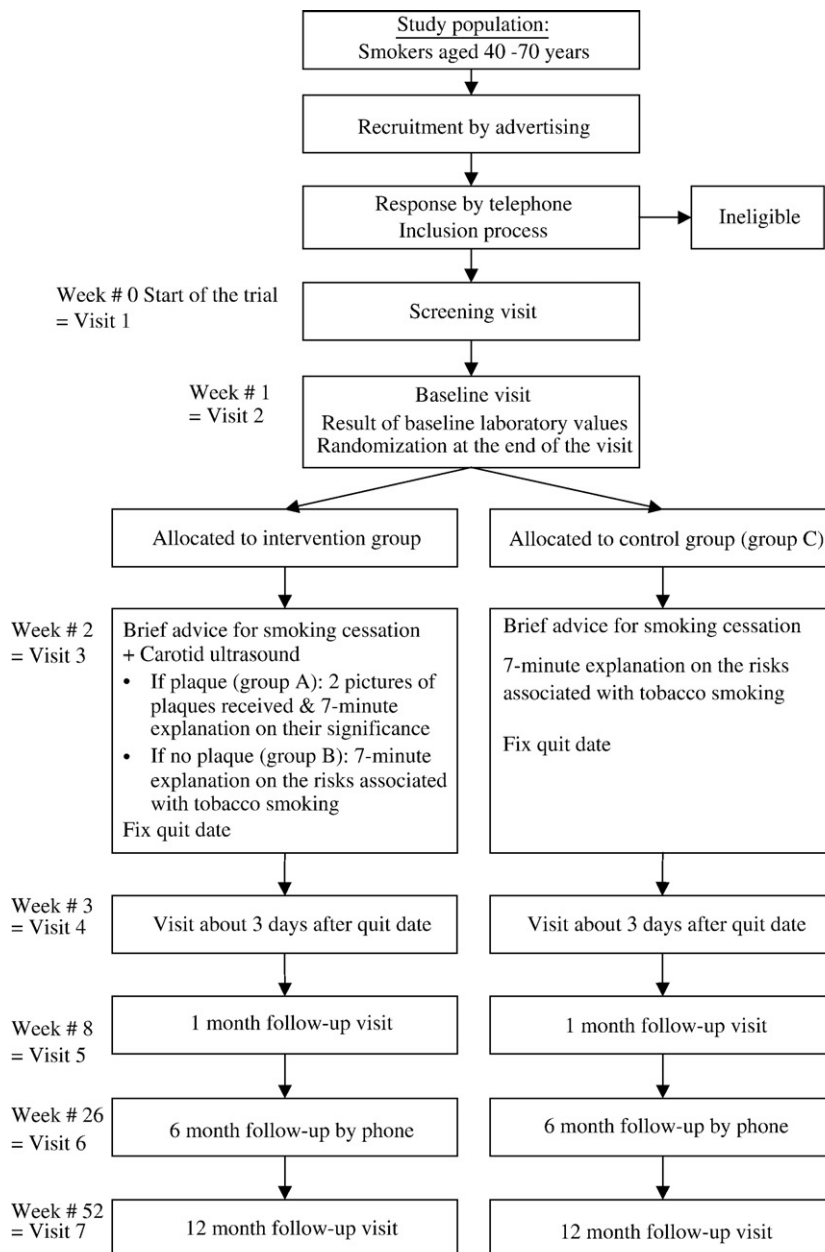


Fig. 1. Flowchart of the trial.

6.3% in the group without screening ( $p=0.03$  and  $0.003$ , respectively), in addition to a brief advice for smoking cessation provided to all smokers [10]. However, this study was performed in a population with low nicotine dependence, as shown by the low daily cigarette use (mean: 10 cigarettes/day, about twice as low as in Switzerland [25]). These results in Seychelles require confirmation in Western countries with higher cigarette consumption and should include a biochemical validation of smoking cessation, which was not performed in this study. To our knowledge, no other study on atherosclerotic plaque screening and adoption of risk-reducing behavior has been conducted so far.

