

# Subclinical atherosclerosis: how and when to treat it?

Laura Gatto<sup>1,2\*</sup> and Francesco Prati<sup>2,3</sup>

<sup>1</sup>*Cardiologia d'Urgenza, Azienda Ospedaliera San Giovanni Addolorata, Roma, Italy;*

<sup>2</sup>*Centro per la Lotta Contro l'Infarto, Fondazione ONLUS, Roma, Italy; and*

<sup>3</sup>*UniCamillus - Saint Camillus International University of Health Sciences, Rome, Italy*

## KEYWORDS

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Risk factor;  
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Atherosclerosis is a condition characterized by a long, initial, asymptomatic phase. Progression of disease could lead to acute coronary events, such as acute myocardial infarction, unstable angina, or sudden cardiac death. However, there are imaging techniques, namely vascular echography and assessment of coronary calcium, capable to make the diagnosis of atherosclerosis at an early stage. There are several studies demonstrating the ability of statins to delay, and in some situation even revert the progression of this condition. Subclinical atherosclerosis is highly prevalent in people with optimal control of the risk factors, and the imaging techniques have been shown to provide an added value over the traditional risk factors: by identifying directly the condition, these techniques allow the reclassification of low-risk to intermediate- or high-risk subjects, thus directing the primary prevention therapeutic strategies, based on high efficacy statins, aimed at delaying or reversing the progression of the disease.

## Introduction

Atherosclerosis is a chronic and progressive inflammatory disease, which starts early in life and whose natural history is characterized by a long subclinical phase. Autopsy studies of young soldiers who died during the Vietnam War showed the presence of coronary atherosclerosis in about 50% of cases, and similar results were obtained from the analysis of the coronaries of adolescents and young adults who died of other causes, as they frequently presented early atherosclerotic lesions and in some cases fibrous plaques. However, atherosclerosis is often diagnosed at an advanced stage or after a cardiovascular event, sometimes fatal and sudden. The exact prevalence of subclinical atherosclerosis is impossible to determine, although it has been estimated in the USA that 50% of men and 64% of women who died of sudden cardiac death did not have a previous manifestation of the disease and most of them were not considered high risk according to the Framingham score.<sup>1</sup> In an evaluation of over 5000 adults aged >65 years enrolled in the Cardiovascular Health Study, the prevalence

of subclinical atherosclerosis was 36% in women and 38.7% in men.<sup>2</sup> Therefore, the need to diagnose this pathology at a very early stage is undoubtedly necessary to implement primary prevention measures that may delay or halt the progression of the disease.

## How to diagnose subclinical atherosclerosis

Currently, the cardiovascular risk stratification is based on the presence of identifiable risk factors and on the levels of some biochemical markers. However, this way of estimating the possibility of developing a coronary event recognizes several limitations, especially in low-risk subgroups, such as women and younger people. The introduction of non-invasive imaging techniques has instead given the possibility to diagnose atherosclerosis easily in asymptomatic subjects. The ultrasound of carotids and peripheral vessels was the first technique used and over the years has been accompanied by more complex methods, such as computerized tomography (CT) and magnetic resonance imaging (MRI).

The carotid intimal-media thickness (CIMT) can be measured both with ultrasounds and with MRI with excellent intra and inter-observer variability, if measured by

\*Corresponding author. Email: lauragatto81@gmail.com

experienced operators and using validated protocols.<sup>3</sup> In a meta-analysis of 14 studies involving 45 828 asymptomatic subjects undergoing a single measurement of CIMT and then followed for an 11-year period, CIMT was associated with the risk of the first myocardial infarction or first stroke.<sup>4</sup> The addition of the CIMT measure to the traditional Framingham Risk Score in 13 145 individuals enrolled in the ARIC study reclassified 23% of all subjects and 13.5% of those initially considered to be at intermediate risk at high risk.<sup>5</sup>

