May subclinical arterial disease help to better detect and treat high-risk asymptomatic individuals?

Alain Simon and Jaime Levenson

The diagnosis of high risk of cardiovascular disease (CVD) in subjects without clinically overt CVD has been somewhat improved by integrating multiple traditional risk factors via appropriate risk score programs. Nevertheless, novel measures of CVD risk are being proposed and debated to further improve high-risk detection by their addition to, or their use in place of, traditional risk factors. Among such measures, non-invasive detection of subclinical arterial disease is a subject of growing interest. It may improve CVD risk evaluation and enable more intensive risk-reduction therapy in subjects judged to be at intermediate risk after preliminary risk factor assessment. However, the clinical utility and cost-effectiveness of high-risk diagnostic and therapeutic strategy guided by subclinical arterial disease remain untested. This uncertainty precludes systematic detection of subclinical arterial disease in routine clinical management for primary prevention, but such detection may be used at the discretion of the physician as a part of CVD risk assessment. *J Hypertens* 23:1939–1945 © 2005 Lippincott Williams & Wilkins.


Keywords: cardiovascular risk, primary prevention, subclinical arterial disease, risk factors, arterial test

Centre de Médecine Préventive Cardiovasculaire, Hôpital Broussais, Assistance Publique Hôpitaux de Paris, Faculté de Médecine René Descartes, Paris, France.

Correspondence and requests for reprints to Prof. Alain Simon, Centre de Médecine Préventive Cardiovasculaire, Hôpital Broussais, 96 rue Didot, 75674 Paris, France.

Tel: +33 1 43959391; fax: +33 1 45 39 11 93; e-mail: alain.simon@brs.ap-hop-paris.fr

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Introduction

Cardiovascular disease (CVD), especially coronary heart disease (CHD) and stroke, remains the most common cause of death despite detection and treatment of the major traditional risk factors such as hypertension, hypercholesterolemia, diabetes, and smoking [1]. Moreover, the yearly decline in mortality due to these factors is slowing down, while their morbidity is increasing dramatically [2]. It is therefore necessary to reinforce their prevention by improving the detection of high CVD risk, which is too often ignored in asymptomatic individuals and requires intensive risk-reduction therapy [3]. Detection of high risk based on traditional cardiovascular risk factors has been improved by the use of risk score programs integrating the multiple risk factors of one individual [3–7]. Nevertheless traditional risk factors are far from accounting for all high-risk CVD conditions [8]. Therefore, novel markers of cardiovascular risk believed to detect high risk better than traditional risk factors alone have been proposed [3,8]. Among them, measures of subclinical arterial disease are the subject of growing interest because they may represent better markers of susceptibility to CVD. This paper, which is not a systematic review of all new risk markers, has concentrated on measures concerning subclinical arterial disease with the aim to clarify the key question of how much its additional detection may improve the predictive value of traditional risk factors and support the use for additional risk-reduction therapy in asymptomatic subjects without present CVD or a past history of clinical CVD.

Principles and limitations of CVD risk assessment by traditional risk factors

Risk score programs

In asymptomatic subjects, traditional risk factors enable recognition of high CVD risk in two different situations. The first, easy to recognize, corresponds to the presence of one (or more) of the following major risk factors: severe hypertension, severe hypercholesterolemia, or diabetes that is synonymous of high CVD risk [4,5]. The second, sometimes termed multifactorial high CVD risk, is more frequent and corresponds to the coexistence of multiple mild to moderate risk factors, which are often unknown because they are common in apparently healthy persons [3,5]. Diagnosis of it has been considerably improved by the use of risk score programs integrating multiple traditional risk factors. The Framingham risk score is the most commonly used of the risk scores available [4,7,8] and integrates age, gender, total, and high-density lipoprotein (HDL) cholesterol, systolic blood pressure, and the presence or absence of current smoking [7]. Risk points are attributed to each factor, and are summed to obtain the total risk score, which is transformed to a percentage probability of development of fatal or non-fatal CHD within 10 years with a threshold for high risk > 20% [5,7]. Such risk calculation can be performed automatically by computer programs or via websites. The Framingham score is invaluable for detecting high-risk status in apparently healthy persons, but has limitations related to its geographic specificity and lack of consideration of other established risk factors. As the
extrapolation of the Framingham score to populations at lower risk than the North American population may overestimate the true CVD risk [9], calculations of CVD risk that are appropriate to specific countries (England, Scotland, Germany, New Zealand, and France) have been proposed [4,8]. The European risk SCORE (Systematic Coronary Risk Score) system was recently derived from prospective European studies [4]. It integrates age, gender, systolic blood pressure, either total cholesterol or the total cholesterol/HDL ratio, and smoking, can be calculated either in high-risk (northern) or low-risk (southern) countries in Europe, and predicts fatal cardiovascular disease over 10 years with a threshold for high risk > 5% [4].

