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Present and future of coronary risk assessment

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The search for subclinical atherosclerosis is carried out in several arterial districts using ultrasonography and computed tomography (CT). Coronary calcium assessed by computerized tomography (calcium score) is a well-validated marker of atherosclerosis and able to correlate with the extent of coronary artery disease and the risk of cardiovascular events. The evaluation of carotid atherosclerosis by ultrasonography is a technically simple and low-cost solution. However, the literature does not provide a sufficient number of evidence to clarify the clinical impact of carotid atherosclerosis and in particular the risk of developing cardiac events. According to the researchers of the Progression of Early Subclinical Atherosclerosis (PESA) study, subclinical atherosclerosis research should preferably be carried out in the femoral district, which is more easily affected by atherosclerosis. Pending the data from the PESA study, which will better clarify the role of ultrasound applied in non-coronary districts, the coronary calcifications seems to be a reasonable solution. It is possible that in the future imaging techniques (CT-PET) capable of studying the extent and functional status of coronary atherosclerosis will further improve the identification of the risk of cardiovascular events.

Imaging techniques for the non-invasive study of atherosclerosis

The search for subclinical atherosclerosis plays a fundamental role in a modern cardiac screening program. It can be performed in different arterial districts and employs two widely used clinical methods: ultrasonography and computed tomography (CT).

Coronary calcium

Coronary calcium assessed by computed tomography (calcium score) is a well validated and reproducible marker of atherosclerosis.[1] Coronary calcifications (CAC) are in fact an expression of an advanced subclinical atherosclerosis[2,3] and, although they are not an expression of plaque instability, their extent correlates with the severity and number of coronary plaques.[2]

The quantification of the calcium score is well standardized and the exposure to X-rays is generally low, with values of ± 1 mSv with current techniques. The index most used in the studies is the Agatston score[4] which showed a high negative predictive value.[5] Three subgroups are usually identified based on the quantification of the Agatston score: (i) Agatston score equal to 0 (absence of calcium), (ii) with value between 1 and 400, and (iii) with value <400.[5] An Agatston score >400 generally correlates with extensive disease, while the absence of CAC is able to exclude coronary stenosis. According to a study of 1764 patients with suspected coronary artery disease (CAD), subjects without calcifications (with zero CAC) had a $<1\%$ chance of having significant coronary artery disease.[5] Overall, CAC appeared very sensitive and moderately specific in recognizing significant coronary narrowing.

According to the Multi-Ethnic Study of Atherosclerosis[6] study, the CAC was very effective in improving the stratification of low [Framingham Risk Score (FRS) of 5.1–10%] and intermediate (FRS 10.1–20%) subjects. For example, in the latter category, the CAC >300 was present in

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24% of subjects with Framingham risk between 15 and 20% and was present in 30% of subjects with Framingham risk >20%.

In fact, the Agatston score must be considered an independent risk factor for coronary heart disease and its use can make the calculation of cardiovascular risk particularly accurate in patients with risk scores around the threshold values of 5% and 10%.[7,8]

A meta-analysis[9] correlated the risk of cardiovascular events with CAC. The relative risk (RR) for cardiovascular events was 2.1 for CAC scores between 1 and 108 and approximately 10 for CAC scores >400.[10] In particular, a high CAC score predicted high risk in subjects considered to be at intermediate cardiovascular risk according to the score Framingham.[11]

Ultrasonography

The evaluation of carotid atherosclerosis by ultrasonography is a technically simple and low-cost solution. Similarly to the CAC, the detection of atherosclerotic plaques is able to reclassify the cardiac risk in a consistent number of subjects stratified by the Framingham Risk Score.[12] Out of 13 145 individuals enrolled in the ARIC study, the carotid plaque and intima-media thickness (IMT) reclassified 23% of all subjects and 13.5% of those initially considered to be at intermediate risk at high risk. In females, however, IMT, unlike the presence of carotid plaque, had no role in defining the risk of cardiovascular events.

