Hypertension is the most widely spread risk factor for premature cardiovascular diseases (CVD) as its incidence is higher compared with the other cardiovascular risk factors such as: cigarette smoking, dyslipidemia or diabetes. Among patients with a recent stroke or transit ischemic attack, the prevalence of hypertension is approximately 70% [1] and history of hypertension is present in 75% of patients with chronic heart failure (HF) [2]. Studies have demonstrated graded associations between higher systolic and diastolic blood pressure and increased CVD risk [3,4] from young to old individuals (from 30 to older than 80 years of age).

Observational and experimental studies show a link between hypertension and the development of atherosclerosis [5-7]. The most frequently cited pathophysiological mechanism of hypertension that may promote atherosclerotic disease is the increased arterial shear stress which promotes arterial smooth muscle hyperpla-
sia and hypertrophy and increases endothelial permeability to plasma electrolytes by endothelial damage, that induces fibromuscular thickening of intima and media of large and small arteries [8]. Despite an unified concept of hypertension and atherosclerosis, these remain two separate disorders that cause similar, but distinct changes on the vascular tree; not every hypertensive individual shows extensive atherosclerosis and also not always atherosclerosis is accompanied by hypertension. Despite certain proves taken all together experimental, pathogenic and epidemiological studies does not clearly show that hypertension in the absence of other atherogenic factors causes atherosclerosis [9].

The early detection of atherosclerosis in subclinical stages currently represents a standard to be reached as the incidence and mortality rate of cardiovascular diseases is in continuous increase. Epidemiological studies have shown correlations between the atherosclerosis in one arterial territory and the involvement of other arteries such as coronary, carotid or femoral arteries [10]. Consecutively, early detection of arterial disease in an apparently healthy population has focused on arteries such as carotid and femoral arteries as they are easy to investigate and low cost. Many echographic parameters have been investigated, but none proved sufficient sensitivity and specificity.

**Carotid and Femoral ultrasound**

Carotid ultrasound is mainly based on the measurement of intima – media thickness (IMT) and the presence and characteristics of plaques. Plaque thickness was showed to predict cardiovascular risk, reason for which intima-media thickness was included in many studies as a risk factor for cardiovascular risk [10]. However more recent studies pinpoint that IMT measured according to Mannheim consensus does not define atherosclerosis, as individuals with the same IMT can have totally different risk for cardiovascular events such as stroke, myocardial infarction etc [11]. IMT is not a sign of early atherosclerosis, but represents smooth muscle hypertrophy/hyperplasia induced by factors including hypertension. Several reasons may explain the impediment brought by IMT over traditional risk factors such as age, sex, blood pressure or hypercholesterolemia. It is measured in the common carotid artery, whereas the advanced lesions tend to appear in the bulb or in the proximal zone of the internal carotid artery. Another reason may be the poor axial resolution of usual carotid echography as the limit of significance is 200 µm outside the possibilities of accurate measurements. Algorithms that provide a more precise measurement or the 3D ultrasound with volumetric determinations may increase ultrasonographic performance. Despite all these drawbacks, ultrasonography remains a low-cost, non-invasive and easy to perform technique that can still have its place in the risk assessment and diagnosis of atherosclerosis. Meta-analysis showed that IMT alone without taking into account plaques, weakly predicts CV risk [12].

The need to study novel risk factors is reiterated by large populations studies that show there is low correlation between traditional risk factors and carotid IMT. If the prevention ESC guide currently proscribes the determination of carotid ultrasound IMT in the CV risk assessment, there is a IIb recommendation for atherosclerotic plaque detection and ankle-brachial index [13].

Plaque is usually defined as the presence of a focal wall thickening at least 50% greater than the surrounding wall vessel or as a focal region with an IMT higher that 1.5 mm that protrudes into the lumen [14]. Plaques have to be characterized by their number, size, shape and echodensity. Plaques are related to both ischemic cardiac or cerebrovascular events, and echolucent much more than calcified plaques increase the risk for acute ischemic incidents. Many studies reveals the greater importance of variables that include plaque area and thickness, rather than IMT for CVD [15,16]. Despite the fact that formal indications have not been established as guideline recommendations, carotid artery plaque assessment with ultrasonography may be considered a risk modifier in CVD prediction.