Limitations of risk score assessment
The Framingham score and other risk scores do not consider several established risk factors such as obesity (especially abdominal obesity), history of premature CHD in first-degree relatives, lack of regular aerobic physical exercise, and psychosocial factors [10]. The metabolic syndrome, which aggregates at least three of five risk factors (abdominal obesity, elevated triglycerides, reduced HDL cholesterol, elevated blood pressure, and elevated fasting glucose) that are not all considered in risk score programs, deserves special attention because it is strongly correlated with high CVD risk [11]. Furthermore, risk evaluation is generally focused on fatal and non-fatal CHD, although ischemic stroke is also a major cause of death and disability [12]. The Framingham risk score program for stroke, which is much less commonly used than the CHD risk score, permits calculation of the risk of stroke by entering the patient’s age, gender, systolic blood pressure, presence or not of antihypertensive therapy, diabetes, smoking, history of CHD, atrial fibrillation, and left ventricular hypertrophy [7]. Nevertheless, there are additional specific risk factors for stroke, including (1) ethnicity, in particular black, Chinese and Japanese; (2) parental history of stroke; and (3) personal history of cardiac disease that may contribute to thromboembolic stroke [12]. Finally, although traditional risk factors may account for 90% of the attributable cardio-vascular risk [13], their prediction of CVD is weak probably because the susceptibility to CVD varies greatly among individuals. Moreover, more than 80% of the global CVD burden is in low-income and middle-income countries where the value of risk factors for predicting CVD has not yet been established [13].

Overall evidence of the predictive value of subclinical arterial disease
The detection of high CVD risk based on traditional risk factors alone probably fails to diagnose a number of high-risk conditions, and therefore measurement of new potential risk factors has been proposed to improve the detection of high-risk asymptomatic subjects [3–6,10, 11,14]. Because an exhaustive review of the large number of new or emerging CVD risk factors cannot be done, we have chosen to focus exclusively on measures concerning subclinical arterial disease that may represent the best markers of susceptibility to CVD. Taking the most commonly used arterial measures (Table 1), we have tried to provide a systematic review of all evidence concerning their predictive role by focusing the literature search on recent evidence in this field (from 1998 to 2004), with reference to several key studies that were completed before this time. Measures were schematically classified into those assessing arterial structure and those assessing arterial function (Table 1).

Arterial structure tests
Ultrasound-assessment of plaque and intima–media thickness
B-mode ultrasound can easily detect the presence of a plaque, a specific marker of atheroma deposit, at various sites prone to atherosclerosis, such as the carotid arteries, abdominal aorta, and femoral arteries [15]. Plaque is defined as a focal thickening of the arterial wall intruding into the arterial lumen, and having maximal thickness > 1.3–1.5 mm according to different definitions. However its measurement has a main limitation due to the necessity to express the result dichotomously by the presence or absence of plaque because the precise quantitative measure of plaque dimension by ultrasound is not yet possible. A probable consequence of such limitation is that evidence supporting the capability of ultrasound plaques to predict CVD is scarce. A prospective pioneering study in middle-aged healthy Finnish men has shown that the presence of a carotid plaque multiplied the short-term incidence of acute myocardial infarction by about

Table 1 Non-invasive tests of subclinical arterial disease and criteria of clinical applicability

