Atherosclerosis Screening by Noninvasive Imaging for Cardiovascular Prevention: A Systematic Review

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BACKGROUND: Noninvasive imaging of atherosclerosis is being increasingly used in clinical practice, with some experts recommending to screen all healthy adults for atherosclerosis and some jurisdictions mandating insurance coverage for atherosclerosis screening. Data on the impact of such screening have not been systematically synthesized.

OBJECTIVES: We aimed to assess whether atherosclerosis screening improves cardiovascular risk factors (CVRF) and clinical outcomes.

DESIGN: This study is a systematic review.

DATA SOURCES: We searched MEDLINE and the Cochrane Clinical Trial Register without language restrictions.

STUDY ELIGIBILITY CRITERIA: We included studies examining the impact of atherosclerosis screening with noninvasive imaging (e.g., carotid ultrasound, coronary calcification) on CVRF, cardiovascular events, or mortality in adults without cardiovascular disease.

RESULTS: We identified four randomized controlled trials (RCT, n=709) and eight non-randomized studies comparing participants with evidence of atherosclerosis on screening to those without (n=2,994). In RCTs, atherosclerosis screening did not improve CVRF, but smoking cessation rates increased (18% vs. 6%, p=0.03) in one RCT. Non-randomized studies found improvements in several intermediate outcomes, such as increased motivation to change lifestyle and increased perception of cardiovascular risk. However, such data were conflicting and limited by the lack of a randomized control group. No studies examined the impact of screening on cardiovascular events or mortality. Heterogeneity in screening methods and studied outcomes did not permit pooling of results.

CONCLUSION: Available evidence about atherosclerosis screening is limited, with mixed results on CVRF control, increased smoking cessation in one RCT, and no data on cardiovascular events. Such screening should be validated by large clinical trials before widespread use.

Previous presentation: Preliminary results were presented at the SGIM 33rd Annual Meeting, April 2010, in Minneapolis.

Received May 13, 2011
Revised July 28, 2011
Accepted August 5, 2011
Published online September 1, 2011

KEY WORDS: atherosclerosis; diagnostic techniques; cardiovascular; coronary disease; health behavior; smoking cessation; clinical trial; systematic review.

J Gen Intern Med 27(2):220–31
DOI: 10.1007/s11606-011-1833-3

BACKGROUND

Several techniques of noninvasive vascular imaging have been proposed in recent years as tools for detecting asymptomatic atherosclerosis without overt cardiovascular disease (CVD).[1–3] Some measures of atherosclerosis have been shown to improve the prediction of coronary heart disease (CHD) events.[4–7] However, good prediction does not necessarily lead to effective prevention.[8,9] Among the important criteria to assess their potential clinical value, novel markers of cardiovascular risk should be assessed by their effect on patient management and outcomes.[10]

Screening for atherosclerosis and knowing the test result might help enhance patient motivation to change unhealthy behaviors,[11,12] such as smoking, or improve lifestyle and adherence to medications. In 2003, a review for the U.S. Preventive Services Task Force (USPSTF) identified only two studies that examined the impact of coronary artery calcification [CAC, by computed tomography (CT)] screening on risk-reducing behaviors.[13] These two studies were not randomized,[14,15] and behavior outcomes were self-reported. Since this publication, new studies[16–18] or studies with other screening techniques[11] have been published.

A substantial amount of controversy remains about the role of screening for atherosclerosis in the clinical setting.[19] Some groups have suggested that imaging should be considered only in certain subgroups of patients, while others advocate a more widespread application (Table 1). Some experts have even suggested screening most healthy adults for atherosclerosis.[3] Such screening is being increasingly used in clinical practice to screen asymptomatic adults.[12,13,20–22] Moreover, insurance coverage for atherosclerosis screening with carotid ultrasound is under consideration;[23] the Texas Legislature passed a new law, effective Jan 1, 2010, mandating broad insurance coverage for atherosclerosis screening, which could lead to a considerable increase in screening.[19] Therefore, a systematic review was performed to assess whether screening for athero-

