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Preclinical atherosclerosis, Metabolic Syndrome and Risk of Cardiovascular Events

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Introduction

Atherosclerotic disease is a chronic disorder developing insidiously throughout the life and usually progressing to an advanced stage by the time symptoms occur. In order to realize cardiovascular (CV) prevention, the detection of asymptomatic but diseased patients is crucial for an early intervention, since in these subjects there are opportunities to alter the progression of disease and the outcome (1).

However, the simply analysis of risk factors don't permits to identify always these subjects since it doesn't informs about the effect that risk factors (RF) had already provoked and may more provoke on the individual vasculature. Besides, the risk factors known predict can explain only the 90 percent of cardiovascular disease (CVD) and traditional algorithms for prediction of CV risk failed to predict a proportion of cardiovascular events (CVE), realizing a "risk factors prediction gap" (2). It may be explained by several reasons: the epidemiology-derived models, based on the prediction of long-term risk, may not accurately predict short-term events, they don't take into consideration emerging and novel risk factors; risk algorithms don't identify, among patients with neither a previous history of CVD nor an high risk for atherosclerotic disease, those who will develop acute myocardial infarction and/or sudden coronary death as first CVD manifestation, and this may be due to the fact that the factors responsible of plaque formation and growth are not necessarily the same responsible of its instability and rupture, being the latter related to inflammation, thrombosis and plaque morphology (3).

So, a possible approach to evaluate the individual global cardiovascular risk with more accurateness is to identify risk factors combination that more easily produces vascular damage, or alternatively, to evaluate directly the arterial wall and its damage degree. The former approach is performed by the evaluation of metabolic syndrome, the latter by the non-invasive study of pre-ATS markers.

Metabolic Syndrome

The metabolic syndrome is a complex of correlated risk factors for CVD and type 2 diabetes mellitus occurrence. Risk factors include high blood pressure, cholesterol, triglycerides levels and fasting glucose, low high-density lipoprotein levels and abdominal obesity. The presence of at least three of these factors is diagnostic of Met-S (16) (see Table 1). It doesn't represent the individual absolute risk for CVD, since it doesn't comprise other elements that are important in the global risk determination, but it is the sign that metabolism abnormalities capable of maintain and enhance themselves are established. Indeed, these metabolic alterations occur together more often that would be expected and the risk associated to their clustering is greater than the sum of the risk associated with each factor alone. Besides, the risk increases with number of MetS components (5).

All the factors characterizing the MetS are responsible for the endothelial dysfunction and for the progression of atherosclerotic lesions. Therefore, it doesn't surprise that the diagnosis of MetS is related to the IMT and to the velocity at which it increases over time (6, 7). The components of MetS interact synergistically to affect vascular thickness and promote the development of subclinical atherosclerosis and overt carotid atherosclerosis (8);

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occurrence of MetS is associated with the acceleration of carotid IMT increase (11). Indeed, it has been observed that the incidence of CVE was higher in subjects affected by MetS, both in those with and in those without pre-ATS, and that the coexistence of MetS and pre-ATS enhanced the risk of CVE. Among the different subgroup of subjects, the greater incidence of events was recorded in those affected by both pre-ATS and MetS, rather than in those affected by only one or neither of these two conditions. Therefore, the presence of pre-ATS enhances the power of MetS to favor cerebro- and cardiovascular events occurrence in twenty years follow-up (10).

Table 1. Criteria for clinical diagnosis of the metabolic syndrome according to the 2009 Joint Scientific Statement on MetS (4).

