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Review

"State-of-Art" paper of the Italian Working Group on Atherosclerosis: Preclinical assessment of early coronary atherosclerosis

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ABSTRACT

Although the early diagnosis and treatment for acute myocardial infarction have improved over the past decades, the morbidity and mortality from coronary artery disease (CAD) remain significant in Europe and worldwide. It is estimated that the majority of people in the developed countries who die suddenly from CAD, have no prior manifestation of disease, and the majority of these individuals are not considered to be at high risk. Accurate identification of individuals at risk of such events before the clinical manifestations is therefore required. This "State-of-Art" paper of the Italian Working Group on Atherosclerosis aims to *i.* provide an overview of both the traditional and emerging non-invasive imaging techniques used to detect early atherosclerosis in the general population with moderate cardiovascular risk; *ii.* identify the rationale for screening asymptomatic patients with preclinical atherosclerotic lesions and the optimal algorithm that should be used to detect them; *iii.* discuss the future directions of atherosclerosis research, with special focus on nanotechnology, aimed at early identification and treatment of low- and intermediate-risk patients.

1. Introduction

Atherosclerosis, once considered only as a lipid storage disease, is a disease of large and medium-sized muscular arteries, characterized by endothelial dysfunction and vascular inflammation. It is the leading cause of deaths worldwide, and its clinical presentations are preceded by subclinical atherosclerosis. It develops gradually as a subclinical condition, and eventually becomes clinically apparent as ischemic heart disease (IHD), cerebrovascular disease, or peripheral arterial disease. Atherosclerosis is the most important form of arteriosclerosis, which includes those pathological processes that cause hardening and thickening of the arteries. Subclinical atherosclerosis, or preclinical atherosclerosis, refers to the early stage of the atherosclerosis within the vascular wall, when the cardiovascular disease is not clinically evident. It is estimated that 50% of men and 64% of women in the developed countries who die suddenly from IHD, have no prior manifestation of disease, and the majority of these individuals are not considered to be at high risk, according to Framingham risk stratification. In the Cardiovascular Health Study, the prevalence of subclinical atherosclerotic disease was 36% in women and 38.7% in men and increased with age [1]. In the Framingham Offspring Study, 38% of women and 41% of men without any symptoms or evidence of IHD, had indeed evidence of aortic atherosclerosis at magnetic resonance imaging (MRI) [1]. Several studies have found increased prevalence of subclinical atherosclerosis in specific populations, such as postmenopausal women [2], women with a family history of premature IHD [3], and patients with metabolic disorders, such as impaired fasting glucose [4] and metabolic syndrome [5]. The incidence of preclinical atherosclerosis in the population of patients who die of sudden death, is especially high. It is estimated that 61% who died of sudden coronary death, has evidence of healed silent ruptures at postmortem [6], indicating that acute plaque rupture occurred commonly in arteries with evidence of previously healed silent ruptures. Given the burden of preclinical atherosclerosis, early detection of the disease before the clinical manifestations, has gained interest over the past decade, because of its high incidence and prevalence in the general population.

This "State-of-Art" paper of the Italian Working Group on Atherosclerosis aims to *i.* provide an overview of both the traditional and emerging non-invasive imaging techniques used to detect early atherosclerosis in the general population with moderate cardiovascular risk; *ii.* identify the rationale for screening asymptomatic patients with preclinical atherosclerotic lesions and the optimal algorithm that should be

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used to detect them; *iii.* discuss the future directions of atherosclerosis research.

2. Risk factors, biomarkers and risk score algorithms

For many years the endothelial damage has been considered as the initial event of atherogenesis. Now it is generally accepted that the onset of atherosclerosis does not require an endothelial damage, but rather a functional modification of the endothelium (endothelial dysfunction), in response to any pathogenic noxae. In recent years, new findings have established that inflammation plays an important role in mediating all stages of this disease, including the progression of atherosclerotic plaque towards thromboembolic complications. This provides important links between risk factors and mechanisms of atherogenesis. In general, risk factors are measurable biological characteristics of an individual, that precede a well-defined disease (e.g., myocardial infarction). Risk factors can be clustered into two categories: systemic and local factors. Systemic factors are represented by non-modifiable cardiovascular risk factors (age, sex, genetic characteristics), whereas modifiable factors are smoking, high cholesterol level, arterial hypertension, obesity and diabetes. Local factors are represented by mechanical stress produced by laminar or turbulent blood flow (shear stress). Several prospective studies, either cohort or randomized trials, in a broad range of populations, have demonstrated independent prediction of cardiovascular events by measuring risk factors, in the context of an integrated analysis represented by risk score algorithms. Main risk score algorithms used to estimate the 10-year individual's chances of developing cardiovascular disease, are listed in Table 1. Risk score algorithms can estimate the risk of cardiovascular events in apparently healthy, asymptomatic individuals, and are used to determine who should be offered pharmacological or non-pharmacological interventions for primary or secondary prevention. The choice of a specific risk score assessment should be individualized, based on patient-specific characteristics. Major limitation of the use of any risk algorithm is that cardiovascular risk can be predicted over a period of 10 years, which may poorly characterize younger patients.