<table>
<thead>
<tr>
<th>Test</th>
<th>Safety</th>
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<td>Ankle-brachial blood pressure index</td>
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<td>Wall stiffness</td>
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<td>Flow-mediated vasodilatation</td>
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<td>Abnormal exercise test</td>
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+, yes; −, no; ?, unknown.
three, and the relative risk increased up to about seven times if plaque causing > 20% stenosis was present [16]. The Rotterdam study in a general population of subjects aged 55 years and older has also shown that ultrasound evidence of a plaque in carotid arteries increased the age-adjusted and sex-adjusted risk of stroke and cerebral infarction about 1.5-fold, irrespective of the plaque location in the carotid arterial tree [17]. Similarly, a recent prospective population-based cohort study in asymptomatic elderly people found that the number of plaques in extra-cranial carotid arteries was associated to increased age-adjusted risk of cardiovascular mortality in the year to come, by about 1.2-fold per 1 U increase [18]. The ability of carotid plaque to predict CVD risk has also been shown prospectively in hypertensive populations such as those of the Verapamil in Hypertension and Atherosclerosis Study [19] and the European Lacidipine Study on Atherosclerosis (ELSA) [20] trials.

B-mode ultrasound also allows the quantitative measurement of large artery wall thickness, specifically the intima–media thickness (IMT). Defined as the distance separating blood/intima and media/adventitia echogenic interfaces, the IMT is principally measured in extra-cranial carotid arteries where both interfaces of interest are best visible. Automated computerized operator-independent reading, currently available and easy to use in everyday practice, allows achieving excellent precision and reproducibility of IMT measures in the common carotid artery [21,22]. Computerized measurement does not work as well on carotid bifurcation and the internal carotid artery as on the common carotid, because both former segments frequently include plaques that disrupt interfaces analyzed by the computerized program [21].

The spatial geometry of carotid bifurcation and the internal carotid artery can be also a source of difficulty for obtaining optimal IMT images allowing accurate automatic computerized reading [21]. Furthermore, the procedure of IMT measurement is not yet standardized as regards the arterial wall, far wall and/or near wall, and as regards the arterial segment within the carotid tree. Thus the IMT is often measured and averaged along a longitudinal segment > 1 cm in length of the proximal common carotid far wall, a site free of atherosclerotic lesion that provides an optimal image of both IMT interfaces. In this case, the IMT is not necessarily a sign of atherosclerosis and may represent hypertension-related hypertrophy [21] – as particularly stressed in several therapeutic trials on the IMT in hypertension such as INSIGHT-IMT [22], PHYLLIS [23] and ELSA [20]. Alternatively, when the IMT is the average of several focal measures in the near and far walls of the common carotid, the bifurcation and the internal carotid, on both sides, it can be considered as a surrogate marker of atherosclerosis because atherosclerotic lesions, which are frequent in the bifurcation and internal carotid, are incorporated into its measurement [20–23]. Despite these methodological problems, there is a body of evidence that increased IMT, whatever its site of measure, is associated with increased incidence of subsequent CVD in asymptomatic subjects [21]. In middle-aged Finnish men without known CVD, the 3-year risk of acute myocardial infarction increased by 11% with each 0.1 mm increase in the common carotid IMT, and the predictive value of the IMT remained significant after adjusting for age, smoking, blood pressure, and total and HDL cholesterol [16]. Similarly, in the asymptomatic subjects of either sex aged 45–64 years of the Atherosclerosis Risk in Communities study [24], an increased IMT above 1 mm at baseline, as compared with IMT values below 1 mm, was associated with a fivefold (women) and twofold (men) increase in age-adjusted and race-adjusted risk of coronary heart disease over a period of 4–7 years; the predictive value of the IMT was weakened but remained significant by adjusting for all major cardiovascular risk factors [24].

The Rotterdam study in asymptomatic subjects aged 55 years or older also confirmed that the risk of stroke and myocardial infarction over a mean follow-up duration of 2.7 years increased continuously with increasing IMT at baseline, by about 1.5 times per IMT standard deviation (0.16 mm); additional adjustment for several cardiovascular risk factors, especially smoking, systolic blood pressure, total and HDL cholesterol, and diabetes, slightly attenuated the predictive value of IMT to about 1.3 times for stroke and myocardial infarction [25]. Similarly, the CHS study in asymptomatic elderly subjects [26] has shown that the risk of myocardial infarction or stroke over a median follow-up duration of 6.2 years increased with the IMT, about fourfold between the quintile with the highest IMT and with the lowest IMT; the predictive value of the IMT remained significant after adjustment for traditional cardiovascular risk factors with a relative risk increase of about three times [26]. The risk prediction of the IMT was also shown in the hypertensive population of the ELSA trial [20]. Evidence of the predictive value of the IMT obtained from primary prevention prospective studies is reinforced by results from studies in secondary prevention, in particular the CLAS study [27], in patients with established coronary artery disease. This study has shown that for each 0.03 mm/year increase in the common carotid IMT, the relative risk for non-fatal myocardial infarction or coronary death was increased 2.1 times and the relative risk for any coronary event 3.1 times. CLAS is the only study until now to have shown the risk prediction of IMT progression and not only that of the baseline value [27].

