Peripheral atherosclerosis evaluation through ultrasound: a promising diagnostic tool for coronary artery disease

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Abstract

Effective treatment, but also proper diagnosis of cardiovascular diseases, remains a major challenge in everyday practice. A quick, safe, and economically acceptable non-invasive procedure should play a leading role in cardiovascular risk assessment before invasive diagnostics is performed. The staging of subclinical atherosclerosis may help in further clinical decisions. Safe, widely available, and relatively inexpensive, ultrasonography is a promising examination that should find wider application in clinical practice. The latest ESC guidelines emphasize the usefulness of carotid ultrasound in the diagnosis of coronary artery disease (CAD) and subclinical assessment of atherosclerosis, which help to determine the level of cardiovascular risk. Ultrasound examination of peripheral arteries, especially superficial vessels such as the femoral arteries, is quite easy, quick, and accurate. Other vascular beds, such as iliac and renal, are more demanding to examine, but can also provide valuable information. This review summarizes important studies comparing the severity of atherosclerosis in ultrasound-visible vascular beds in patients with established CAD. We especially emphasize the benefits of the combined assessment of atherosclerosis features, which were characterized by high sensitivity and specificity in the diagnosis of CAD and other serious cardiovascular diseases.

INTRODUCTION

Cardiovascular diseases (CVD) are the leading cause of death in Western countries. Between 2005 and 2015, the number of deaths from CVD increased by 12.5% worldwide. An estimated 17.9 million people died from CVD, representing 32% of all global deaths. Of these deaths, 85% were due to myocardial infarction and stroke. Atherosclerosis, as the main pathophysiological process of CVD, remains the leading cause of morbidity and mortality in developed countries and can be detected even in young adults and children. Coronary artery disease (CAD) and peripheral artery disease (PAD) have a common underlying pathology of atherosclerosis. The comorbidity of CAD and PAD has long been well-known. The incidence of both significant and non-significant atherosclerotic lesions in peripheral arteries in patients with established CAD is presented in Figure 1. The risk factors of both are well-defined. Risk factors (hypertension, diabetes, smoking, hypercholesterolemia) with accompanying typical angina have traditionally served as an indication for invasive coronary angiography (CA). However, in daily clinical practice, many patients do not present the typical syndrome of CAD. Thus the invasive diagnosis should be preceded by a noninvasive test. Furthermore, patients without electrocardiography findings and increased troponin levels may benefit from non-invasive diagnostics.

In accordance with the recent guidelines established by the European Society of Cardiology (ESC), following the exclusion of acute coronary syndrome (ACS), diagnostic imaging modalities such as coronary computed tomography angiography or single-photon emission computed tomography are recommended. Despite many advantages, these examinations have contraindications, are less available, and cost-prohibitive (Table 1). Moreover, recent ESC guidelines indicate solely carotid artery ultrasonography (CAUS) as a tool that should be considered for detecting CAD plaque in suspected patients. A review of current guidelines and
promising approaches to atherosclerotic plaque assessment is necessary to enhance the diagnosis, management, and treatment of CAD in clinical practice.

The available, costless, safe, and sensitive tool in atherosclerosis assessment is ultrasonography (US). Most studies investigated carotid and femoral arteries, although their superficial location allows US imaging with high resolution. Other vascular beds, such as the renal arteries, abdominal aorta, and iliac arteries, may pose challenges to accessibility. Despite some limitations is useful to detect high risk patients given that the US become appropriable for risk stratification22.

In this review, we: i) underline coexisting PAD and CAD, ii) describe the role of vascular US in CAD diagnosis, and iii) characterize the usefulness of US in CVD risk assessment.

**CAROTID ARTERIES**

Atherosclerosis is the most common cause of both carotid and coronary artery stenotic disease. The plaques were detected in carotids in 31% of patients during the PESA (Progression of Early Subclinical Atherosclerosis) Study 23. Ruptures of atherosclerotic plaques, which can lead to thrombus formation, can clinically manifest as stroke or as ACS 24. Many reports suggest a correlation between the presence of atherosclerosis in the coronary arteries and carotid arteries. Proving such correlations can help identify the presence of atherosclerotic plaques in the coronary arteries using a non-invasive imaging modality - CAUS. Reports of an association between the presence of atherosclerotic plaques in the carotid arteries in CAUS and the presence of atherosclerotic plaques in the coronary arteries have been demonstrated in observational studies - prospective and cohort studies (Table 2).