The effect on behaviors of testing for subclinical CVD with other measurements than atherosclerotic plaques has also been poorly studied [1,5]. A systematic review for the U.S. Preventive Services Task Force identified only 2 studies that had examined the impact of EBCT to measure coronary artery calcification on subsequent risk-reducing behaviors [5]. In a retrospective survey, participants found to have coronary calcification were more likely to subsequently use aspirin (RR: 1.86), lipid-lowering medication (RR: 3.56), vitamin E (RR: 1.62), and to decrease consumption of dietary fat (RR: 1.58), after adjustment for demographic characteristics and cardiovascular risk factors, than those without calcification [26]. In

a survey of 144 active smokers who underwent screening for coronary calcification, patients with coronary calcification were more likely to perceive increased cardiovascular risk (42 vs. 13%;  $p < 0.01$ ) and 59% reported to be more motivated to quit smoking after the EBCT, but the presence of coronary calcification was not associated with smoking behavioral change [11]. However, these 2 studies were not randomized, and all behaviors were self-reported.

A RCT included 450 asymptomatic active-duty US Army personnel aged 39–45 years found that coronary calcification screening by EBCT did not lead to improved risk factor control, as measured by the Framingham Risk Score [12]. This study included relatively healthy, young adults (mean age: 42 years) with a low prevalence of smoking, other modifiable risk factors (mean Framingham Risk Score: 5% in 10 years) and coronary calcification (15%) [1]; this study yielded similar smoking cessation rates between both groups (5/13 vs. 4/17). A subgroup analysis showed that the motivating factor was presumably the presence of subclinical CVD, as those receiving information on calcification ( $n: 59/405 = 15\%$ ) had a trend toward smaller increase in absolute 10-year cardiovascular risk (0.21%; 95%CI:  $-0.97\%$  to  $1.39\%$ ) compared to those from whom information was withheld (1.52%; 95% CI:  $0.40\%$ – $2.63\%$ ,  $p = 0.13$ ) [12]. Another potential limitation of this trial was the  $2 \times 2$  factorial design with 2 interventions (information on calcification vs. no information; intensive vs. usual care) that may have had an effect on the same outcomes, which might bias the results toward the null hypothesis. The results of this trial also underline the need for additional research to assess the impact of other new tests of subclinical CVD, such as carotid ultrasound, and the importance to focus these future trials on higher risk patients [1].

In summary, testing for subclinical CVD might increase the rates of smoking cessation and cardiovascular risk factor control, but there are too few studies to enable solid conclusions. Additional trials are needed to assess the impact of subclinical CVD testing as a motivational tool [1,3].

#### 1.4. Rationale for using carotid ultrasound for subclinical CVD

There is no consensus on the best available method to assess subclinical CVD [3,4,27]. The large ongoing Multi-Ethnic Study of Atherosclerosis (MESA) will help to identify the noninvasive subclinical disease measures that best predict risk, but results will not be available before 2008 or even later [28]. Based on available data, the 2004 NHLBI Working Group on Subclinical Disease Testing concluded that the main candidates of subclinical CVD for identifying high-risk persons, and which deserve further future clinical trials, were carotid ultrasound to measure arterial wall and electron beam computed tomography (EBCT) to measure coronary artery calcification, because these tests appear to be best at identifying persons at higher risk and these 2 technologies are widely available [3]. However, no test for subclinical CVD has been definitely recommended for screening yet [4,6,7].

Carotid ultrasonography gives the opportunity to visualize the arterial wall, including intima-media thickness (IMT) and atherosclerotic plaques. Increased IMT has been associated with an increased risk of myocardial infarction and stroke [29,30]. Many studies found that these associations remained after adjustment for traditional risk factors [29,30]. Moreover,

ultrasonography is noninvasive and safe [27], as it does not produce ionizing radiation and has not been associated with adverse effects. While many prospective studies have focused on the role of IMT to predict the risk of CVD, several studies [30,31] have also assessed the role of atherosclerotic plaques measured by carotid ultrasound. Discrete plaques can be reliably detected and localized by scanning of the extracranial carotid arteries [27,30]. Several diameters for plaque sizes (maximum excursion into the vessel lumen) have been used in the literature [31], but a focal thickening of at least 50% greater than the surrounding wall is commonly used [30], including in the large Rotterdam Study, and is also recommended by the US Task Force on noninvasive atherosclerosis measurement [27], and the Mannheim Intima-Media Thickness Consensus [32]. Within the Rotterdam Study, a reproducibility study for plaques in the carotid artery on either side resulted in a kappa statistics of 0.67, indicating moderate agreement [30].