Coronary calcification deposit measured by computed tomography

Coronary calcification is a marker of coronary atherosclerosis within the coronary vasculature, which can be detected and quantified by electron beam (or helical) computed tomography [28]. In general, a high deposit of coronary calcium suggests the probability of a vulnerable
plaque, but cannot indicate the site of the specific vulnerable lesion [28]. On the other hand, vulnerable lesions and severe coronary stenoses may exist in the absence of a coronary calcium deposit [28]. A few prospective studies have shown that a coronary calcium deposit may predict future cardiovascular events in asymptomatic subjects [29–31], but there is still debate as to whether the presence of coronary calcifications adds prognostic information to that provided by traditional risk factors. A first longitudinal study with a follow-up duration of 19 months supported the additional predictive value of coronary calcifications, especially if they were abundant, with impressive odds ratios of coronary artery disease ranging from 20 to 35 [29]. This finding was confirmed by a recent longitudinal study of 35 months in a large group of male and female adults without known cardiovascular disease. This study showed that the coronary calcium score was predictive of hard and soft coronary events in men (relative risks of about 4 and 27, respectively) and of soft events in women (relative risk of about 3), after correction for age, smoking, hypercholesterolemia, diabetes, and hypertension [30]. In contradiction with these two studies, another prospective study has shown that coronary calcifications did not provide incremental prognostic information to the Framingham coronary risk assessment in high-risk asymptomatic subjects [31].

**Ankle brachial blood pressure index measurement**

The ankle brachial blood pressure index (ABI) is a simple and inexpensive test, calculating the ratio of systolic pressures in the legs and the brachial arteries measured with Doppler sensor. It permits detection of asymptomatic lower-extremity peripheral arterial disease [3] because ABI < 0.90 in either leg is considered evidence of obstructive peripheral arterial disease. Nevertheless, prevalence studies of peripheral artery disease have shown that advanced obstructive lesions, likely to be detected by ABI, are frequent in older subjects, especially if smokers or diabetics, but are rare in younger subjects before 50 years [32,33]. Furthermore, several data support the capability of decreased ABI to predict coronary, CVD, and all-cause mortality in asymptomatic older subjects [3]. In particular, high relative risks of CVD mortality (6.3), CHD mortality (4.8), and all-cause mortality (3.1) were found in elderly men and women with decreased ABI, and the predictive ability persisted after exclusion of persons with known CVD at baseline and after adjustment for traditional risk factors such as age, sex, serum cholesterol, glycemia, and smoking [34].

**Arterial function tests**

**Arterial stiffening**

The stiffening (or sclerotic) component of large (conduit) artery disease can be detected by measuring arterial wall motion (distension) or pulse wave velocity (generally between carotid and femoral sites) or by quantitative analysis of pulse wave contour (wave reflections). These measurements can be performed in superficial arteries including the brachial, carotid, femoral, and radial arteries by means of various techniques such as ultrasound, mechanography, and tonometry, often with the assistance of computerized image analysis systems such as the echo tracking system [35–37]. Two of these techniques may have a potential diagnostic application, namely the measurement of pulse wave velocity and that of augmentation index (wave reflections) [6]. Measurement of arterial stiffness provides quantitative information regarding the status of the elastic properties of the arterial system, but arterial stiffening is not necessarily a sign of atherosclerosis and may also represent effects of hypertension and/or aging on large artery walls [35]. Although a large number of physiological and pharmacological and therapeutic studies have been accumulated using arterial stiffening measures, there is not yet sufficient and concordant evidence that arterial stiffening might be a predictor of coronary and cardiovascular events. A few studies in special groups of very old subjects or patients with end-stage renal disease have suggested that aortic pulse wave velocity predicts fatal cardiovascular events [38,39]. By contrast, a recent study in asymptomatic elderly men is inconsistent with the latter studies by showing that stiffness of the carotid artery lacked additive prognostic value, contrary to carotid artery plaques burden [18]. These preliminary observations therefore need further validation in larger and less specific populations with longer follow-up durations.

