Primary Cardiovascular Disease Prevention: Risk Factors Control vs. Imaging Subclinical Atherosclerosis

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Introduction

During the last four decades a substantial fall in cardiovascular disease (CVD) mortality has been observed worldwide[1] to a large extent attributable to the reduction of major risk factors[2]. However, due to the significant increase in obesity and diabetes CVD incidence rates will not reduce as far over the next years. Risk prediction in asymptomatic individuals remains a major challenge. Primary preventive treatment is currently based on the assessment of individual’s global risk mainly through screening of conventional risk factors and their treatment with lifestyle intervention and pharmacotherapy, often based on multivariate risk equations, and yet a large proportion of CVD still occurs in individuals who are classified as carrying low- or intermediate-risk according to the risk scores. Atherosclerosis is the most common pathophysiologic process underlying CVD, often after a prolonged asymptomatic phase during which it may be possible to modify the course of the disease. Unlike conventional probabilistic risk scores, non-invasive imaging techniques such as carotid intima-media thickness (CIMT) along with plaque assessment (Figure 2), measured by B-mode ultrasound, and coronary calcium scoring (CAC) detected by CT scan have the advantage of direct visualization of the consequences of atherosclerosis on the arterial system. We consider the proposal that imaging of subclinical atherosclerosis is superior to risk equations as it directly identifies the disease and can effectively predict the risk of future CV events in low- and intermediate-risk individuals. In addition, imaging can improve the adherence to guidelines based treatment in patients and their physicians.

Highlights

The burden of cardiovascular disease in developed countries has shown dramatic improvements over the last 50 years, largely due the identification and control of major risk factors including, smoking hypertension and high cholesterol. However, due to the significant increase in obesity and diabetes CVD incidence rates will not reduce as far over the next years. Risk prediction in asymptomatic individuals remains a major challenge. Primary preventive treatment is currently based on the assessment of individual’s global risk mainly through screening of conventional risk factors and their treatment with lifestyle intervention and pharmacotherapy, often based on multivariate risk equations, and yet a large proportion of CVD still occurs in individuals who are classified as carrying low- or intermediate-risk according to the risk scores. Atherosclerosis is the most common pathophysiologic process underlying CVD, often after a prolonged asymptomatic phase during which it may be possible to modify the course of the disease. Unlike conventional probabilistic risk scores, non-invasive imaging techniques such as carotid intima-media thickness (CIMT) along with plaque assessment (Figure 2), measured by B-mode ultrasound, and coronary calcium scoring (CAC) detected by CT scan have the advantage of direct visualization of the consequences of atherosclerosis on the arterial system. We consider the proposal that imaging of subclinical atherosclerosis is superior to risk equations as it directly identifies the disease and can effectively predict the risk of future CV events in low- and intermediate-risk individuals. In addition, imaging can improve the adherence to guidelines based treatment in patients and their physicians.

Keywords: atherosclerosis, primary prevention, risk factors

Citation: Vancheri F, Faggiano P, Henein MY. Primary Cardiovascular Disease Prevention: Risk Factors Control vs. Imaging Subclinical Atherosclerosis. International Cardiovascular Forum Journal. 2020;19:2-7, DOI: 10.17987/icfj.v19i0.633
those who did not[14]. Conversely, about one fifth of patients with coronary artery disease (CAD) do not carry any of the conventional risk factors[12]. The age of initiation and the rate of progression of atherosclerosis may markedly differ among individuals and cannot be predicted by risk factors based assessment models. Moreover, conventional risk screening tools do not give information about the pathophysiologic consequences of the risk exposure and do not take into account the length of exposure which can greatly increase the CVD risk[15,16].