Coronary calcium (CAC, coronary artery calcium) is another marker of recognized subclinical atherosclerosis and is found in coronaries long before the development of clinically significant stenoses. The developments in recent years of CT (computed tomography) technology have allowed us to obtain images without motion artefacts and to quantify more precisely the CAC. The Agatston score represents the most widely used and validated coronary calcium measurement method with very low intra- and inter-observer variability. The CAC identifies the calcified plaques with an accuracy comparable to that of intracoronary ultrasounds and correlates very well with the presence and extent of coronary artery disease, rather than with the severity of the stenosis. In many studies, a CAC score <100 is usually associated with mild coronary artery disease, while a score >400 generally correlates with extensive disease.<sup>3</sup> The absence of CAC is highly predictive of the absence of coronary stenoses and in a study of 1764 patients with suspected CAD, those with zero CAC had a <1% probability of having significant coronary artery disease.<sup>6</sup> In a study involving 8855 asymptomatic, low- and intermediate-risk adults, the CAC score is associated with cardiac events with an incremental value with respect to age and other cardiovascular risk factors. As demonstrated in a sub-analysis of the MESA study, a CAC >300 is found in one-fourth of patients with the Framingham risk score between 15% and 30%.<sup>7</sup> However, the CAC score also provides independent prognostic information, and on the basis of extensive observational studies it is able to predict mortality for all causes more accurately than traditional risk scores.

Some imaging methods study specific vascular districts, however, given the systemic nature of atherosclerosis, the multiple district analysis is able to quantify more fully the atherosclerotic burden and to define its distribution. This is the context of the PESA study (Progression of Early Subclinical Atherosclerosis) which prospectively enrolled 4184 asymptomatic subjects employed by the bank Sant'Ander of Madrid, aged between 40 and 54 (average age 45 years, 63% males) to study the extent of atherosclerosis in various vascular districts (carotid arteries, aorta, iliac-femoral axis, and coronary arteries) by vascular ultrasound and coronary CT. The diagnosis of subclinical atherosclerosis was made in the presence of at least one plaque or a CAC  $\geq 1$  and was classified as focal (one site concerned), intermediate (2-3 sites concerned) or generalized (4-6 sites concerned). The authors defined the plaque as a focal protrusion inside the vessel lumen with a thickness >0.5 mm or >50% of the surrounding average-intimal thickness or in general a diffuse intimal-media thickening >1.5 mm. Subclinical atherosclerosis was diagnosed in 63%

of the population and in 41% of cases, it was classified as intermediate (28%) or generalized (13%). The plaques were found more frequently in the iliac-femoral district (44%), followed by the carotids (31%) and the aorta (25%). In contrast, coronary calcifications were only demonstrated in 18% of the participants: CAC 1-99 in 14%, 100-399 in 3%, and > 400 in 0.7%. In this study, the presence of subclinical atherosclerosis increased with age in both sexes and in all vascular districts and the extent of the pathology in men between 40 and 45 years was similar to that of women 5-10 years older. Instead, generalized atherosclerosis was prevalent in men and older subjects and was associated with obesity and other cardiovascular risk factors. The authors then studied the correlation with traditional risk scores: the average 10-year Framingham risk score in the PESA cohort was 6%, with 85% of those enrolled presenting a low risk, 14% an intermediate risk, and 1% a high risk. Among the participants with a low risk at 10 years, 58% had subclinical atherosclerosis which showed an intermediate or generalized extension in 36% of cases. Among the subjects classified as high risk according to Framingham, the diagnosis of subclinical atherosclerosis was made in 95% of the cases, 86% of which with intermediate or generalized extension. These associations were confirmed for each vascular district studied and analysed separately. The PESA study, therefore, allows us to conclude that subclinical atherosclerosis is highly prevalent in asymptomatic middle-aged subjects especially in the iliac-femoral district; furthermore, the study foresees a clinical follow-up at 6 years, still in progress, and whose results will be fundamental to clarify whether the diagnosis of atherosclerosis at a very early stage can impact on the primary prevention of cardiovascular events.<sup>8</sup>