Table 1. Recommendations on Screening for Atherosclerosis in Asymptomatic Adults

Organization, publication year	Imaging method	Screening recommendation per group
Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III), 2002[53]	CAC	Persons with no CVRFs: Not recommended CAC is an option for advanced risk assessment in appropriately selected persons Multiple CVRFs: High CAC score provides a rationale for intensified LDL-lowering therapy Elderly: High CAC score could help decide to introduce LDL-lowering drugs for primary prevention
American Diabetes Association, 2003[54]	ABI	ABI should be performed in diabetics >50 years. If normal, ABI to be repeated every 5 years ABI should be considered in diabetics <50 years if other PAD risk factors (e.g., smoking, hypertension, hyperlipidemia, or duration of diabetes >10 years)
International Task Force for Prevention of Coronary Heart Disease, 2005[55]	CAC and carotid ultrasound	CAC recommended in most persons. Lowering of target LDL-cholesterol according to results of screening
Society of Heart Attack Prevention and Eradication (SHAPE), 2006[3*]	CAC and carotid ultrasound	Screening every 5 years all men aged 45–75 years and women aged 55–75 years who have at least one CVRF
ACC/AHA 2005 guidelines for the management of patients with peripheral arterial disease, 2006[56]	ABI	Detection of asymptomatic lower extremity PAD should be identified by examination and/or measurement of the ABI (class I recommendation, Level of evidence: B)[†]
Joint Task Force of the European Society of Cardiology and other societies on cardiovascular disease prevention in clinical practice, 2007[57]	CAC	Intermediate-risk persons[‡] can be useful to target treatment
	MRI	Not enough evidence to recommend use to detect coronary artery stenoses
	Carotid ultrasound	Carotid ultrasound can add information beyond assessment of traditional risk factors, which may help make decisions about medical therapy for primary prevention. Uncertainty regarding formal incorporation into existing algorithms used in asymptomatic persons
U.S. Preventive Services Task Force (USPSTF), 2009[49]	CAC, ABI, carotid ultrasound	Not enough evidence to determine the balance between benefits and harms of using non-traditional risk factors for CHD risk assessment (I Statement: insufficient evidence)[‡]
2010 ACCF/AHA Guideline for Assessment of Cardiovascular Risk in Asymptomatic Adults, 2010[48‖]	Carotid ultrasound and ABI	Measurement may be reasonable in intermediate-risk adults[§] (class IIa Recommendation, Level of evidence: B)[†]
	CAC	Measurement may be reasonable in intermediate-risk adults and in diabetics ≥40 years (class IIa Recommendation, Level of evidence: B)[†] Measurement might be reasonable in low- to intermediate-risk adults[‡] (6–10% 10-year risk; class IIb Recommendation, Level of evidence: B)[†]
	Angio CT	Persons at low risk (<6% 10-year risk) should not undergo CAC measurement (class III—no benefit Recommendation, Level of evidence: B)
Working Group on Nuclear Cardiology and Cardiac CT of the European Society of Cardiology, 2010[58]	CAC	CAC should be considered in intermediate-risk adults: high calcium scores identify subjects at high risk who may benefit from aggressive secondary prevention strategies Coronary CT angiography currently not recommended as a screening tool in asymptomatic adults
ACCF/SCCT/ACR/AHA/ASE/ASNC/NASCI/SCAI/SCMR Appropriate Use Criteria for Cardiac Computed Tomography 2010[59]	CAC	Appropriateness[¶] according to CHD risk[§] Low-risk persons: Inappropriate Intermediate-risk persons: Appropriate High-risk persons: Uncertain Low-risk persons with family history of premature CHD: Appropriate
	Angio CT	Low-risk persons: Inappropriate Intermediate-risk persons: Inappropriate High-risk persons: Uncertain

CVD cardiovascular disease, CHD coronary heart disease, ABI ankle–brachial index, CVRF cardiovascular risk factor, EBCT electron beam computer tomography, CAC coronary artery calcification, PAD peripheral artery disease, ACC American College of Cardiology, ACCF American College of Cardiology Foundation, AHA American Heart Association, SCCT Society of Cardiovascular Computed Tomography, ACR American College of Radiology, ASE American Society of Echocardiography, ASNC the American Society of Nuclear Cardiology, NASCI North American Society for Cardiovascular Imaging, SCAI Society for Cardiovascular Angiography and Interventions, SCMR Society for Cardiovascular Magnetic Resonance

[*] *The SHAPE Task Force has issued a press release, reacting to the new ACCF/AHA 2010 guidelines for Assessment of Cardiovascular Risk in Asymptomatic Adults coronary, stating that: CIMT or CACS are recommended for intermediate-risk adults aged 45–80 and men ≥35 with diabetes or have family history of premature coronary disease, and to be repeated every 3–5 years, depending on risk level assessed at the first test*[60]

[†] *Classification of recommendations and Level of Evidence according to ACC/AHA Guideline Writing Committees*

[‡] *Grades of recommendations according to the USPSTF*

[§] *Low CHD risk: 10-year absolute CHD risk <10%. Intermediate CHD risk: 10-year CHD risk 10–20%. Among women and younger men, an expanded intermediate risk of 6–20% may be appropriate. High CHD risk: presence of diabetes mellitus in a patient ≥40 years, peripheral arterial disease or other coronary risk equivalents, or the 10-year absolute CHD risk >20%*

[‖] *The ACC/AHA made these recommendations, recognizing the absence of current evidence for improved net health outcomes: no evidence is available to show that risk assessment using atherosclerosis screening improves clinical outcomes by reducing mortality or morbidity from CAD*[48]

[¶] *Appropriate test: generally acceptable and a reasonable approach for the indication. Uncertain test for specific indication: generally acceptable and may be a reasonable approach for the indication. Inappropriate test for specific indication: not generally acceptable and not a reasonable approach for the indication*

sclerosis improves cardiovascular risk factors (CVRF) and clinical outcomes.