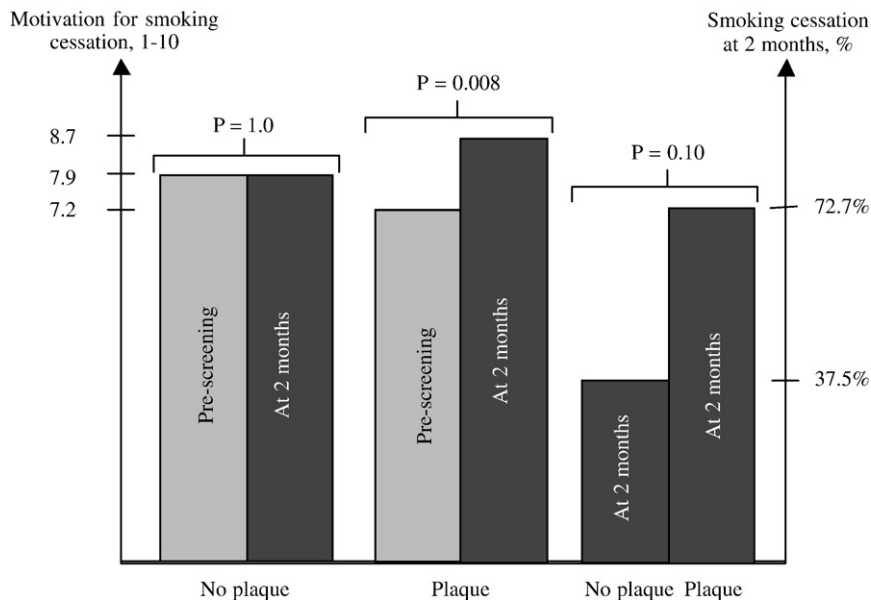
Several population-based studies have prospectively validated the predictive risk conveyed by carotid plaques on future cardiovascular events [30,31]. In 6389 participants of the Rotterdam Study, the presence of carotid plaques predicted myocardial infarction equally well as carotid IMT [30]. In a prospective study of 1288 Finnish men, the presence of  $\geq 1$  carotid plaque was associated with a 4.15-fold (95% confidence interval [CI], 1.51–11.47) increased risk of myocardial infarction, as compared to a 2.17-fold (CI 0.70–6.74) risk for IMT of 1.0 mm [31]. Although the best carotid measurement to predict future cardiovascular events is still subject to controversy, presence of carotid plaques is a categorical variable that might be useful in clinical practice as a decision aid to initiate either medications for primary prevention or behavioral change of unhealthy behaviors. In addition, patients may better understand the notion of atherosclerotic plaques, visualized on pictures, than the more abstract concept of high IMT, underlying a potential educational/motivational role of showing pictures in order to influence patients' behavior [1,10].

#### 1.5. Subjects

Smokers will be recruited from the general population by newspaper advertisements. Eligible smokers will be women and men aged 40–70 years with smoking of  $\geq 10$  cigarettes/day during the previous year, with no period of continuous smoking abstinence longer than 3 months in the past year [16]. We will exclude smokers with cardiovascular, life-threatening or psychiatric disease, currently using NRT or other pharmacological agents to quit smoking, those with current substance abuse (cannabis, other illicit drugs, alcohol abuse), recent carotid ultrasound ( $< 1$  year) to assess subclinical CVD, or difficulty to obtain good ultrasound imaging of the carotids (past radiotherapy or major surgery of the neck).