Measure	Categorical Cut Points
Elevated waist circumference*	Population- and country-specific definitions
Elevated triglycerides (drug treatment for elevated triglycerides is an alternate indicator†)	≥150 mg/dL (1.7 mmol/L)
Reduced HDL-C (drug treatment for reduced HDL-C is an alternate indicator†)	<40 mg/dL (1.0 mmol/L) in males; <50 mg/dL (1.3 mmol/L) in females
Elevated blood pressure (antihypertensive drug treatment in a patient with a history of hypertension is an alternate indicator)	Systolic ≥130 and/or diastolic ≥85 mm Hg
Elevated fasting glucose‡ (drug treatment of elevated glucose is an alternate indicator)	≥100 mg/dL

HDL-C indicates high density cholesterol;
*It is recommended that the IDF cut points be used for non-Europeans and either the IDF or AHA/NHLBI cut points used for people of European origin until more data are available.
†The most commonly used drugs for elevated triglycerides and reduced HDL-C are fibrates and nicotinic acid. A patient taking 1 of these drugs can be presumed to have high triglycerides and low HDL-C. High-dose ω-3 fatty acids presumes high triglycerides.
‡Most patients with type 2 diabetes mellitus will have the metabolic syndrome by the proposed criteria.

Several studies have confirmed the association between MetS and CVD. MetS is correlated with 2-fold increased risk of developing CVD over the next 5 or 10 years, 2- to 4-fold increased risk of stroke, 3- to 4- fold increased risk of MI, and 2-fold increased risk of dying from such an event (11), regardless of a previous history of CVD (12) or the diagnostic criteria used (16). A study conducted in elderly failed to demonstrate a relationship between MetS and CV risk (14). Moreover, the prospective studies that investigated the relationship between MetS and CVE, were carried out for long follow-up period, until to 20 years (15). It suggests that MetS prognostic power is better on long term follow-up, while on short term (5-10 years) the traditional risk scores are more accurate (16); it may be explained by the role that the MetS have in the initiation and progression of atherosclerotic process, rather than in the plaque instability.

Preclinical atherosclerosis

Atherosclerotic process develops gradually over the year. First lesions are detectable in children and adolescents: they are fatty streaks that alter arterial tunicae and layers leading to a structural transformation of arterial wall without giving clinical signs; over time, they turn into atherosclerotic plaques that determine luminal restriction and symptoms appearance; they are vulnerable to complications related to plaque instability, that manifests as acute events (see Figure 1). The endothelium dysfunction have a crucial role in this process, since it represents both the final pathway whereby the CV risk factors provokes atherosclerotic lesions, and the factor determining the plaque vulnerability and the complications arising.

During the early stage of this process, the anatomical but not functional alterations determine the absence of symptoms, although structural damage, even if minimal, is already present. This stage is named "preclinical atherosclerosis" (pre-ATS) and it is the sign that "something is beginning to change" in the vascular wall; but it is potentially susceptible to correction, thus, its detection advises that it would be useful to intervene. Preclinical lesions don't occur

after the same time interval or with the exposure to the same number of CV risk factors in all patients (20). Indeed, in different subjects the vascular response to the same pathogen factor is various. This variability is probably due to genetic susceptibility, enhancement effect of the combination of risk factors, time and intensity of exposition to the same risk factors, interaction with environmental factors.

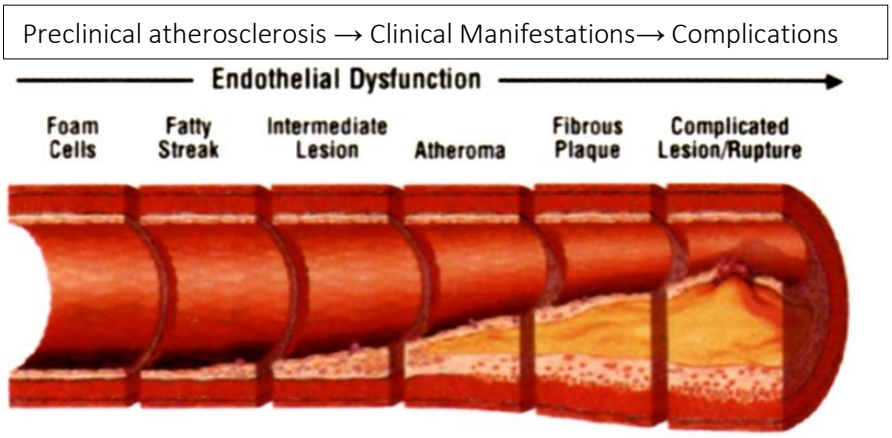


Figure1. The natural history of atherosclerotic disease. From Stary HC et al. Circulaton1995; 92:1355-74