METHODS

Study Selection

Studies had to meet four inclusion criteria: (1) the study population had to be adults without preexisting CVD [myocardial infarction, stroke, transient ischemic attack, or peripheral arterial disease (PAD)]; (2) imaging of atherosclerosis had to be done by noninvasive techniques,[20] such as ultrasonography (carotid intima–media thickness or carotid plaques), conventional abdominal radiography (aortic calcifications), CT (CAC), ankle/brachial index (ABI), or flow-mediated brachial artery endothelial vasodilatation to assess endothelial dysfunction; (3) studies had to report follow-up clinical events, such as all-cause or cardiovascular (CV) mortality, acute coronary syndrome (ACS), stroke, documented PAD, or intermediate clinical outcomes, such as CVRF control (smoking cessation, blood lipid control, diet change, weight reduction, or physical activity improvement) or changes in health behavior (e.g., increased motivation to change lifestyle, increased perception of cardiovascular risk, adherence to medication); and (4) the intervention group had to be compared with a control group of adults who did not receive the screening intervention (randomized controlled trials, RCTs) or a control group who did not have evidence of atherosclerosis upon screening, as reported in available non-randomized studies; these non-randomized studies did not report comparisons with a control group of adults who were not screened for markers of atherosclerosis. The search strategy was not limited to RCTs because of the likely low numbers of such studies[13] and to assess whether observational studies showed patterns that might be consistent with potential impact of atherosclerosis screening. Studies that assessed the impact of surgical procedures (e.g., screening for aortic aneurysm followed by surgery) were excluded. The numerous studies that assessed risk prediction of atherosclerosis markers[5] or that assessed cardiac stress imaging tests were not included as such studies have been previously reviewed.[24–27] We did not include studies that only examined changes in prescription rates of CV preventive medications (e.g., aspirin, statins) after atherosclerosis screening since prescription rates are mainly related to physicians' decisions; the aim of the present systematic review was to assess whether the results of screening given to patients lead to increased motivation[12] (e.g., lifestyle changes, adherence rates to CV preventive medication), with subsequent improvement in CVRF control and clinical outcomes. If follow-up outcomes other than prescription rates were reported, such studies were not excluded.

Outcomes

The primary outcomes were clinical events, such as all-cause and CV mortality, ACS, stroke, documented PAD, or a change in CVRF control at follow-up (i.e., differences in smoking cessation rates, lipid, and blood pressure changes). Secondary outcomes were modification in adherence rates to CV preventive medication, risk perception of developing heart disease, quality of life, and changes in health behavior (e.g., increased motivation to change lifestyle, physical activity, diet).

Search Strategy

MEDLINE (1966 through April 2009) and the Cochrane Controlled Clinical Trial register (1996 through April 2009) were searched using a recommended approach for systematic reviews of RCTs with a predefined search strategy.[28] All languages were considered eligible. For MEDLINE, three comprehensive search themes were combined using the Boolean operator "and." The first theme representing the patient population of interest was created using the following terms which appeared as exploded MeSH headings—CV diseases/prevention and control—or as text words—coronary or aortic or aorta. The second theme for the screening method of interest used the following terms—magnetic resonance angiography or radiography, abdominal or radiography, thoracic or tomography, x-ray, computed or ultrasonography, or ankle/blood supply or brachial artery/blood supply—or the terms appearing as text words—computed tomography or ultrasonography or ankle–brachial index, or flow-mediated vasodilatation. The third theme, which defined the outcome of interest, was created using the exploded MeSH headings: counseling or preventive health services or motivation or behavior, including smoking cessation, as well as coronary disease and mortality for RCTs. For the Cochrane Controlled Clinical Trial register, a similar search strategy used text words, for which the comprehensive search themes "patient population," "screening method," and "studied outcome" were combined using the Boolean term "and."

Data Extraction and Quality Assessment

In a two-step selection process, two investigators (RA and VdB) independently reviewed the titles and abstracts of all citations to identify studies meeting the inclusion criteria. When in doubt about eligibility on the first screen, full-text articles were obtained. Articles selected by either both or only one author were selected for full-text review. In addition, one investigator (RA) screened the reference list of identified studies on the first screen and major reviews on the topic for other potentially relevant studies.[12,13,29–31] The same two investigators reviewed the relevant reports in full text for eligibility and independently extracted data from all studies fulfilling eligibility criteria. Data extraction included characteristics of the screening intervention, type of study, baseline clinical characteristics of the participants, and relevant outcomes. Authors of the studies were contacted for additional information when needed.[32]

Study design was considered as the primary study quality measure;[33] studies with a control group that did not receive the screening intervention (RCTs) were considered stronger than those with a control group that had the screening intervention but did not present evidence of atherosclerosis (non-randomized studies). For the RCTs, the Jadad quality

score was reported, adapting it to the present situation;[34] blinding of study participants to intervention was not included as this is difficult to achieve in studies of lifestyle interventions. Items used to assess study quality were: methods of randomization (two points) and reporting of losses to follow-up (one point), thus leading to a maximum score of three points.

Statistical Analysis

A flowchart summarized the number of trials identified, excluded and included. Due to major variations in both screening methods and studied outcomes, the results were not combined in a meta-analysis and only individual study results were reported.

RESULTS

A total of 2,634 unique citations were identified, including 1,783 from MEDLINE and 851 additional from the Cochrane Controlled Clinical Trial register (Fig. 1). After a two-step screening process, 12 articles fulfilled the inclusion criteria.[11,14–18,32,35–39] Using the abstract and title on the first screen, 13 disagreements concerning eligibility for a full-text review occurred between the two reviewers (kappa=0.81). For the second screen, which was based on the full-text review of 41 studies, there was one disagreement (kappa=0.94). This disagreement was resolved by consensus.