### The role of statins in the treatment of subclinical atherosclerosis

The diagnosis of atherosclerosis at a very early stage is of fundamental importance because it allows the prompt implementation of primary prevention therapeutic measures. While all patients must be encouraged to change their lifestyle (attention to diet and exercise and smoking cessation), it is instead under discussion which patients need to be treated with pharmacological measures. Numerous studies have demonstrated the effectiveness of statins not only in reducing cardiovascular morbidity and mortality but also in slowing the progression of atherosclerosis and in some cases, even in inducing regression.

Highly effective statin therapy has been shown to reduce CIMT in individuals with familial hypercholesterolaemia, a population at high risk of developing atherosclerosis at an early age. The ASAP study (Atorvastatin vs. Simvastatin on Atherosclerosis Progression) randomized 325 subjects with familial dyslipidaemia to atorvastatin treatment at a dose of 80 mg a day or with simvastatin 40 mg. After 2 years, atorvastatin-treated patients experienced a significant reduction in CIMT of 0.031 mm compared to baseline, while in the other treatment arm an increase of 0.036 mm was observed instead.<sup>9</sup> The METEOR trial (The Measuring Effects on Intima-Media Thickness: an Evaluation of Rosuvastatin)

has instead demonstrated the efficacy of high-dose rosuvastatin in arresting subclinical atherosclerosis. The study included 984 subjects randomized to treatment with 40 mg of rosuvastatin or placebo. In order to be enrolled, patients had to present their age as the only cardiovascular risk factor or in general a 10-year Framingham risk score estimated to be <10%, a moderate intimal carotid thickening (between 1.2 and 3.5 mm) and high-low-density lipoprotein (LDL) cholesterol levels (average 154 mg/dL). In all patients, the CIMT was measured in 12 different points along all the carotid axes. After 2 years, rosuvastatin not only proved effective, compared to placebo, in improving the lipid profile but also in slowing the progression of the intimal-media thickness. The maximum CIMT value change for all 12 analysed carotid sites was  $-0.0014$  mm/year for the rosuvastatin group vs.  $0.0131$  mm/year for the placebo group ( $P < 0.001$ ). The maximum CIMT value change for the rosuvastatin group was  $-0.0038$  mm/year for common carotids ( $P < 0.001$ ),  $-0.0040$  mm/year for the carotid bulb ( $P < 0.001$ ) and  $0.0039$  mm/year for the internal carotids ( $P = 0.02$ ). The efficacy of rosuvastatin was maintained in all subgroups of patients based on gender, age, race, body mass index, and based on the presence of other cardiovascular risk factors including hypertension and basal cholesterol values. The authors of the study, therefore, concluded that in low-risk subjects high-dose rosuvastatin treatment is able to slow the progression of subclinical atherosclerosis measured through intimal-media thickness.<sup>10</sup> Even more, definitive results were achieved by a meta-analysis, which included 11 studies for a total of 3806 patients (average age of 58.7 years, 67% of males), in which the use of different types of statins, after a follow-up average of 25 months, not only is it associated with a slowdown in the progression of the CIMT but in some cases even with its regression.<sup>11</sup>