Starting from the recommendations that indicate the importance of plaques in the CV risk assessment, an index denominated carotid artery plaque score (PS) was calculated by summing each plaque taking into account it maximum thickness in the ipsilateral carotid artery and by adding the bilateral carotid plaque scores is obtained a total PS. Terzi proved on more than 50,000 patients that plaque score (PS) had a higher dignostic value for predicting future myocardial infarction events compared with IMT [17].

Another group [18] made use of another index of assessment, the atherosclerosis burden score (ABS), a
score that sums the number of carotid and femoral bifurcations with plaques. The predictive value of ABS surpassed IMT, carotid/femoral plaque scores in the detection of coronary artery disease in a cohort of patients with coronary angiography. In the ABS study mentioned above both left and right carotid and femoral arteries were examined (four arterial sites). Carotid investigation included common carotid artery (CCA), bulb, and the origin of the internal and external branches. Femoral arteries were examined from 4 cm above bifurcation to 4 cm in the superficial branch as well as the origin of the profound branchial branch. All in all, ABS proved to be a better predictor of peripheral atherosclerosis as it takes into account not only a short segment of the common carotid artery that may be free of plaques, but a wider area throughout multiple locations of the arterial tree increasing the likelihood to accurately detect atherosclerosis. The hypothesis that the presence of atherosclerosis on carotid arteries is associated with plaques on other arterial branches such as femoral was infirmed in the CAFES-CAVE study, where 30% of the patients with normal carotid arteries had significant plaques on femoral arteries [19], observations confirmed also by other studies [20].

To exemplify the lack of clinical significance of IMT, we report the case of two patients with the value of IMT within the normal range, although one has important plaques at carotid (figure 1) and femoral bifurcations (figure 2), and implicitly a high ABS, while the other has no plaques at the same arterial zones investigated (figure 3 and 4). In the case of the patient with numerous plaques, aortic PWA and augmentation indexes sustained the high cardiovascular risk.

### Ankle–brachial index

The ankle–brachial index (ABI) is an easy to perform and reproducible screening test available even in the early stages of atherosclerotic disease, when it can be considered an surrogate marker for atherosclerosis. ABI was found to have important prognostic information for future cardiovascular events [21]. An ABI of less than 0.9 indicates a stenosis of more than 50% between the aorta and the distal arteries of the inferior
Figure 2. Femoral bifurcation displaying a large plaque (3.2 mm in its maximum diameter) with a thin fibrous cap.

Figure 3. Carotid bifurcation with no plaques.
Arterial stiffness

The aging of the large artery wall is characterized by a reduction in the elastin content, along with an increased amount of collagen and changes between cells and matrix leading to increased arterial stiffness defined by an increased rigidity of the artery wall that can occur in association with increased age and/or various other CV risk factors. Arterial stiffness is commonly measured using either aortic pulse wave velocity (PWV) or arterial augmentation index. The concept of vascular aging can be motorized through changes in arterial stiffness. The predictive value of arterial stiffness for CV events has been well demonstrated in various trials with the largest amount of evidence for aortic stiffness, measured through carotid-femoral pulse wave velocity (cfPWV). Many studies and reviews consistently showed the independent predictive value of aortic stiffness for fatal and nonfatal CV events taking a PWV threshold of 12 m/s has the point from where increases the arterial damage [24]. The Sixth Joint Task Force of
the European Society of Cardiology suggests to use PWV as marker of CV risk only for individuals close to cut-off, but regular use in all patients to improve CV risk classification is not recommended [13].

Gaps in evidence

The lack of homogeneity in the definition and measurement of ultrasound or hemodynamic parameters for the assessment of CV risk urged the development of new standardized scores with less variability and higher intra and inter individual reproducibility such as carotid artery plaque score (PS), atherosclerosis burden score (ABS). Although continuous improvement is made in the field there are still gaps to be filled through large clinical trial.

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Conflicts of interest

The authors confirm that there are no conflicts of interest.

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