RCTs Comparing Participants Randomized to Atherosclerosis Screening

Four RCTs included a total of 709 participants.[11,16,32,35] Heterogeneity in screening methods and the studied outcomes did not allow pooling of results or description of overall results. Semiquantitative assessments of the study results are described in Table 2. No RCTs examined the impact of screening on CV events or mortality. Overall, screening for atherosclerosis did not improve CVRF, except for increased smoking cessation rates (18% vs. 6%, p=0.03) in one RCT;[11] other RCTs included only few smokers (Table 3). Two RCTs found no improvement on quality of life.

RCT of Carotid Ultrasound by Bovet et al.[11]. In 153 smokers randomly allocated to carotid ultrasound, providing pictures of their own atherosclerotic plaques improved the rates of smoking cessation from 18% in the screened group vs. 6% in the group without screening (p=0.03, Table 3) in addition to brief advice for smoking cessation. The absence of biochemical validation of smoking cessation was the major limitation of this trial. It was undertaken in the Seychelles islands, in a population with low

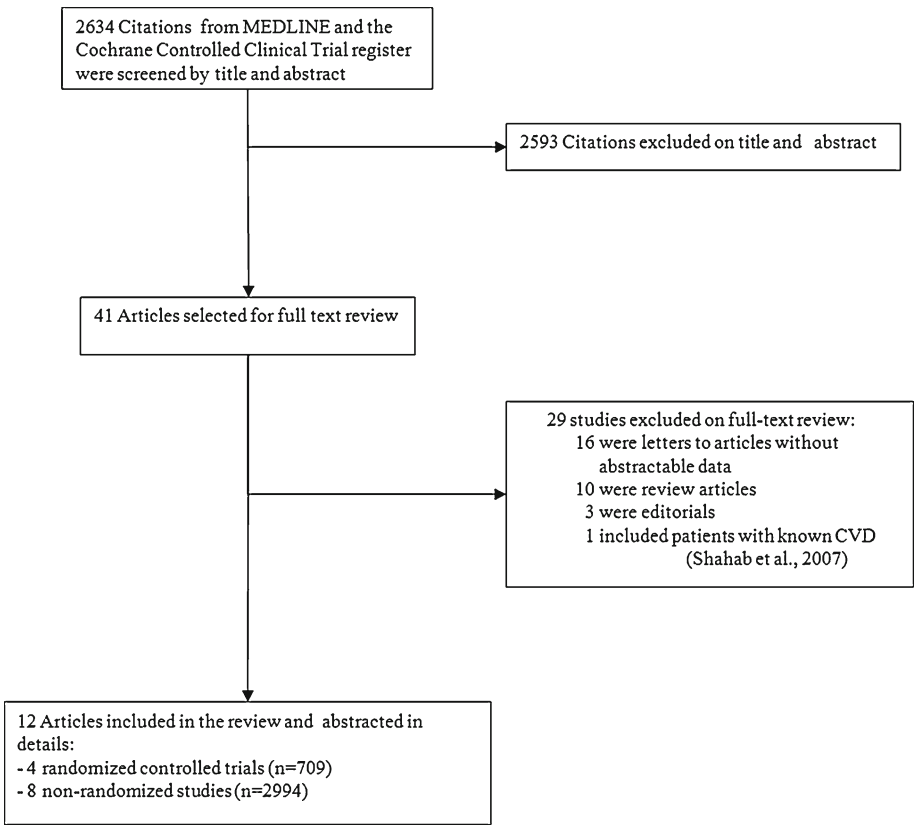

Figure. 1. Flowchart of included studies. ***CVD*** **cardiovascular disease.**

Table 2. Semiquantitative Assessment of Study Results

Study	Imaging method	Smoking cessation		Risk perception of developing heart disease	Improvement in			Motivation to make lifestyle changes	Quality of life	Clinical cardiovascular outcomes (CVD, CHD), or mortality
		Effect on cessation/No. (%) of smokers	Motivation for smoking cessation		Diet	Physical activity	Blood lipids			
Randomized controlled trials										
Bovet et al. (2002)[11]	Ultrasound	++ 153 (100%)								
O'Malley et al. (2003)[16]	EBCT	↔ 30 (7%)			↔	↔	↔	↔	↔	
Lederman et al. (2007)[35]	DHCT	↔ 2 (4%)			↔		–			
Obuchowski et al. (2007)[32]	EBCT								↔	
Non-randomized studies										
Wong et al. (1996)[15]	EBCT	↔ (% NR)			++	↔				
OMalley et al. (2002)[14]	EBCT	↔ 99 (100%)	↔	++						
Kalia et al. (2006)[17]	EBCT	↔ 53 (10%)			++	↔				–*
Sandwell et al. (2006)[39]	EBCT			++	++	↔	++			
Wyman et al. (2007)[18]	EBCT			++				↔		
Korcarz et al. (2008)[37]	Ultrasound			++				++		
Orakzai et al. (2008)[38]	EBCT				++	++				–*
Rodondi et al. (2008)[36]	Ultrasound	↔ 30 (100%)	+†					++		

Detailed results are provided in Tables 3 and 4

CAC coronary artery calcification, DHCT double helical computed tomography, CHD coronary heart disease, CVD cardiovascular disease, EBCT electron beam computer tomography, ↔ No change, ++ increase or improvement, – less controlled, % NR % of smokers not reported

**Exclusion of participants with clinical outcomes*

†Pattern of higher quit rates compared to those without plaques (73% vs. 38%, p=0.10)

nicotine dependence (mean: ten cigarettes/day, about half the amount as in Western countries). No other RCTs that evaluated the effect of carotid ultrasound atherosclerotic plaque screening on risk-reducing behavior were found.