There are also reports that carotid atherosclerosis, and carotid artery stenosis (CAS), are independent predictors of major adverse cardiovascular events in patients without preexisting CAD (respectively, HR=1.69; p=0.07 and HR=3.17; p<0.01) 25. They also showed that the incidence of clinically significant severe CAS (>50%) was progressively increased among patients with non-obstructive CAD, single vessel disease (VD), double VD, triple VD, and left main coronary artery disease. In the Japanese population, the prevalence of carotid stenosis diagnosed in CAUS was 14.5% in single VD and 29.8% in multivessel disease (p<0.0001)16. Also, in patients with confirmed CAD, the majority (about 95%) showed atherosclerotic changes in the carotid arteries, with 15% showing hemodynamically significant CAS 8. The result of the study by Puz et al. is also significant, as they found no differences in the incidence of carotid atherosclerosis between patients with stable and unstable CAD (15.3% vs. 19%, respectively)15. Another study also confirmed the hypothesis that critical CAS is more common in patients with CAD 26. It has also been shown that maximal plaque area can reflect the clinical severity of CAD and can be used as a simple, non-invasive indicator of the severity of coronary atherosclerosis 27. One study confirmed that the presence of plaques is a better predictor of CAD and the Framingham risk scale than intima-media thickness (IMT). This study found that patients with CAD had a higher rate of clinical (referred to as the presence of plaque) or subclinical (referred to as IMT) carotid atherosclerosis 28. In the study by Morito et al. also IMT and plaque score (PS) were assessed in a population of Japanese patients and compared with CA data 29. It was shown that a high PS showed the strongest predictive value for the presence and/or severity of CAS. A study by Kandasi et al. examined the relationship between CAD and common carotid artery (CCA) wall morphology also using CAUS. They showed that the strongest predictor of CAD was the presence of calcified atherosclerotic plaque compared to the presence of fibrous plaque and thickened IMT 30. Moreover, in the study group, none of the subjects with normal CCA wall morphology had significant coronary artery lesions. Another meta-analysis confirmed that atherosclerosis affects both the carotid and coronary systems, although not always in identical phenotypes 31. It confirmed that carotid artery testing is useful in any case of suspected CAD. It cites publications showing a correlation between CAS and significant CAD (r=0.53, P<0.001) and between carotid and coronary calcification (r=0.61, P<0.001). The studies cited in this meta-analysis 32-36 and others are summarized in Table 2.

Reduction of Atherothrombosis for Continued Health (REACH) registry with 4-year follow-up (23 364 patients) showed that the risk of coronary events increased by 22% in patients with versus without carotid
atherosclerosis \(^{37}\). The prevalence of critical CAS has been shown to correlate with the number of critically stenosed coronary arteries. Patients (n=109) with severe CAD (three-vessel disease) were also examined for CAS with CCT \(^{38}\). Significant lesions included cervical and intracranial segments of both the internal carotid artery (ICA) and the right vertebral artery. An autopsy study by Molnár et al, comparing the extent of atherosclerosis in the carotid, coronary and femoral arteries showed correlations among patients who died of ischemic stroke. The authors found a significant correlation between the external carotid and left anterior descended coronary artery (r=0.458, p=0.028) \(^{39}\).