To comprise the basis of pre-ATS assessment, we also must remember that the atherosclerosis is a systemic and multidistrict disease that begins at the same time but progresses with different velocity in the various districts affected. The different hemodynamic characteristics and the different responses to RF explain why some districts are involved before others or why their involvement is associated with different RF. Population studies demonstrate that the severity of atherosclerosis in one arterial territory is related to the involvement of the other districts (17). So, the identification of atherosclerotic damage in different artery, indirectly informs us of coronary damage. Among the different districts, the carotid arteries are the first involved, and the more easily assessed. These characteristics make them an optimal target for screening investigations.

Preclinical atherosclerosis assessment.

The understanding of role of the vascular endothelium in the atherosclerotic disease and the identification of subsequent stages of arterial wall damage has led to the development of invasive and non-invasive techniques to anatomical or functional assessment of pre-ATS.

The carotid artery scanning through ultrasonography to evaluate intima-media thickness (IMT) identifies pre-ATS carotid involvement (but it may detect also carotid plaques that are sign of advanced atherosclerosis). The ankle-brachial index (ABI) evaluates the ileo-femoral-popliteal axis involvement. The measurement of the coronary calcium score by coronary computed tomography (CT) assesses the atherosclerotic burden in coronary artery. These techniques are the most widespread and an amount of data confirmed their predictive value for cardiovascular events and their utility in CV risk stratification. So, they appear among the imaging methods recommended by the last ESC guidelines of CVD prevention for risk assessment in asymptomatic adults at moderate risk (1).

However, other techniques allow evaluating pre-ATS, but they are less used since data about their predictive value are inconclusive, or their use is limited by invasiveness or availability, so they are nowadays research tools or investigation suitable for specific purposes. They include methods that assess endothelial dysfunction, vascular stiffness and techniques that visualize directly arterial wall.

Among the techniques which evaluate the endothelial dysfunction, the most wide used is the brachial flow-mediated dilatation (FMD), that assesses the vasomotor capacity of a large artery such as the brachial one; endothelial dysfunction may also be detected by venous occlusion pletismography and peripheral arterial tonometry, that are more influenced by small arteries and microcirculation function, or may be assessed by dosage of levels of circulating marker such as cellular adhesion molecules, von Willebrand factor, oxidized low density lipoproteins (LDL) and endothelial progenitor cells.

The arterial stiffness, which is related also but not only to atherosclerotic process, can be evaluated by the pulse wave velocity (PWV) and by photophlethysmographic assessment of pulse wave reflection in finger digital arteries (19).

The direct visualization of artery wall may be obtained through multislice CT coronary angiography that gives imagines of the coronary district; or

through the magnetic resonance (RM) imaging of coronary wall, that is capable of identify positive remodeling in patient with subclinical atherosclerosis. Also the ophthalmoscopy allows the direct visualization of artery atherosclerosis but in retinal district; the wall-lumen ratio of small arteries can be measured invasively through subcutaneous gluteal biopsy (1).

All these methods are related to coronary atherosclerosis but the role in CV risk assessment is not established for all these.

In this review we limited the discussion to the technique that for easiness of execution or wide availability are suitable for large-scale CV risk prediction.

Intima media thickness and carotid ultrasound

Carotid artery IMT is the distance between the media-adventitia and the intima-media interfaces measured in a longitudinal scansion through B-mode ultrasonography. Its value correlates with anatomical layers thickness (see Figure 2).