RCT of CT by O'Malley et al.[16]. This RCT included 450 asymptomatic active-duty US Army personnel aged 39–45 years.[16] CAC screening by CT did not lead to improved CVRF control or change in the Framingham Risk Score (Table 3). This study has the highest Jadad quality score (3/3). Screening had little effect on smoking rates (5/13 in intervention vs. 4/17 in the control group), but few smokers were randomized. Among its limitations, the study participants were young adults with a low 10-year CHD risk of 6% and a low prevalence of CAC (15%).[12]

A subgroup analysis showed that the presence of coronary calcifications ("risk marker") might be a motivating factor. Among those with CAC (n=59), those who learned that they had calcifications had a smaller, albeit non-statistically significant, increase in the 10-year Framingham Risk Score compared with those who did not receive such information (0.21% vs. 1.52% increase in risk score, p=0.13).[16] Another potential limitation of this trial was the 2×2 factorial design with two interventions (information on calcification vs. no information intensive vs. usual care) as this may have had an effect on the same outcomes; this might have biased the results toward the null hypothesis.[40]

RCT of CT by Lederman et al.[35]. This study of 56 postmenopausal women randomized to either CAC screening plus a counseling session or the control group (conventional counseling) found that the intervention CT group had less improvement in LDL-cholesterol compared with the control group (Table 3). The high proportion of women with low CAC score (mean score=1.37) might partly explain the results as these women screened for CAC might have been reassured that they were not at high risk of CHD.

RCT of Total Body Scan by Obuchowski et al.[32]. In a pilot study, 50 white adults self-referred from advertisements were randomized to total body scan with CAC screening or no screening and followed for 2 years. Among 3 of the 25 screened subjects who had a CAC score ≥100, cardiac catheterization showed three-vessel occlusive disease in one patient who subsequently underwent coronary bypass grafting; the two others had normal cardiac stress testing and no clinical events. No other participant had clinical events during follow-up, but the small sample size limits the interpretation of the results. Self-reported quality of life measured by the SF-36 did not differ between screened and control subjects over time,

Table 3. Characteristics of Randomized Controlled Trials Included in the Systematic Review

Source	Jadad quality score*	Participants, no. (% men)	Mean age (range, years)	Intervention/ screening method	Description of lesion (% screened with lesion)	Follow-up	Outcomes	Comments
Bovet et al. 2002[11]	3	153 (85)	46 (25–64)	US of carotid and femoral arteries vs. no US	Atheromatous plaques† (73)	6 month	With screening, increased smoking cessation rates (18% vs. 6%, p=0.03). Increased smoking cessation rates in those screened with plaques compared to those without (22% vs. 5%, p=0.003).	All smokers albeit low nicotine dependence (mean 10 cigarettes/ day); no biochemical validation of smoking cessation (self-report); no measure of the impact on other CV risk factors or other behavioral changes
O'Malley et al. 2003[16]	3	450 (79)	42 (39–45)	EBCT results given vs. EBCT results withheld	CAC‡ (15)	1 year	With screening and results given, no change in the 10 year Framingham Risk Score (+0.30% vs. +0.36%, p=0.80). With calcifications on CT (n=59) and results given smaller increase in risk (+0.21% vs. +1.52%, p=0.13). No effect on anxiety score for the two groups	Predominantly male military population, overall low 10-year CHD risk (5.8%); few smokers (n=30, 7%)
Lederman et al. 2007[35]	3	56 (0)	64 (55–75)	DHCT vs. no DHCT	CAC§ (27)	1 years	In CT group, less improvement in LDL-C: 1.15±26.80 vs. −17.43±29.18 mg/dL (p<0.05)	Only postmenopausal women recruited from a single clinical facility; very few smokers (n=2); interpretation of the images of their coronary arteries received from a radiologist
Obuchowski et al. 2007[32]	2	50 (50)	NA (45–68)	TBS vs. no TBS	CAC‖ (12)	2 years	Incidence of clinical symptomatic disease: three participants found to have CAC score ≥100, one subsequently underwent CABG	Pilot study; not able to differentiate specific effect of coronary screening from the screening of other body parts; no CVRF outcomes evaluated

US ultrasound, CV cardiovascular, EBCT electron beam computed tomography, CAC coronary artery calcification, DHCT double helical computed tomography, LDL-C low-density lipoprotein cholesterol, BP blood pressure, NA not available from manuscript, TBS total body scan, CAD coronary artery disease, CABG coronary artery bypass graft

**Jadad scores range from 0 to 5 with higher scores indicating better methodological quality. Items considered were: methods of randomization (two points) and reporting of losses to follow-up (one point), thus leading to a maximum score of three points for study quality. We did not include "blinding of study participants to intervention" as this is difficult to achieve in lifestyle intervention studies. Adapted from Jadad et al.[34]*

†Defined as a focal wall thickening of ≥1 mm

‡CAC score>0 considered significant (using the Agatston scoring method)[61]

§CAC score≥10 considered significant

‖CAC score≥100 considered significant

except for one of the eight subscales (fewer role limitation due to physical health problem in screened subjects).