Advances in the US have also increased the role of this method in the stratification of patients with CAD. The US is used to detect subclinical atherosclerosis, particularly by evaluating the plaque (height, total area) in the carotid arteries, and is increasingly used in making clinical decisions regarding the treatment of atherosclerosis \(^{40-42}\). This method is now standardized in the 2020 American Society of Echocardiography (ASE) guidelines \(^{43}\). The benefits of arterial US can also be achieved in asymptomatic patients. As described in a systematic review by Peters et al, who showed that imaging of subclinical atherosclerosis as an adjunct to conventional risk factor assessment can improve risk prediction of cardiovascular events (CVE) in asymptomatic individuals \(^{44}\). Relevant evidence includes: CIMT, carotid plaques, and/or coronary arteries calcium score (CACS). In addition to the mere co-occurrence of plaques in the mentioned arteries, the phenotype of the plaques may also be effective in patient risk stratification. A closer analysis of plaques was also studied by Zhao et al, in which they found a significant correlation between plaque phenotype and carotid artery plaque composition \(^{45}\). They also found that mixed coronary plaque may suggest high-risk carotid plaque. In addition, a study was conducted to investigate plaque composition concerning the incidence of stroke and CAD in a group of asymptomatic individuals who had subclinical atherosclerosis in CAUS \(^{46}\). Plaque features were assessed by resonance imaging - the presence of specific plaque components (intimal hemorrhage [IPH], lipid-rich necrotic core, and calcification, and measures of plaque size). A study showed that the presence of IPH in carotid atherosclerotic plaque is an independent risk factor for stroke and CAD. The article by Uematsu et al. on ultrasound evaluation of the carotid artery highlighted the assessment of atherosclerotic plaque echo lucent as a predictor of coronary events \(^{47}\). Echolucent carotid artery plaques are characterized by being rich in macrophages and lipids. Susceptible plaques can be stabilized by statins. The study aimed to identify patients who are at high risk but could benefit from lipid-lowering therapy for secondary prevention. As it turned out, the evaluation of carotid artery echolucency was useful in this selection and made it possible to predict secondary coronary events in patients with CAD after statin therapy. The study also showed that the prognostic effect of lipid-lowering therapy depends on the echolucency of atherosclerotic plaque in the carotid artery \(^{48}\). In addition to phenotypic plaque characteristics, it has been shown that assessment of neovascularization can be useful in risk stratification of patients at cardiovascular risk. This can be assessed by quantitative analysis by contrast-enhanced ultrasound of the carotid artery. Based on the common underlying pathology of atherosclerosis in the 2 arterial systems, the study of carotid arteries in CAD and vice versa became clinically important to accurately identify patients who could benefit from aggressive preventive therapy as well as prompt treatment \(^{49, 50}\).

**ARTERIES OF LOW EXTRAMITAS**

It is estimated that in 2016 around 120 million people were afflicted with lower extremity PAD and as much as 48% of them could have CAD or other CVD \(^{51}\). Moreover, PAD can lead to acute limb ischemia, amputation, or even death. It is often caused by atherosclerotic plaque in the lower extremity artery (LEA) and classically it manifests as cramping and pain, which is alleviated by rest. These symptoms may present in different areas depending on the afflicted artery or be completely absent. Among risk factors of PAD, we can find many cardiovascular risks factors like age, tobacco usage, hypertension, and diabetes mellitus \(^{52}\). The interest of researchers in LEA was usually directed toward femoral bifurcation and common femoral and superficial femoral arteries. The range of examinations differed from paper to paper, but most of the time was between 1-2 cm proximally and distally from bifurcation. Sometimes, other arteries like popliteal and tibial were described.

Khoury et al. showed that patients with CAD with extra coronary arteries assessed by the US had a signi-
ificantly higher incidence of atherosclerotic plaques in the femoral arteries than those with normal coronary arteries (77% vs. 42%) 9. Moreover, the risk of CAD was significantly associated with femoral plaques (OR 5.6, p=0.02). Cho et al. observed a high prevalence of asymptomatic CAD in patients with lower extremity PAD 53. The prevalence of CAD in patients with PAD was 62%, and only 13% of them had angina and 72% had multi-vessel disease. Diabetes significantly increased the risk of CAD in patients with PAD and the odds ratio (OR) of having multi-vessel CAD was 2.5 (1.1-5.9, p=0.037). In another study, Kumar et al. rated the sensitivity of PAD in predicting coronary artery stenosis as 80%, the specificity as 82%, and the accuracy as 81%54. The Peripheral Arterial Disease in Interventional Patients Study (PIPS), a prospective cohort study revealed, that among patients who had confirmed CAD by CA (n=5745), those with PAD had a higher prevalence of left main and multivessel CAD (87.2% vs. 75.5%, p=0.006), and previous coronary artery bypass surgery (CABG) (35.8% vs. 23.1%, p=0.008) 55. In a post mortem study authors found among patients who died for stroke significant correlations between the deep femoral artery and left anterior descendent coronary arteries (r=0.513; p=0.012) 39.