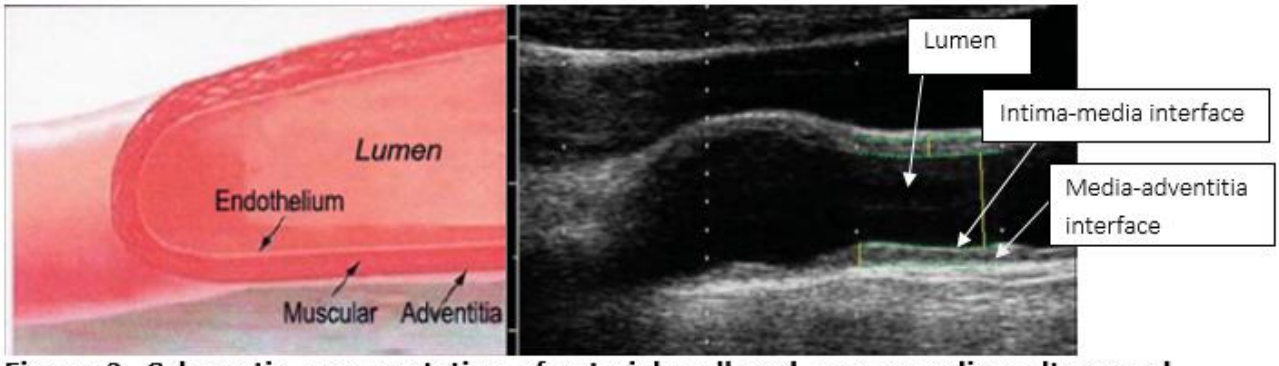


Figure 2. Schematic representation of arterial wall and corresponding ultrasound image annotated for anatomic landmarks (19).

Intima-media thickness varies with age gender and ethnicity and with the segment considered: it increase with age and is thicker in man than in women and in carotid bulb (CB) than in the other segments. Differences in measurement are registered also between ultrasound equipment used. All these factors make difficult to identify normal values, besides, cardiovascular risk gradually increases with rising IMT. However, a threshold value >0.9 mm is considered abnormal and it is a sign of early atherosclerosis (19).

Plaque, instead, is sign of later stages of atherosclerosis: is defined as a focal structure of the inner vessel wall that encroaches into the arterial lumen at least ≥0.5 mm (or >50%) of the surrounding IMT, or any IMT measurement ≥1.5 mm.

IMT depends not only on early atherosclerosis but also on smooth muscle hypertrophy or hyperplasia, related to genetic factors, hypertension, and age-related sclerosis (1). Among risk factors, it correlates with traditional (hypertension, dyslipidemia, type 2 diabetes mellitus, smoking) and non traditional (homocysteine, inflammation's markers as C-reactive protein and fibrinogen, uric acid, type 1 diabetes or gestational diabetes) risk factors exposure (20).

Different segment of carotid artery seems to be influenced by different factors and related to different outcomes. Diastolic blood pressure and fasting glucose relate better to the common carotid artery (CCA); plaques are more often located in CB or in internal carotid artery (ICA) than in CCA, probably because the first two tracts are submitted to low shear stress and to marked oscillations in the direction of wall shear stress, conditions that favors the plaque formation (19).

It predicts the occurrence of myocardial and cerebrovascular events independently of CV risk factors (21). Increased IMT is related to rates of coronary heart disease (CHD), stroke, myocardial infarction and cardiovascular mortality. A recent meta-analysis calculated that every 0.1 mm rise in the IMT values increases the rate of myocardial infarction of 10–15% and the rate of stroke of 13–18% (22). This correlation has been observed in several categories of asymptomatic subjects with CV risk factors , such as women in post-menopausal period (23), subjects with low HDL-cholesterol levels (24), metabolic syndrome (25) or with a cluster of CRF including age > 45 years and family history of cardiovascular disease (26) but also in young subjects (27) and in subjects without risk factors; in subject with and without previous vascular disease. A thicker IMT is also a negative prognostic factor after percutaneous coronary intervention (PCI) (28) and after coronary artery bypass graft (CABG) (29).