In contrast to risk factors, biomarkers are biological indicators of disease, that are involved in its development without necessarily be the cause [7]. Below is a description of the major biomarkers that have been associated with different stages of atherogenesis.

2.1. Inflammatory markers

Since inflammation plays an important role in the initial development of atherosclerosis, many inflammatory markers such as C reactive protein (CRP), cytokines [interleukin (IL)-1, IL-6 and IL-18], Receptor for Advanced Glycation End-products (RAGE) and galectin-3, have been used for early evaluation of preclinical atherosclerosis [8]. CRP is a circulating pentraxin, predominantly produced in the liver. CRP has been implicated in multiple mechanisms of atherogenesis and plaque vulnerability, including increased expression of adhesion molecules, reduction of nitric oxide synthesis, alterations of the complement system and inhibition of intrinsic fibrinolysis [9]. Many epidemiologic studies have shown a significant association between elevated CRP and prevalence of atherosclerosis [9]. A specific range of CRP levels is used to predict the risk of cardiovascular disease (CVD). Thus, levels of CRP above 1.0 mg/L indicate that there is a low risk of developing CVD. If CRP levels are between 1.0 and 3.0 mg/L, the risk is intermediate, whereas CRP levels >3.0 mg/L indicate high risk. If patients have CRP greater than 10.0 mg/L, they should be evaluated for non-cardiovascular diseases.

Additional biomarkers that have been extensively studied in recent years, are soluble RAGE and Galectin-3. RAGE is a ubiquitous receptor, usually expressed at low levels in epithelial, neuronal, vascular and inflammatory cells. Galectin-3 is expressed in the epithelial and inflammatory cells such as macrophages. The expression of RAGE and Galectin-3 is upregulated after stress, inflammation and injury. The soluble form of RAGE (sRAGE) and Galectin-3 can be considered as indicators of destabilization of vulnerable plaque.

Cytokines such as IL-1α and β, IL-6, IL-18 and TNFα, are proinflammatory cytokines and central mediators in the cytokine network. Their transcripts are expressed in the vessel wall, suggesting that these cytokines might contribute to the development and progression of vascular diseases [10].

2.2. Lipid metabolic markers

Main lipid metabolic markers that are being used are apolipoproteins B and A-I (APO B, APO A-I), lipoprotein-associated phospholipase A2 (Lp-PLA2) and lipoprotein (a). APO-B is the protein component of atherogenic lipoproteins such as very low density lipoproteins (VLDL), intermediate density lipoproteins (IDL) and low density lipoproteins (LDL). APO A-1 is the protein component of non-atherogenic high density lipoprotein (HDL) cholesterol. APO-B and APO A-1 are important predictors for cardiovascular risk, with opposite effects on the atherogenic process. Since they are associated with an increased and decreased atherosclerotic process, respectively, the ratio between the two values appears to be a more useful indicator of atherosclerotic risk.

Lp(a) is linked to apolipoprotein(a) (apo A) by a single disulfide bond, and shows a structural similarity with plasminogen. Lp(a) can interfere with plasma fibrinolysis by inhibiting the generation of the

Table 1
Algorithms for risk prediction.

	Framingham risk score	PROCAM	Heart-score	QRISK2	Reynolds	CARRISMA score	NHANES score	SCORE (2003)	INTERHEART
Age (years)	≤74	≤65	≤65	≤74	≤60	≤60	≤60	≤65	≤65
Sex difference	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Prediction variables	Cholesterolemia, smoke SAP, T2DM	Cholesterolemia, smoke	Cholesterolemia, BMI	SAP, history of CVD, smoke cholesterolemia, BMI	Smoke, BMI, cholesterolemia SAP, T2DM, CRP, history of CVD	BMI, physical activity, smoke	SAP, smoke, T2DM, BMI	Cholesterolemia, smoke SAP	Smoke, history of hypertension or diabetes, diet, BMI, physical activity alcohol, cholesterolemia
Endpoint defintion	AP, cardiovascular death stroke, PAD, HF, TIA, ictus	Myocardial infarction	Cardiovascular death PAD	Myocardial infarction, AP CAD, stroke, TIA, PAD Cardiovascular death	Myocardial infarction coronary revascularization cardiovascular death	Myocardial infarction PAD, stroke, TIA	Myocardial infarction PAD, stroke, TIA	Cardiovascular death (IHD, arrhythmias, HF, stroke aortic aneurysm PAD	Myocardial infarction

Legend: AP, angina pectoris; CAD, coronary artery disease; TIA, transient ischemic attack; PAD, peripheral artery disease; HF, heart failure; AF, atrial fibrillation; RA, rheumatoid arthritis; BMI, body mass index; T2DM, type 2 diabetes; SAP, systolic arterial pressure; CARRISMA, CARdiovascular RISk Management; PROCAM, Prospective Cardiovascular Munster; NHANES, National Health and Nutrition Examination Survey; SCORE, Systematic COronary Risk Evaluation; IHD, ischemic heart disease, CRP, C reactive protein; CVD, cardiovascular disease.