Non-randomized Studies with a Control Group Without Evidence of Atherosclerosis at Screening

Two thousand nine hundred ninety-four participants were included in eight non-randomized prospective or retrospective studies comparing participants with evidence of atherosclerosis on screening to those without (Table 4). No studies examined the impact of screening on CV events or mortality or on quality of life. These studies assessed the impact of atherosclerosis screening on patient behaviors and CVRFs. Heterogeneity in screening methods and studied outcomes did not permit pooling of results. Semiquantitative and detailed assessments of the study results are described in Tables 2 and 4. Four studies found increased risk perception of developing CHD. Four studies found self-reported improvement in diet. However, two RCTs did not show an effect on improvement in diet. One study found improvement in blood lipid levels, and two of three studies showed increased motivation to make lifestyle changes. One study found increased motivation for smoking cessation in smokers with carotid plaques compared to those without (8.7 vs. 7.2/10, p=0.008) and a pattern of higher quit rates (73% vs. 38%, p=0.10);[36] the three other studies did not find improved smoking cessation rates. Physical activity did not differ between the two groups, except in one study. These behaviors were all self-reported. Concerning drug adherence, one study found that individuals with CAC scores in the fourth quartile were more likely (multivariate-adjusted OR=9.26, 95%CI=4.13–20.76) to continue statins compared to those with CAC scores in the first quartile.[17] However, no formal measurement of adherence such as drug dispensers with electronic monitoring or pill count was performed. The study populations were often not population-based as participants were frequently referred for atherosclerosis screening by their general practitioner.

DISCUSSION

This systematic review found that available evidence about atherosclerosis screening using noninvasive imaging was limited and yielded mixed results. In the RCTs, screening for atherosclerosis did not improve CVRF, but an increased smoking cessation rate (18% vs. 6%, p=0.03) was found in a single RCT.[11] Non-randomized studies showed potential positive effects of atherosclerosis screening on "intermediate" outcomes, such as increased motivation to change lifestyle[36,37] and an increased perception of CV risk.[14,18,37,39] However, such data were based on self-report and limited by the lack of a randomized control group. We found no studies that evaluated the impact of screening on CV events or mortality. These results are important in the context of substantial controversy about the role of screening for atherosclerosis.[19]

Consistent with the results of atherosclerosis screening on smoking cessation, mainly derived from the RCT by Bovet et al.,[11] a recent Cochrane review evaluated the impact of visual feedback of medical images in changing health behavior[41] and reported a statistically significant increase in smoking cessation behaviors (OR=2.81, 95% CI=1.23–6.41) after pooling the data from three studies.[11,16,42] Because of the exclusion of studies in patients with preexisting CVD, the present review did not include the study by Shahab et al.[42] and did not pool data on smoking cessation behaviors because of clinical heterogeneity (different timing for assessment of smoking cessation behaviors, very few smokers in one RCT).[16] These data on smoking cessation behaviors require confirmation with a larger RCT that includes smokers with higher daily cigarette consumption than in the Seychelles islands,[11] as well as a biochemical validation of smoking cessation, one being currently performed.[43]

Increased cardiovascular risk perception after atherosclerosis screening was found, consistent with recent systematic review findings that receiving global CHD risk information increased the accuracy in CHD risk perception.[44] However, no study compared the incremental effectiveness of providing feedback on atherosclerosis imaging in addition to global CHD risk. Moreover, data from the present review showing increased CHD risk perception were all derived from non-randomized studies. Overall, other results are also consistent with this recent Cochrane review on feedback of medical imaging described above.[41] This review (that did not specifically examine atherosclerosis screening) found mixed results concerning the impact of visual feedback of images on health behavior. Risk perception and clinical events were not assessed.

What are potential harms of atherosclerosis imaging? One study showed an increase in anxiety levels after such screening,[15] which was not found in two other studies[16,43] (Tables 3 and 4). Another study found that atherosclerosis screening may result in subsequent invasive testing and increased healthcare utilization.[32] However, other potential harms of atherosclerosis screening, such as radiation exposure and subsequent malignancy,[8] were not assessed in the reviewed studies. Another potential harm might be false reassurance, with the pursuit of unhealthy lifestyle. The slightly lower smoking cessation rate in those without plaques (5%) compared with the non-screened group (6%) in one RCT[11] might be related to false reassurance, although data are conflicting on the impact of false reassurance after a negative screening test.[45]

The major limitation of the present systematic review, inherent to the available studies, is the small number of available RCTs. The reported results mainly rely on data from non-randomized studies, these studies showing more positive results than RCTs, except for smoking cessation. There was also clinical heterogeneity in the screening methods used and the studied outcomes. The pooling results in this case seemed inadequate. For smoking cessation, no studies provided a confirmation of smoking cessation by biochemical validation, as recommended.[46] These limitations were inherent to the available studies and confirm the need for more RCTs in this field.[47] No studies examined the impact of screening on CV events or mortality. This is likely related to the need of a very large sample size for such trials; the NHLBI working group has estimated that a trial on the impact of such screening on clinical cardiovascular events would likely require >10,000 participants.[20]