The predictive value holds true for both carotid bifurcation and common carotid artery, although the

first reflects primarily atherosclerosis and the second vascular hypertrophy. From separated analysis of cardio and cerebrovascular events rates emerges that ICA IMT is stronger associated with incident myocardial infarction, while CCA IMT is stronger associated with stoke incidence (30). Besides, predictive value seems to be greater in women than in men. The relative risk for events is slightly lower after adjustment for the presence of traditional risk factors, but it remains elevated at higher IMT value. The risk for cardio and cerebro-vascular events is non linearly related to IMT, since it increases more rapidly at lower than at higher IMT value (1, 31).

Even though, the evidence to support the carotid IMT measurement to help risk stratification is limited. Has been calculated that presence of a plaque and increased carotid IMT add little to each other for predicting CV events in top of traditional risk score, such as Framingham or SCORE (32), although it permits reclassifying patients in another risk category in ARIC study, and stratify with more accurateness CV risk (the ARIC study has published a calculator incorporating IMT and plaque assessment to Framingham risk score) (33). Thus it is not recommended as screening investigation for overall asymptomatic patients, but as tool for further risk stratification and assess end-organ damage in patients at intermediate risk (34). A recent systematic review concluded that the added predictive value may be primarily found in asymptomatic individuals at intermediate CV risk. Thus, in these subjects, it may help to make decisions about the appropriateness of medical treatment for primary prevention.

Also plaque characteristics are predictive for CV events: echo lucent stenotic plaques are related to a much higher risk of cerebrovascular events than other plaque types (1).

However, increased CIMT is evident when atherosclerotic damage is already present, thus is a later predictor of coronary disease compared to other pre-ATS marker such as endothelial dysfunction that become evident earlier.

Ankle-brachial index

The ankle-brachial index (ABI) is the ratio between the blood pressure in ankle and that in brachial artery. It is performed through automated device or with a continuous wave Doppler unit and a sphygmomanometer (see Figure 3). Physiologic ratio is > or = 1. An ABI < 0.9 is a marker of peripheral artery disease (PAD) since indicates ≥50% stenosis between the aorta and the distal leg arteries, and then advanced atherosclerosis, although yet asymptomatic (34).

The ABI value is related with all CV risk factors, particularly with smoke and diabetes mellitus and age.

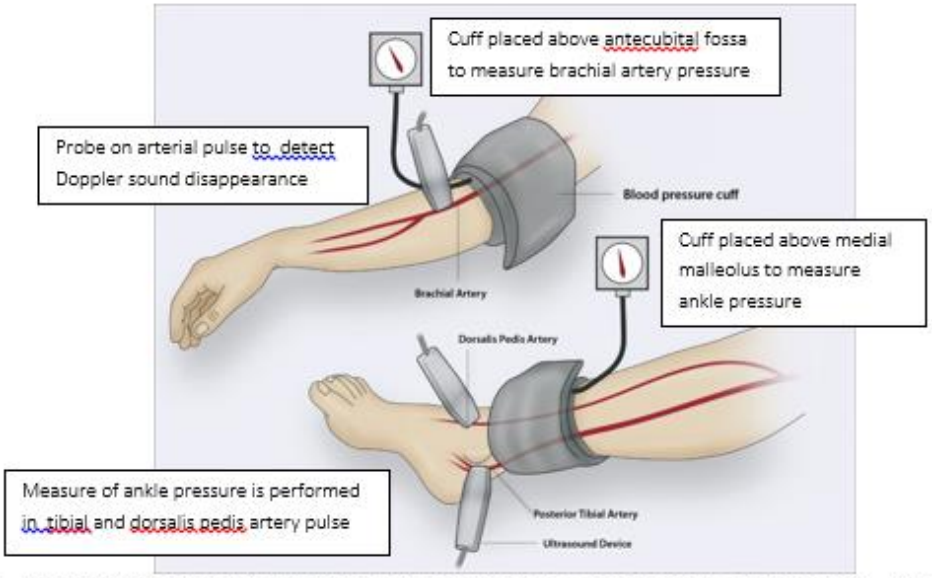


Figure 3. Measurement of the brachial systolic pressure and ankle systolic pressure with a sphygmomanometer and a Doppler ultrasound device.