#### 1.6. Baseline assessment

We will assess motivation to change, based on visual 10-item ladder scores (from 1 to 10) to measure stage of change for smoking cessation, diet, physical activity and general health improvement [12]. We will also collect data on medical



**Fig. 2.** Smoking outcomes in the pilot study ( $n=30$ ). Between baseline and 2 months after plaque screening, motivation for smoking cessation increased (from 7.4 to 8.4/10,  $p=0.02$ ), particularly in smokers with plaques (7.2 to 8.7,  $p=0.008$ ). At 2 months, smoking quit rate was 63%, with a quit rate of 73% in smokers with plaques vs. 38% in smokers without plaques ( $p=0.10$ ).

and smoking history, home and work smoking environment, education, medication use, and measure weight, height, blood pressure, fasting glucose and lipids. For potential harms of screening, we will assess stress, with the 4-item Perceived Stress Scale [33], quality of life by the SF-36 and depression by the Beck Depression Inventory [34].

### 1.7. Carotid ultrasound protocol

B-mode ultrasonography (Vingmed 5; General Electric, Wisconsin, US) will be performed by a trained observer blinded to clinical information. Carotid plaques will be defined as a focal widening >50% relative to adjacent segment, as recommended by the US Task Force on noninvasive atherosclerosis measurement [27] and as defined in the Rotterdam Study [30]. Although the best carotid measurement to predict future cardiovascular events is subject to controversy [27], as described above, presence of carotid plaques is a dichotomized variable that might be easily understood by the patients and potentially useful to motivate for behavioral change.

### 1.8. Pilot study

We recruited 30 regular smokers, aged 40–70 years, by newspaper advertising, and performed a 2-month observational pre-post pilot study to assess the feasibility and optimal processes of studying the impact of carotid atherosclerotic plaque screening [20]. Briefly, all smokers underwent smoking cessation counseling, nicotine replacement therapy, a carotid ultrasound, an educational tutorial on atherosclerosis (as described above), baseline and 2-month psychological and motivation to change assessment, and assessment of smoking cessation and atherosclerosis knowledge at 2 months. Participants had a mean (SD) duration of smoking of 34 (7) years, with a consumption of 22 (9) cigarettes/day. Carotid plaques

were present in 22 smokers (73%). Between baseline and 2 months after plaque screening, motivation for smoking cessation increased, particularly in those with plaques (Fig. 2). At 2 months, smoking quit rate was 63%, with a pattern of a higher quit rate in those with plaques vs. in those without plaques (73% vs. 38%,  $p=0.10$ ). 96% responded correctly to  $\geq 80\%$  of questions regarding atherosclerosis knowledge at baseline and 2 months. This pilot study has shown that enrolling smokers for this study was effective and that carotid plaque screening is feasible and appears to increase motivation for smoking cessation.

## 2. Planned analyses

Data analysis for the primary research question of the rates of smoking cessation at 1 year will be addressed by comparing these rates using a chi-square test. We will compare smoking cessation in patients randomized to plaque screening to those without plaque screening and perform subgroup analyses, as described in Table 1. Our primary analysis will be intention-to-treat (or “intention-to-screen analysis”), in which all measurements will be included and the participants will be analyzed according to their original randomized group, unless they have died to an untraceable address [15]. Participants who are lost during follow-up will be considered as persistent

**Table 1**  
Planned analysis: comparisons among groups

Groups to be compared
Main intention-to-treat analysis
1 Plaque screening vs. no plaque screening (group A+B vs. C from Fig. 1)
Subgroup analyses
2 Those with plaque vs. no plaque screening (group A vs. C from Fig. 1)
3 Those with plaque vs. those w/o plaque (group A vs. B from Fig. 1)

smokers. However, our goal will be to obtain full follow-up data on all randomized participants.