**Brachial artery flow-mediated vasodilatation**

Brachial artery flow-mediated dilation (FMD) is a promising marker of endothelial function that can be measured by determining the dilatation of the brachial artery due to the release of nitric oxide by transient high flow induced by a few minutes of forearm ischemia [40,41]. FMD is therefore currently considered as a valuable surrogate marker of nitric oxide release. However, evidence supporting FMD to be considered as a predictor of cardiovascular events is still insufficient. A recent study in participants in the Framingham study has shown that FMD was related with many cardiovascular risk factors, suggesting that FMD may be an integrator of the effects of cardiovascular risk factors on the arterial wall [42]. Moreover, several studies have suggested that brachial FMD may have prognostic value in identifying subjects at risk of developing cardiovascular disease [40,43–45], but all these studies have a relatively small sample size and it is unknown whether this prognostic information is independent of, or additional to, that provided by traditional cardiovascular risk factors.

**Exercise electrocardiography test abnormality**

Exercise electrocardiography testing of asymptomatic subjects without known CHD and with low or intermediate
CVD risk is not recommended, since it yields numerous false-positive findings that may result in psychological and work-related problems [46]. In asymptomatic subjects with high CVD risk, false-positive data are reduced in incidence and electrocardiography exercise test abnormalities may provide additional diagnostic and prognostic information [46]. The diagnostic value of detection of silent CHD may be improved by taking into account not only ST-segment depression, but also other exercise responses such as exercise capacity [46] or other stress imaging testing such as thallium imaging, particularly useful in the presence of left ventricular hypertrophy generally associated with hypertension [46]. The real value of exercise test abnormalities such as ST-segment depression, failure to achieve target heart rate and reduced exercise capacity is the provision of additional prognostic information to prediction of CHD in subjects with multiple risk factors [3,46], especially men at high risk with 10-year Framingham CHD risk ≥ 20% [47].

Clinical utility of subclinical arterial tests

Choice of test

If novel measures of subclinical arterial disease are to be used, it is important to know which tests should be performed. This should mainly depend on several criteria of clinical applicability (Table 1), including non-invasiveness and safety, simplicity and standardization of measurement, precision, and reproducibility, low cost, and definition of cut-points of risk [14]. All the criteria are not fulfilled by any of the aforementioned tests of subclinical arterial disease. B-mode ultrasound detection of arterial wall thickening is an attractive measure because it is relatively simple and inexpensive, and it enables precise visualization of early arterial disease, but it still lacks measurement standardization and widely accepted cut-points of IMT for defining risk categories do not exist [21]. Measurement of coronary calcification has the theoretical advantage that it may be viewed as direct imaging of coronary atherosclerosis, but the technique of measurement involved is sophisticated and expensive, and induces X-ray exposure [28]. Simplicity and standardization of measurement and good precision and reproducibility are clearly not yet features of arterial stiffness indices and brachial flow-mediated vasodilatation [35,36], which must be measured in experienced laboratories and cannot become a part of routine clinical assessment of CVD risk. Finally there is as yet no agreement and no clear recommendations concerning the choice of tests for detecting subclinical arterial disease, and in practice the choice depends on the technical equipment available and the experience of the vascular laboratory [3].

Prognostic utility

The major purpose for the detection of subclinical arterial disease is to identify asymptomatic subjects who may be at higher CVD risk than estimated by traditional risk factors. Regarding this purpose, it is obvious that subjects designated at high risk by traditional risk factors do not need subclinical arterial measures since they already qualify for intensive therapeutic intervention. In contrast, subjects at intermediate risk (e.g. 10–20% probability of CHD at 10 years) may benefit from measures of subclinical arterial disease, and the recommendation to use them to stratify risk has been underlined by European Society of Hypertension–European Society of Cardiology guidelines [6], which suggest that they may be useful especially in hypertensive patients at intermediate risk. Nevertheless, the subclinical arterial measures may be useful provided these measures have been found to provide incremental risk information over and above that provided by traditional risk factors (Table 1). As already discussed in detail, this additional prognostic value has been relatively well demonstrated for three measures of subclinical arterial disease: (1) carotid IMT, and to a lesser extent ultrasound plaque in peripheral arteries; (2) ABI in older subjects, especially if smokers or diabetics – it is insensitive for detecting early obstructive lesion in younger subjects and therefore cannot serve as a valuable screening tool before 50 years of age [32,33]; and (iii) exercise electrocardiography testing abnormality in asymptomatic men with high CVD risk. Opinion is much more divided as to whether coronary calcification adds to the prognostic information provided by the Framingham risk assessment score [48]. Although the detection of coronary calcification has been used over the past 10 years to evaluate asymptomatic individuals for risk of developing CHD, a statement regarding its clinical utility in primary prevention has recently been delayed because its prognostic value has yet to be adequately evaluated [49]. Finally, there is still a lack of sufficient evidence that arterial stiffness indices and brachial FMD add to risk prediction beyond that achievable with traditional risk factors, and both tests need to be evaluated further in prospective large trials.