A reduced ABI is related to multifocal ATS: it is associated with presence and extension of coronary atherosclerosis, and with IMT values in femoral and carotid districts (35).

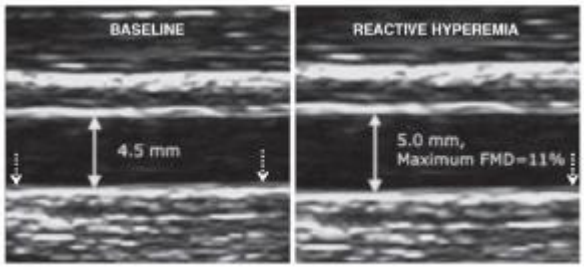
It identifies a subgroup of subject, also among asymptomatic for PAD, at higher risk coronary heart disease: it is predictive of development of angina, myocardial infarction, congestive heart failure, CABG surgery, stroke, or carotid surgery (36). It

confers twice 10-years CV mortality and major coronary event (non fatal MI, unstable angina, myocardial revascularization) risk compared with the overall rate in each Framingham category. It is associated with an incidence of CV morbid and fatal events of about 20% in 10 years (37). In PAD subgroup of CAPRIE study, for every 0.1 reduction in ABI a 10.2% increase of risk of dying or CV events occurrence was registered (38).

The prevalence of a reduced ABI is about of 25-50% in subjects selected for history of diabetes, smoke habitus or age>70 years (39); for this reason TASC II Consensus Document recommended its assessment in these population, in subject at intermediate risk according Framingham score and in subjects complaining symptoms of claudicatio (40).

Flow-mediated vasodilatation

Endothelial function may be explored evaluating vasomotor response to a stimulus that determines the release of vasoactive substances by endothelium and requires its integrity. It may be realized, in a noninvasive manner, inducing a transitory ischemia on brachial district through the inflation of a sphygmomanometer cuff on proximal or mid-forearm, and assessing the artery diameter by ultrasound. The ischemia provokes the reduction of peripheral resistances mediated by adenosine and, then, after the cuff deflation, a reactive hyperemia; the shear stress on endothelium, in turn, leads to NO release and brachial artery dilatation (41). The FMD is calculated as the ratio of the difference between the maximum diameter post-occlusion and baseline diameter to the baseline diameter, and is expressed as a percentage (see Figure 4). This variability in vasomotion represents a barometer of the other endothelium key functions (42).



A B

Figure 4. Ultrasound image of the brachial artery at (A) baseline and (B) 1 min after hyperemic stimulus. Corretti M C et al. *J Am Coll Cardiol*. 2002; 39(2):257-265 (43).

FMV has been shown to be affected by CV traditional risk factors, such as age, elevated cholesterol levels, diabetes mellitus, hypertension, active and passive smoking, and less traditional, such as microalbuminuria, obesity, inflammation (42). The FMD impairment correlates with number of risk factors present and with other pre-ATS markers such as IMT (44). Has been hypothesized that, respect to IMT, endothelial dysfunction it may be an earlier predictor of CAD, while the morphological changes of artery well are better correlated with the extension and severity of coronary artery disease (46). In the other hand, morphological alterations are predictive of FMD (44), and it may depends on the common pathogenesis, but also on the impairment of the dilatation capacity of artery wall consequent to the structural damage induced by the atherosclerosis (such as the loss of the elastic component of extracellular matrix and the reduced smooth cell responsiveness to NO) (46). Thus, FMD evaluation may be more useful in subject at low-moderate risk and affected by early atherosclerosis.