However, the literature does not provide a sufficient number of evidence to clarify the clinical impact of carotid atherosclerosis and in particular the risk of developing cardiac events. The Progression of Early Subclinical Atherosclerosis (PESA) study, which provides for a six-year clinical follow-up, will make an important contribution to clarifying these aspects and in particular the role of early diagnosis.[13]

Carotid intimal-media thickness

The evaluation of the average carotid intimal-media thickness is based on a scientific basis; both the intima and the media are in fact involved in atherogenesis and its progression.[14] The close association between average intimal thickness of the common carotid and cardiovascular risk factors has been demonstrated in numerous studies.[15,16] The relationship between mean IMT and cardiovascular disease is less convincing. Studies have shown that intima-media thickening is able to predict cardiovascular events and stroke.[17,18] However, in a more recent meta-analysis of 14 studies and over 40 000 asymptomatic subjects, the additive value of IMT to clinical risk results expressed by the Framingham Risk Score was very low (only 0.8% were correctly reclassified).[19]

Presence of atherosclerosis according to age and arterial district explored

The PESA study investigated the presence of atherosclerosis in various arterial districts and in different age groups.[20,21] The presence of atherosclerotic plaques assessed by ultrasonography was defined as a protrusion within the lumen >0.5 mm or >50% of the reference tracts or a diffuse intima-media thickness > 1.5 mm. Coronary heart disease was instead defined by the presence of an AGATSTON score of at least 1, indicating a minimal calcific component. Atherosclerosis was also classified as focal (one affected site), intermediate (2–3 affected sites) or generalized (4–6 affected sites).

In subjects aged between 40 and 44 years, carotid atherosclerotic disease was detected in 28% of the males. The percentage rose to 37% when atherosclerosis was searched for in the iliac-femoral axis and dropped to 15% in the coronary district. In the subsequent age groups, between 45 and 49 years and between 50 and 54 years, there was a gradual increase in the percentage of subjects affected by atherosclerosis. Focusing attention on subjects aged between 50 and 54 years, the one in which an initial primary prevention cardiology visit is usually suggested, the percentage of atherosclerosis in the carotid, iliac-femoral and coronary districts were, in the male sex, 48%, 72%, and 43%, respectively.

It is interesting to note that the iliac femoral district is by far the most affected by atherosclerosis and that over 7 out of 10 subjects have atherosclerosis in the 50–54 age group. Another interesting aspect lies in the lower involvement of coronary atherosclerosis, especially under the age of 50, even if the comparison is made difficult by the use of different methods (calcium score for coronary arteries instead of ultrasound).

Among the subjects classified as high risk according to Framingham, the diagnosis of subclinical atherosclerosis was made in 95% of cases, 86% of which with intermediate or generalized extension. The PESA study, therefore, concluded that subclinical atherosclerosis is highly prevalent in asymptomatic middle-aged subjects, especially in the iliac-femoral area.

Genetic cardiovascular risk and atherosclerosis

Family history of ischaemic heart disease is still considered an important coronary risk factor. In recent years, genetics has proposed itself as a more precise solution in defining the risk of developing atherosclerosis or myocardial infarct. The search for carriers of rare monogenic mutations, which carried a vastly increased risk of developing coronary heart disease, was insisted upon. However, the risk of developing cardiovascular disease must be considered polygenic and must therefore be related to multiple mutations of the genome, which together can identify a slice of the population at risk for cardiac events. Since 2007, over 50 independent loci have been identified that were associated with the possibility of developing coronary heart disease.[22] These alleles, when aggregated into a polygenic risk score, are able to predict coronary events.

Polygenic risk for coronary heart disease identification is now a reality. Khera *et al.*[23] quantified polygenic risk in over 50 000 subjects. The risk of developing cardiovascular events increased by 91% in subjects who belonged to the top quintile, compared to those who belonged to the lowest quintile. However, lifestyle played an important role,

being able to modify genetic risk. For example, in the subgroup with the highest genetic risk, a healthy lifestyle was associated with a 46% reduction in relative risk of coronary events (HR 0.54).

Other studies have documented that there is a close relationship between polygenic risk and the extent of atherosclerosis.[24,25] The polygenic risk correlated both with the plaque burden, assessed by coronary CT, and with the coronary calcium score value.

How to look for atherosclerosis

Arterial site and imaging techniques to explore it

According to the researchers of the PESA study, subclinical atherosclerosis research should preferably be carried out in the femoral district, which is more easily affected by atherosclerosis. However, there remains a tendency to search for atherosclerosis in districts that we could define as more noble (brain and heart) using carotid ultrasound or coronary calcium score.