Contradictory results were obtained from studies that evaluated the efficacy of statins taking into account the other marker of subclinical atherosclerosis, the calcium score. The Francis Heart Study is a randomized trial that compared the use of a polypharmacy (atorvastatin 20 mg, vitamin C, and vitamin E) to placebo in 1005 asymptomatic subjects, aged between 50 and 70 years and with CAC higher than 80th percentile expected by gender and age. All patients were also treated with aspirin (81 mg) for a period of about 4 years. Despite a significant reduction in the values of total and fractionated cholesterol, the use of atorvastatin did not cause any effect on the progression of the Agatston score ( $P = 0.80$ ), resulting, however, in a reduction in cardiovascular events that although not significant in the general population of the trial (6.9% vs. 9.9%,  $P = 0.08$ ), became so in some particular subgroups of patients, such as those with baseline CAC > 400 (8.7% vs. 15.0%,  $P = 0.046$ ) and in those with positive family history for ischaemic heart disease (7.2% vs. 12.5%,  $P = 0.040$ ).<sup>12</sup> A meta-analysis of five studies, conducted by Henein and Owen,<sup>13</sup> explained these inconsistencies, where the authors concluded that the use of statins does not reduce CAC progression, but rather reduces the luminal narrowing that is generally due to the pathological deposit of soft inflammatory tissue, while the increase of the calcium score is due to a tissue mineralization on which it is difficult for

statins to have any effect. To resolve any doubt, the American guidelines that in 2013 suggested to consider statin treatment in subjects with Agatston score  $\geq 300$ .<sup>14</sup> A sub-analysis of the CONFIRM study (COronary CT Angiography Evaluation For Clinical Outcomes: An International Multicenter) is very recent, in which treatment with statins has been linked to mortality and other cardiac events. The study involved 8016 patients with subclinical atherosclerosis who underwent quantification of coronary calcium by means of the Agatston score and quantification of coronary artery disease by counting the coronary segments involved (SIS Score). After a mean follow-up of 2.5 years, patients who were not on statin treatment had an incremental risk of mortality for all causes with increasing CAC score [CAC 1-99: hazard ratio (HR) 1.65, CAC 100-299: HR 2.19, and CAC  $\geq 300$ : HR 2.98] and of the SIS score (SIS 1: HR 1.62, SIS 2-3: 2.48, and SIS  $\geq 4$ : 2.95). In contrast, this type of correlation was not found for patients on chronic statin therapy. Similar results were also obtained for the risk of adverse cardiac events, such as myocardial infarction, unstable angina, and new coronary revascularizations.<sup>15</sup>

Therefore, if the usefulness of statins is undoubted, it remains to define what is the threshold value of LDL desirable in this category of patients. Probably also for the subclinical atherosclerosis the law of the 'lower is better' is valid as shown by an elegant sub-analysis of the PESA study, in which Fernández-Friera *et al.* extracted from the general cohort 1179 patients considered 'free' from cardiovascular risk factors, defined as non-smokers, with blood pressure values <140/90 mmHg, fasting blood glucose <126 mg/dL, total cholesterol <240 mg/dL, LDL cholesterol <160 mg/dL, and high-density lipoprotein cholesterol > 40 mg/dL. Despite the absence of traditional risk factors, subclinical atherosclerosis was highly prevalent in this cohort (49.7%), with 46.7% of subjects presenting with plaques in peripheral vessels and 11% coronary calcifications. The authors also identified an additional subgroup of 740 patients with 'optimal' control of risk factors (blood pressure <120/80 mmHg, fasting blood glucose <100 mg/dL, and total cholesterol <200 mg/dL), which however presented atherosclerosis in 37.8% of cases. Multivariate analysis showed that independent factors for the presence and extent of subclinical atherosclerosis were age, male sex, and the basal value of LDL cholesterol; in particular, they found a linear relationship between LDL values and the increase in the prevalence of subclinical atherosclerosis, which went from 11% in patients with LDL values between 60 and 70 mg/dL to reach 64% in subgroup with LDL between 150 and 160 mg/dL. This progressive increase was observed in both sexes, for the number of vascular districts involved and for each vascular district analysed separately.<sup>16</sup>

## Conclusions

Subclinical atherosclerosis is highly prevalent also in subjects with optimal control of risk factors and imaging techniques have shown an added value compared to traditional risk scores: by directly identifying the pathology they allow

to reclassify as high-risk subjects initially considered at mild or intermediate risk and more correctly guide the primary prevention therapeutic strategies based on the use of highly effective statins that slow the progression of the disease.

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