The FMD is related to coronary endothelial function (47) and it has independent prognostic role in asymptomatic subjects, being predictive of CVE, also after statistical correction for CV RF (48) but adds little to the predictive model involving traditional risk factors (49). Since some studies conducted on elderly cohort have reported no predictive value over traditional RF, has been suggested that it may be less predictive in older subjects due to the limited arterial distensibility (51). It shows prognostic value in patient with established CVD or at moderate to high risk for CVD occurrence, since its impairment is associated with CVD such as CV death, myocardial infarction, stroke, congestive heart failure, intermittent claudication, percutaneous intervention, cardiac bypass graft surgery and restenosis (49).

Some authors rise the question that the different measurement protocols, with cuff placement in proximal or distal limb, may result in more or less NO-dependents vessel responses (distal limb method seems to be more NO dependent); however, this don't seems to reduce the predictive value of this technique; therefore, this suggests that the predictive value of FMD doesn't depend solely on the endothelial NO metabolism (50).

Coronary Calcium Score

The coronary calcium content is the solely

consequence of atherosclerotic disease, with exception of chronic renal failure that determines artery wall calcification. Through multidetector CT it is possible to quantify calcified lesion in term of Agatston score (52). This score is related to the atherosclerotic burden, but it has some limits: although a zero score generally predicts an excellent prognosis, it cannot rule out coronary stenosis, especially in younger patients presenting an acute coronary syndrome, either unstable angina or non ST-elevation myocardial infarction (1) since atherosclerosis not always leads to artery wall calcification. Besides, coronary calcifications don't inform about the plaque stability (53) or the luminal narrowing degree.

However calcium score shows a prognostic value, since higher score correlate with increased risk of myocardial infarction independent of classical RF (54). Has been calculated that every one standard-deviation increase of log-transformed CAC score, the risk of CVD is 2.1-fold higher. Respect to IMT, it has similar predictive value, since hazards ratios for total CVD and coronary heart disease are been recorded with the two techniques, although IMT is more stronger related to cerebrovascular disease than CAC score, while CAC score is a better predictor of incident CVD (55).

Computed tomography coronary angiography

After injection of contrast agents, CT permits coronary artery lumen visualization and then CAD detecting (see Figure 5). It requires patients selection (adequate breath holding capability, sinus rhythm, low Agatston score, adequate weight are essential) and has some limits (visualization of the arteries treated with stents, of the native arteries post bypass graft and of the artery with high grade calcification segments) but shows high sensitivities (95–99%) and specificities (64–83%) for the detection of at least one stenosis at coronary angiography (56). It also demonstrates high negative predictive values (97–99%) and patients in whom CTA rule out coronary stenosis have an excellent prognosis (57). Although it allows to individuate subclinical atherosclerosis and to characterize the plaque nature, there are no data to recommend it as a screening investigation in asymptomatic individuals with prevention purpose (1). Instead, CTA is recommended in the setting of the non-invasive diagnosis of stable coronary artery disease, where it may be useful both in subjects at the lower range of intermediate pre-test probability for CAD disease and in those with a stress test result that contradicts clinical judgment (56).

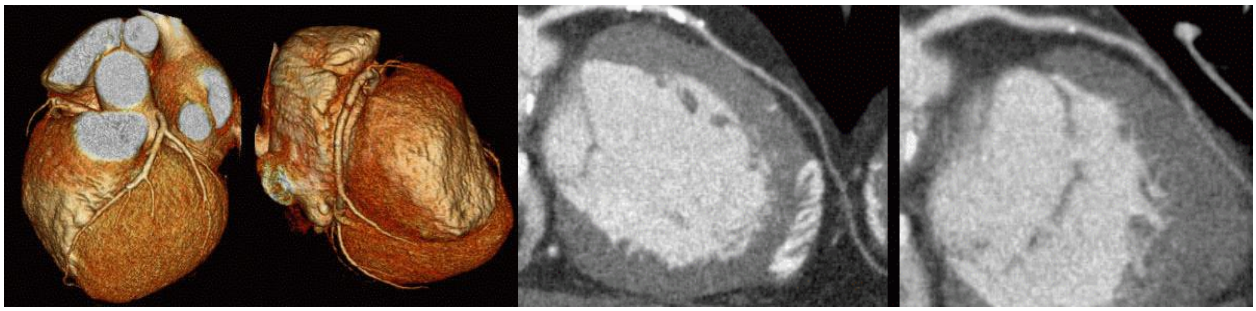


Figure 5. On the left two 3D volume rendering images and on the right two 2D CT coronary angiography scanning.