For sample size estimation, the primary hypothesis of this trial is that atherosclerotic plaque screening would influence patients' behavior, in particular increase the rate of smoking cessation. Based on the results of a previous RCT in a population with low nicotine dependence, plaque screening resulted in higher smoking cessation rates at 6 months with 17.6% in the screened group and 22.2% in those with plaques vs. 6.3% in the group without screening [10]. We might also assume that the smoking cessation rate would be higher in our control group than in the study by Bovet et al. [10], because of repeated counseling sessions at each visit performed by a nurse trained in smoking cessation. About 10% of smokers stopped smoking in the control groups of trials of nicotine replacement [35]. Based on the study by Bovet et al. described above [10] and accounting for the different setting, we might estimate that the rates of smoking cessation would be 20% at 1 year in the screened group. The doubling in the rate of smoking cessation is a conservative assumption, as compared to the about 3-fold increased rate in the study by Bovet et al. [10]. In addition, smokers in the previous trial were randomly selected from the general population (i.e. they were not necessary ready to change or not even thinking of it), a contrast with our current study where only volunteers will be selected. However, it is difficult to predict the effectiveness of our intervention from a low (previous trial) to high (current trial) nicotine dependence setting. A doubling would already be highly relevant from a clinical and public health perspective, and potentially cost-effective, as it would be similar to the results of pharmacotherapy for tobacco dependence, which approximately double the 1-year rates of abstinence in RCTs [36]. Setting a 2-sided alpha of 0.05 and a power of 80%, we need to include 219 smokers per group and a total of 438 smokers to find a similar effect size in those screened vs. not screened. To account for potential dropouts, we have conservatively assumed a 20% loss to follow-up, and will increase our sample size by 20% to 526 smokers. Therefore, we plan to recruit a total of 530 smokers. Two previous studies on the effectiveness of subclinical CVD screening found a 10% and 1% dropout rates respectively [10,12].

Data analysis for the secondary research questions of the changes in LDL-cholesterol, HbA1c (if diabetes), and blood pressure levels from baseline to the 1-year visit between the screened group and the group without screening will be addressed by comparing the mean changes in these cardiovascular risk factors using two-sample *t*-tests. Because the distribution of hs-CRP levels is skewed, median change in hs-CRP levels will be compared with the Wilcoxon rank-sum test. Our primary analysis will be intention-to-treat, regardless of compliance.

### 3. Discussion

Given the burden of illness due to CVD [37], particularly that related to tobacco smoking [38], there is a need to develop new strategies to improve the primary prevention of CVD. Despite overwhelming evidence on the role of major cardiovascular risk factors to predict future cardiovascular events [39,40] and the proven benefits of treating them [22,23,36],

cardiovascular risk factors remain elevated in a large majority of the population [41]. The AHA Prevention V Conference suggested the potential for more routine use of office-based risk assessment for initial risk stratification [42]. The use of tests to assess subclinical CVD might provide useful information not only to improve risk prediction, but also to better motivate patients to change unhealthy behaviors, such as smoking [10] and/or compliance to treatment, and subsequently improve control of other risk factors [1]. The use of these tests for such purposes is widely practiced, but their effectiveness has been poorly studied [1,5]. Moreover, most new technologies, which are often expensive, never undergo formal evaluation, prior to being implemented within the standard of care [12]. Techniques to assess subclinical CVD are promising tools [2], but a thorough evaluation is needed prior to being implemented within the standard of care.

Plaque screening, if effective, might be a useful strategy to enhance smoking cessation and improve cardiovascular risk factor control. In addition, such an intervention could be potentially very cost-effective. The cost of years of living gained using NRT is particularly low compared to interventions on other risk factors (at largely less than \$ 10,000/year of life gained) [43], and cost-effectiveness of similar magnitude might be expected if carotid ultrasound screening is effective to improve smoking cessation, particularly if control of other cardiovascular risk factors is also improved by carotid screening.

If testing is not an effective tool for cessation and/or control of other risk factors, such testing might represent an important waste of expenditure [3], and healthcare expenditures should be used for other strategies for smoking cessation and cardiovascular risk factor control.

This trial will fill an important gap in knowledge by assessing whether plaque screening improves 1-year smoking cessation rates and control of other cardiovascular risk factors.

### Acknowledgments

This trial is supported by research grants from the Swiss National Science Foundation (SNSF 3200B0-116097) and the Swiss Heart Foundation.

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