What are the potential clinical and research implications of these findings? The mixed findings and limited data on atherosclerosis screening are important in the context of

Table 4. Non-randomized Studies Comparing Participants with Evidence of Atherosclerosis on Screening to Those Without

Source, year	Design	Participants, no. (% men)	Mean age (years, range)	Screening method	Description of lesion (% screened with lesion)	Follow-up	Main outcome	Results	Comments
Wong et al. 1996[15]	Retrospective	703 (80)	54 (28–84)	EBCT	CAC* (56)	1–2 years	CV risk-reducing behaviors	In a multivariate analysis†, showing results of EBCT associated with weight loss (OR=1.67, $p<0.001$), decreased dietary fat intake (OR 1.58, $p=0.02$), increased anxiety (OR= 2.73, $p=0.01$), medical visits (OR=1.61, $p=0.01$) and hospitalizations (OR=1.18, $p<0.05$) No significant change in smoking cessation	Possible selection bias as participants self-referred; all results self-reported (questionnaire); causal relationship between EBCT results and CV risk-reducing behaviors cannot be inferred.
O'Malley et al. 2002[14]	Prospective	99 (68)	50 (NA)	EBCT	CAC* (42)	Mean, 8±4 month	Change in motivation to alter smoking behavior	Participants with CAC had increased perception of MI risk compared to those without (40% vs. 12%, $p=0.002$). Overall, 59% of participants reported increased motivation for smoking cessation, but no significant difference in smoking motivation and cessation between the two groups	All participants smokers; possible selection bias as 75% of participants self-referred and military personnel; no biochemical validation of smoking cessation; no measure of change of other CVRF
Kalia et al. 2006[17]	Prospective	505 (82)	61 (NA)	EBCT	CAC* (42)	Mean, 3±2 years	Lipid-lowering drug use	In a multivariate analysis‡, 4th quartile CAC scores§ associated with statin therapy compared to 1st quartile (OR=10.0, CI= 2.3–23.4), with dietary modification‖ (64% vs. 41%, $p=0.001$). No change in smoking cessation rates across quartiles (1st quartile 67%, 4th quartile 70%)	All participants on statin therapy at baseline; no objective measure of CVRF; all results self-reported (questionnaire); adherence to statin therapy can only partially be inferred from the proportion of participants on statins at follow-up; possible selection bias as participants referred by GP; not all potential confounders taken into account
Sandwell et al. 2006[39]	Prospective	364 (51)	68 (55–80)	EBCT	CAC¶ (65)	6 months	Perceived risk of CHD, lifestyle changes, medical interventions	Increased risk perception and worry of developing CHD across CAC categories¶ (risk perception of CHD in those considered at low risk, 1.1 vs. 2.1/3 in those considered at high risk, $p<0.001$, mean worry 1.7 vs. 2.79/5, $p<0.001$) High-risk participants more likely to discuss results with their physician, have a cholesterol test, receive additional cardiac testing, (all $P_{trend}<0.001$) Subgroup analysis of participants who reported having an unhealthy lifestyle before EBCT‡‡	No objective measure of lifestyle modification, drug adherence and of CVRF, as all results self-reported (questionnaire); study population selected from a community-based cohort

Table 4. (Continued)

Source, year	Design	Participants, no. (% men)	Mean age (years, range)	Screening method	Description of lesion (% screened with lesion)	Follow-up	Main outcome	Results	Comments
Wyman et al. 2007[18,32]	Pre/post survey, pilot study	50 (62)	54 (34–82)	US	Carotid atheromatous plaques (58)	No	Participants' motivation regarding health related behaviors; physician treatment plans	Perceived higher risk of developing CHD in participants with plaques (mean score increase 4.28 to 3.85, p=0.01), but no increased motivation to make lifestyle changes	Small pilot study; participants had to have ≥2 CVRFs to be included in the study (participants with diabetes excluded), all had a history of hyperlipidemia and 48% had a family history of early CHD; all were recruited in a university cardiology clinic
Korcarz et al. 2008[37]	Pre/post survey, multicenter study	263 (49)	58 (45–70)	US	Carotid atheromatous plaques (58) and increased CIMT[#] (59)	No	Participants' motivation regarding health related behaviors; physician treatment plans	Increased subjects' motivation to exercise in those with plaques or increased CIMT (0.54 vs. 0.77; p<0.001), to make dietary changes[**] (0.30 vs. 0.42; p<0.001), to take cholesterol medication (−0.23 vs. 0.69; p<0.001) and more prone to recognize increased CHD risk (−0.21 vs. 0.61; p<0.001)	Participants were men aged ≥45 years or women aged ≥55 years (or ≥45 years if family history of CHD) with ≥1 additional CVRF; only patient motivation evaluated, not their actions; no clinical outcomes
Orakzai et al. 2008[38]	Prospective	980 (78)	60 (NA)	EBCT	CAC[*] (76)	Mean, 3±2 years	Lifestyle changes	In a multivariate analysis[‡], 4th quartile CAC scores[††], associated with change in diet (OR=2.66, CI=1.63–4.32) increased exercise (OR=2.03, CI=1.26–3.27) compared to 1st quartile scores	No objective measure of lifestyle modification as all results self-reported (questionnaire); possible selection bias as all participants either self-referred or referred by a GP
Rodondi et al. 2008[36]	Prospective pilot study	30 (67)	52 (40–70)	US	Carotid atheromatous plaques (78)	2 months	Motivation for smoking cessation	Increased motivation for smoking cessation in smokers with plaques (8.7 vs. 7.2/10, p=0.008) and higher quit rates compared to those without plaques (73% vs. 38%, p=0.10)	Small pilot study; all participants were smokers; no biochemical validation of smoking cessation