Atherosclerosis is the most common pathophysiologic process underlying CVD[17]. Some components of the atherogenesis may explain the limited value of risk scores. The systemic inflammatory vascular process that results in atherosclerosis starts in early life and progresses with age[18]. Therefore, atherosclerosis has a prolonged asymptomatic phase during which it is possible to modify the course of the disease, and the rate of progression of the lesions which may vary among individuals. Endothelial dysfunction, activation of inflammatory cells, smooth muscle proliferation and coronary calcification may occur at early stages even in the absence of clinical manifestations[19,20]. Thus, subclinical atherosclerosis should be considered as an early indicator of atherosclerotic burden and a memory of lifetime risk factor exposure. Its timely recognition is an important clinical target that can prevent or slow the progression to overt CVD.

Unlike conventional probabilistic risk scores, non-invasive imaging techniques such as carotid intima-media thickness (CIMT) (Figure 1) along with plaque assessment (Figure 2), measured by B-mode ultrasound, and coronary calcium scoring (CAC) detected by CT scan (Figure 3), have the advantage of direct visualization of the consequences of atherosclerosis on the arterial wall, allowing measurement of the lifetime cumulative effects of all risk factors[21-23]. Being a systemic disease, the severity of atherosclerosis in one arterial territory is associated with the involvement of other arteries, although coronary and carotid are the two predominantly involved systems.

A positive association has been reported between the extent of cross-sectional measurements of CIMT and the risk of subsequent CV events in general populations, independent of traditional risk factors[24,25]. However, the addition of CIMT to traditional CV risk prediction models is associated with only small or no improvement in the performance of the model[26-28]. However, CIMT when associated with information about additional carotid plaques formations can significantly improve the CV risk prediction[29]. Several studies indicate that reduction of atherosclerosis burden with risk factors control results in reduction in CV events[30,31]. Although statin treatment has been associated with slower progression of CIMT, there is no definitive evidence of a relationship between CIMT regression or progression and CV subsequent events[24,32-35]. Methodological and biological explanations may account for this discordance. The mean annual change in CIMT is very small, far less than 1 mm [36], thus measurements done several months after the first measurement by different sonographers, at different carotid sites, may produce large variability[37-38]. In addition, CIMT reflects both intimal thickening due to atherosclerosis and smooth muscle remodeling of the muscular
wall, hence the rate of annual CIMT change over time is non-linear and may be different among individuals[35]. Overall, the available results indicate that CIMT has a limited incremental value compared with conventional risk prediction scores and its use in clinical practice to improve CV risk assessment is not recommended by current guidelines[5,39]. New imaging modalities, such as intima-media grey-scale median (IM-GSM) and fully automated on-screen carotid intima-media thickness measurement have been recently introduced[40,41]. IM-GSM can differentiate between adaptive intimal thickening due to remodeling from pathological intimal thickening as a result of early atherosclerosis. Fully automated on-screen CIMT measurement minimizes the operator bias and can greatly improve the accuracy and reproducibility of measurements.

Carotid plaques are more effective than CIMT in predicting future CV events and are strictly associated with conventional risk factors and with other measures of atherosclerotic disease, such as aortic stiffness[42-44]. The assessment of carotid disease has been traditionally based on the degree of stenosis in order to evaluate the clinical risk. However, the development of symptoms does not follow a linear relationship with the degree of stenosis[45]. A compensatory outward remodeling may accommodate a large plaque with negligible hemodynamic effects[46]. Therefore, a clinically meaningful estimate of the burden of carotid disease relies on the direct assessment of the plaque morphology which is a measure of the effects of atherosclerosis. B-mode ultrasound is widely used in the assessment of plaque area for predicting future events[47]. The recently introduced three-dimensional ultrasound technology allows accurate quantification of the plaque volume[48]. The wide range of volume that can be detected enables more accurate assessment of regression or progression of the disease in single individuals[49]. Characteristics of plaque morphology, including surface irregularity, echolucency, degree of luminal stenosis and calcification, are strictly related with CV risk factors and have been shown to accurately predict the development of both coronary and cerebrovascular events[43,50]. Plaque composition, ranging from echolucent high-risk plaques to echodense stable ones, evaluated with standardized methods based on grey-scale pixel analysis,[51] can identify individuals at high risk of CV events[52,53]. Lipid-lowering therapy has been shown to modify the plaque composition and its ultrasound echogenicity even after few months of treatment[54].