The calcium score is a well-validated method, little exposed to an interpretative subjectivity and able to stratify the risk of cardiovascular events, as demonstrated by several clinical studies.

The search for atherosclerosis using ultrasound may represent a reasonable solution. We await the data from the PESA study to clarify whether the diagnosis of atherosclerosis in the fourth to fifth decade or at a still very early stage may impact on the primary prevention of cardiovascular events.[13]

Extent and type of atherosclerosis

Some imaging methods study specific vascular districts but, given the systemic nature of atherosclerosis, the multiple district analysis is able to more fully quantify the atherosclerotic burden and define its distribution. In secondary prevention, the extent of coronary artery disease correlates with clinical events. The Syntax score is an excellent tool for stratifying risk and suggesting the most suitable revascularization technique.[26] Similarly, the presence of multivessel coronary artery disease has been considered an important clinical variable for several years.[27] The follow-up of the PESA study will clarify the role prognostic of the extent of atherosclerosis in primary prevention.

The composition of atherosclerosis is a second variable capable of identifying those at risk of cardiac events. The presence of a low attenuation signal on CT angiography indicates the presence of lipids with reasonable accuracy. Motoyama *et al.*[28] demonstrated in a study conducted with coronary CT in over 1000 subjects, that the presence of high-risk plaques (vessel remodelling and signal attenuation, indicating a lipid composition), presented a worse prognosis. In the presence of the two variables, the risk of developing acute coronary syndrome was 22.2% vs. 3.7% in their absence ($P > 0.001$).

In the future, PET-CT could further improve risk stratification of cardiac events. The method is potentially able to provide information on the functional state of coronary atherosclerosis and in particular to evaluate the inflammatory component,[29,30] thus offering information comparable to that obtained with invasive intra-coronary methods.[31]

When to look for atherosclerosis

There is no doubt that the presence and extent of atherosclerosis is a function of age. A question that many people ask is when to resort to the first screening. According to the PESA[13] study, the presence of subclinical atherosclerosis increased with age in both sexes and in all vascular districts. The extent of the disease in men between the ages of 40 and 45 was similar to that of women 5–10 years older.

According to some, a very early evaluation is preferable, starting from the age of 20, simply using femoral ultrasonography.[13,32] In the presence of an initial atherosclerosis, it is possible to resort to a correct diet and lifestyle, and possibly the use of a lipid-lowering therapy.

We find a different approach more pragmatic, which involves screening for atherosclerosis starting from the fourth decade (45–50 years), anticipating checks to those with multiple risk factors or, in a future scenario, to those who have a high polygenic risk. In this way, the issue of reducing cardiovascular risk is addressed in the age group in which the risk of heart attack increases consistently.

Final considerations

The presence of sub-clinical atherosclerosis has a clear prognostic significance. Nonetheless, many cardiologists do not consider it in a primary prevention program. In the risk cards, the possibility of suffering a heart attack, stratified by age, is a function of the classic risk factors, but is not based on the search for atherosclerotic plaques.

In the most recent guidelines on the treatment of cholesterolaemia,[33] the presence of critical atherosclerosis (>50%) in at least one district (coronary or peripheral) modifies the target of LDL cholesterol, which, similarly to secondary prevention protocols, must be pushed below of the cut-off of 55 mg/dL.

The conclusion is acceptable. However, some aspects remain to be clarified.

It has not been well established what is the extent of narrowing on ultrasound to be considered as a cut-off to suggest a more aggressive therapy. For example, it seems reasonable to insist on therapy to reduce LDL cholesterol even in subjects with plaques below 50%.

The ideal method for searching for atherosclerosis has not been established. Pending the data from the PESA study, which will better clarify the role of ultrasound applied in non-coronary districts, the CAC seems to be a reasonable solution. More refined methods, such as CT or PET-CT (but at a far greater cost) could further improve risk stratification.

Another element of uncertainty, which has already been mentioned, concerns the age at which to carry out a first screening. Many agree on the need to propose a screening

at the time of reaching the age of 45–50, when the risk of cardiac events becomes concrete.

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