EBCT electron beam computed tomography, CAC coronary artery calcification, CV cardiovascular, OR odds ratio, CI confidence interval, NA not available, MI myocardial infarction, CVRF cardiovascular risk factors, GP general practitioner, CHD coronary heart disease, US ultrasound, CIMT carotid intima–media thickness

[*] *CAC score >0 considered significant (using the Agatston scoring method)*[61]

[†] *Multiple logistic regression model adjusting for age, gender, history of high cholesterol, hypertension, tobacco use and family history of CHD*

[‡] *Multiple logistic regression model adjusting for age, gender, hypertension, diabetes, tobacco use and family history of CHD*

[§] *1st quartile (CAC score<30), 2nd quartile (CAC score=31–149), 3rd quartile (CAC score=150–526), 4th quartile (CAC score≥527)*

[||] *Reported as a concerted effort to maintain a healthier diet*

[¶] *Categorization of participants in three categories according to CAC scores: low (0–10), intermediate (11 to 400), and high (>400)*

[#] *Carotid IMT ≥75 percentile for age, sex and race*

[**] *Dietary changes such as eating at least five servings each day of high fiber foods, limiting saturated and trans fats, limiting sugars*

[††] *1st quartile (CAC score 0), 2nd quartile (CAC score 1–99), 3rd quartile (CAC score 100–399), 4th quartile (CAC score≥400)*

[‡‡] *Subgroup analysis of participants who reported having an unhealthy lifestyle before EBCT. Those in the high-risk group more likely to report changes aimed at reducing dietary fat (39% of participants vs. 68%; P_{trend}=0.007), cholesterol (P_{trend}=0.03), and salt (P_{trend}=0.059) compared with those in the low and moderate risk group. No significant increase in exercise (p=0.109)*

controversy about the role of screening for atherosclerosis,[19] with controversial recommendations (Table 1). Recognizing the absence of current evidence for improved net health outcomes from atherosclerosis screening, the ACC/AHA has recently suggested that it may be reasonable to measure carotid intima–media thickness (IMT) or CAC among asymptomatic adults at intermediate CHD risk.[48] The USPSTF did not recommend any of the available imaging modalities.[49] It is common that new, often expensive, technologies do not undergo formal evaluation prior to being implemented within standard of care.[50,51] Population-wide screening might concern a large population, with substantial public health and cost implications.[23] For example, the Society of Cardiovascular Computed Tomography estimates that more than 200,000 Americans had CAC screening in 2008 at a cost of about US $50 million.[22] Such screening might become a profitable business, including sometimes by using patients' concerns as the motor for screening.[52] Cost effectiveness studies should assess whether costs associated with atherosclerosis screening[23] and potential long-term harms, such as radiation exposure and subsequent malignancy,[8] might be outweighed by potential benefits, such as increased smoking cessation and improved adherence (albeit with limited data), more effective targeting of preventive therapy to those who really need it, or a reduction in major cardiovascular events.[47] Modeling might help determine the screening procedures and the target population to design future large-scale, expensive RCTs.[47] Given limited RCT data, scientific societies should make cautious recommendations on extensive use of atherosclerosis screening.

In summary, this systematic review shows that available evidence about atherosclerosis screening using noninvasive imaging is limited, with mixed results on CVRF control and increased smoking cessation in a single RCT. Absence of proof of benefit is certainly not proof of absence of benefit. However, the potential advantages of atherosclerosis screening need to be demonstrated by large-scale RCTs.[8,50] Not conducting such trials would leave clinicians with no scientific basis for making decisions regarding newly proposed, and sometimes expensive, methods for identifying high CHD risk adults.[20,47] Such trials should likely target intermediate-risk adults, as suggested by others,[1,20,47] and/or those with a high likelihood of atherosclerosis,[12] given the pattern of more benefits of atherosclerosis screening in the small group with calcification in the highest quality trial.[16] Such trials should assess the impact of atherosclerosis screening on relevant clinical outcomes, including cardiovascular risk factors, smoking cessation, and, ideally, cardiovascular events,[47] before its widespread implementation.

Acknowledgments/Funding: *Dr. Rodondi's and Dr. Cornuz's researches on atherosclerosis screening, as well as a randomized controlled trial of atherosclerosis screening on smoking cessation (PI: Dr N. Rodondi), are supported by grants from the Swiss National Science Foundation (SNSF 3200B0-116097), the Swiss Tobacco Prevention Funds (Federal Office of Public Health, FPT 08.002282), and the Swiss Heart Foundation. Dr. Auer's research on cardiovascular prevention is supported by grants from the Swiss National Science Foundation (SNSF SPUM 33CM30-124112 and PBLAP3-136774).*

Conflict of Interest: *None disclosed.*

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