Pulse wave velocity

The arterial stiffness is a consequence of structural alteration related to the atherosclerosis process and other causes of vascular damage, and it is consequence and cause of cardiovascular disease. The pulse wave velocity is measured recording arterial pulse wave in two different sites and calculating the propagation velocity by their retard of appearance and their distance (see Figure 6); it is expression of arterial stiffness. The carotid-femoral PWV is the gold standard measure to assess the aortic stiffness (58). The normal value is <10 m/s (59). The PWV increases in presence of CV risk factors such as hypertension, hypercholesterolemia, diabetes mellitus and renal dysfunction. It is an independent risk marker for cardiovascular mortality and cerebrovascular events, and has prognostic value equivalent to other marker of pre-ATS. Has been calculated that the PWV has additive value above and beyond the traditional risk factors score, and when it is evaluated, a proportion of subject at intermediate risk could be reclassified into a higher or lower risk category (60).

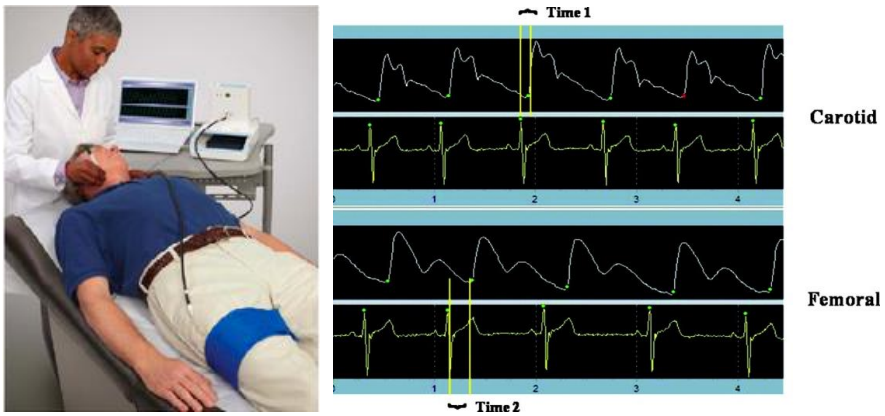


Figure 6. PWV is measured recording pulse wave in two different sites and calculating their distance and the retard wherewith it appears in distal site, if recorded simultaneously, or their retard respect to the QRS complex of ECG used as reference frame, if recorded on separated occasion.

Conclusion.

The CVD represent nowadays the first cause of mortality and disability in western country. But atherosclerosis disease is a gradually process that develops over decades, giving the time to carry out prevention and intervention strategy. Great attention should be made on the analysis of RF and on their correction, especially when they are clustered in a manner that enhances them. For this reason, it's important to prevent the development of MetS abnormalities (for example with daily physical activity and Mediterranean diet) and to detect it early so as start pharmacological treatment of modifiable risk factors. Moreover, in order to address the therapeutic efforts to the subjects that can receive greater benefit, it is important to have tool to identify subjects affected but non symptomatic yet. For this purpose, non-invasive techniques capable of evaluating arterial wall and endothelial function should enter in routinely evaluation of cardiovascular risk. In particular, according to ESC guidelines (1), carotid ultrasonography, brachial-ankle index measurement and computed tomography for coronary calcium assessment should be taken in mind for further risk stratification of asymptomatic adults at moderate risk. The detection of subclinical lesions indicates the need of a more aggressive management of risk factors, possibly with the help of drug treatment.

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