The progression of intimal atherosclerosis results in coronary artery calcification (CAC). In symptomatic patients, CAC has been shown to compromise myocardial perfusion even in the absence of significant luminal stenosis[55]. CAC quantification, assessed by CT scan, improves risk prediction beyond traditional risk factors[56-58]. When CAC score is added to the risk model, patients at intermediate risk according to conventional score, are accurately reclassified into low or high risk categories. In a large study of individuals at intermediate risk, the net reclassification index (NRI), which indicates the proportion of individuals correctly reclassified to higher or lower risk categories by incorporating a new test into the risk assessment model, showed that one in five and one in three were reclassified to low and high risk categories, respectively[59]. In appropriately selected asymptomatic individuals the addition of CAC to conventional risk factors may greatly improve the clinical risk prediction[60-62]. However, the relationship between CAC, risk factors and coronary stenosis is complex. About one fifth of asymptomatic individuals with CAC Agatston score zero have significant coronary stenosis at coronary angiography[63]. Conversely, about one third without high levels of conventional risk factors have extensive CAC[64]. Only age and male gender are strictly related to CAC. Although quantification of CAC scoring is limited by costs and radiation exposure, scanning of CAC has been proposed to monitor CVD progression and the effects of treatment[65]. The degree of baseline CAC score is the most important determinant for progression, which is more rapid when the baseline CAC score is high[66]. Traditional risk factors seem less important for CAC progression. CAC progression is not affected by lipid-lowering treatment with statins, even if LDL cholesterol is reduced[67]. Overall, these observations support the hypothesis that arterial calcification and atherosclerosis are different pathologic process which frequently coexist[68,69].
Significant CAC is associated with calcification in aortic and mitral valve [Figures 4 and 5][70,71]. This may suggest the presence of a common atherosclerotic pathway, although there are structural and histological differences. Aortic valve and mitral annulus calcifications have been recently assessed by echocardiography as a tool to reclassify low- and intermediate-risk patients to a higher risk class[28,72]. A semi-quantitative echocardiographic calcium score including aortic valve and root, the mitral valve and annulus, and the sub-mitral apparatus, showed a moderate correlation with coronary calcium[73]. Although echocardiography is not an ideal method for detection of valvar calcification because of its low specificity in distinguishing between calcification and dense collagen, this non-invasive technique might be used in routine clinical practice as a low cost and radiation free calcium score based reclassification of cardiac risk.

A further, but usually underestimated, advantage of imaging subclinical atherosclerosis compared to conventional risk-assessment tools, is the possibility to visualize the vascular effects of asymptomatic atherosclerosis. Despite the development of several global CV risk algorithm based on clinical risk factors, there is a large gap between the prevention guidelines and their adherence and control of CV risk factors[10]. There are some possible explanations: risk estimation tools are not routinely used in clinical practice and the judgements of physicians tend to be subjective[74]; whether the risk is correctly communicated to the patients and whether they clearly understand the information is unknown[75]; as a consequence, adherence to treatment is inadequate[76].

Visualization of subclinical atherosclerosis may stimulate physicians to provide appropriate pharmacological prescriptions and enhance patient’s motivation to adhere to medications treatment and adopt lifestyle changes. VVIPIVA, a large study using pictorial information about patients carotid ultrasound results has shown a significant improvement in the risk scoring and total and LDL-cholesterol at 1-year follow-up[77]. Although compared to control group the overall difference was small, it is well known that even small reduction in the risk factors have long-term benefit at population level[78]. However, smaller studies using CAC score or carotid plaques ultrasound showed conflicting results[79,80].

Imaging of subclinical atherosclerosis is superior to risk equations as it directly identifies the disease and can effectively predict the risk of future CV events in low- and intermediate-risk individuals. In addition, imaging can improve the adherence to guidelines based treatment in patients and their physicians.

Declarations of Interest
The authors declare no conflicts of interest.

Acknowledgements
The authors state that they abide by the “Requirements for Ethical Publishing in Biomedical Journals” [81].

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