Therapeutic utility

The measurement of subclinical arterial disease may be clinically useful by providing support and motivation for additional lifestyle changes or drug therapies and for better monitoring the effects of therapy. That detecting subclinical arterial disease may be used to determine the intensity of risk-reduction therapy is the direct consequence of its potential ability to reclassify a subject designated at intermediate risk into the high-risk category. This reclassification will enable a subject to benefit from more intensive treatment including changes in lifestyle (smoking cessation, dietary change, weight loss, exercise) and reinforcement of drug therapy. Nevertheless, the benefit of a therapeutic strategy guided by subclinical CVD is uncertain, and randomized, controlled trials are required to support its effectiveness. Subclinical arterial disease may also be used for monitoring the
effectiveness of risk-intervention therapy. For example, treatment should be intensified if subclinical arterial disease does progress or even does not regress but the validity of this approach has not been established, and its demonstration will require appropriate therapeutic trials.

**Practical considerations**

In practice, the detection of subclinical arterial disease for screening on a population-wide basis should be discouraged until the number of uncertainties still existing about their prognostic and therapeutic utility has been better clarified. Subjects at low risk as determined by risk factor assessment do not need to search for subclinical arterial changes since their treatment on the basis of only these changes is without support at present. Subjects at high risk as determined by traditional risk factors do not require subclinical arterial disease detection because they should have risk factors treated intensively no matter what such detection reveals. Finally, subjects considered to have intermediate or uncertain CVD risk after preliminary assessment of traditional risk factors may benefit, at the discretion of their physicians, from selective use of appropriate subclinical arterial markers, including, in particular, simple and inexpensive ultrasound measures of IMT and plaques in peripheral arteries, which may aid further evaluation and guide therapeutic intervention.

**Cost-effectiveness**

The purpose of detecting high-risk asymptomatic individuals is to provide preferential and intensive risk-reduction therapy to them, since the benefit of risk-reduction therapy is proportional to the baseline risk of the person receiving that therapy [14,50,51]. It is therefore necessary to treat high-risk subjects to obtain the greatest benefit in terms of individual reduction of risk. This high CVD risk strategy may be less costly by focusing aggressive and costly treatment on subjects with high CVD risk resulting from the presence of subclinical arterial disease, and also avoiding unnecessary intensive risk-reduction therapy in those at intermediate or low risk on the condition that potential high-risk conditions have been excluded through the search for subclinical arterial disease [14]. This latter point leads to the question of whether the detection of subclinical arterial disease proposed to aid risk evaluation and therapy in the primary prevention of CVD is cost-effective. Although prevention costs may increase through the measurement of subclinical arterial disease, the great differences in cost existing between candidate markers of subclinical arterial disease must be taken into account. Finally, even low-risk subjects may be better detected and managed less expensively through the addition of subclinical arterial disease detection to initial assessment of traditional risk factors. These important questions need to be answered by appropriate studies.

**Conclusion**

Improvement of detection of asymptomatic high CVD risk individuals is needed for better targeting of intensive risk-reduction treatment and optimization of the cost-effectiveness of primary prevention. Detection of high CVD risk is still based on traditional risk factor assessment in clinical practice. Non-invasive detection of subclinical arterial disease may add substantially to the prognostic information obtained with traditional risk factors, but it should not be used for screening of entire populations or as an alternative to traditional risk factors. However, it has given rise to growing interest in tracking subclinical arterial disease in asymptomatic patients designated to be at intermediate or uncertain risk after preliminary traditional risk factor assessment.

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**References**