During a 10-year follow-up observation after performing an ultrasound examination of carotid and femoral bifurcations, there was no CVE in the group with a completely normal ultrasonographical image of those arteries 56. With increased severity of lesions risk of both progression to more advanced group and CVE grew. Worth noting is that 68% of registered CVEs in the study group were myocardial infarctions (MI). In another observational study, femoral plaques were presented as an individual risk factor of CVE 57. Unfortunately, some research came to different conclusions as only irregular surface and ulcerations of plaques in common femoral arteries were found to be the sole predictors of major adverse CVE58. Classical cardiovascular risk (CVR) factors corresponded with the presence of subclinical atherosclerosis in femoral arteries. Femoral plaques alone are strongly associated with CCT- assessed CACS, however, adding CVR factors and carotid plaques to the model diagnostic OR was further increased 59. Traditional risk factors including previous CVE were also associated with the Ultrasonographic Lower Limbs Atherosclerosis (ULLA) score calculated during an ultrasonographical examination of LEA from femoropopliteal to para malleolar region 60. This way of examining patients is better in detecting PAD than the ankle-brachial index (ABI) 61. US assessment of femoral total plaque area (TPA), maximal plaque height (MPH), and IMT associated with severity of CAD detected by CA 62-64. Examination of femoral TPA had the biggest sensitivity of detecting CAD and was a better method than calculating ABI 62. However, we must bear in mind that reproducibility of IMT results is worse in older, and patients afflicted with CVDs. Moreover, it also decreases, when IMT increases 65. Another study noticed that the best way of assessing the risk may be sex- dependent. In women, the most important risk factor was femoral TPA, but in men, it was femoral MPH. However, in both women and men, the most representative lesions were localized in the proximal femoral artery 66. The elevated CVD risk is only partially attributable to shared CVD risk factors, such that at any given level of CVD risk factors, PAD is independently related to future CVD events and mortality 67. PAD has also been shown to be predictive of future CVD events even when adjusted for other markers of subclinical atherosclerosis 68.

AORTA AND ILIAC ARTERIES

The incidence of atherosclerosis of the abdominal aorta and iliac arteries is common. Among 4002 middle-aged patients, the prevalence of subclinical atherosclerosis was 63%. The plaques were detected in the aorta (25%) and iliofemoral arteries (44%) 23. The subclinical disease was detected in 58%, with an intermediate or generalized disease in 36% of patients with low Framingham Heart Study (FHS) 10-year risk. This suggests the added value of US imaging for the diagnosis and prevention of atherosclerosis. A higher prevalence of atherosclerosis in the aorta was shown in another study69. In 261 patients subjected to dual-source CCTA 69.3% had aortic plaques, mostly at the distal part of the abdominal aorta. The plaques were characterized as mixed (43%), calcified (24%), and soft (2%). Mixed and calcified plaques were the most often present in the abdominal aorta and its branches. In another study, the authors found similar rates of atherosclerotic lesions in the abdominal aorta (68%) as well as in the iliac arteries (35.6%) among asymptomatic patients based on CTTA 7. The association with significant coronary artery stenosis was strongest for atherosclerotic lesions with stenosis (725%, especially in the abdominal aorta (aOR 16.39) and any common iliac artery (aOR 7.32). Rangel et al. examined the frequency of association of CAD with aortoiliac lesions during
Aortic arteriography performed after CA. They found that 46% of patients had atherosclerotic aortoiliac lesions, and the number of affected coronary arteries was directly related to the frequency and extent of aortoiliac lesions. The findings from another study showed that patients with CVD had a higher prevalence of abdominal aortic plaques compared to patients without CVD (37.3% vs 17%)\(^7\). Patients with the three-vessel disease had a higher prevalence of the plaques than patients with two- and one-vessel disease (44.7% vs 35% vs 27%). Thus, abdominal aortic plaques were an independent factor of CVD presence and severity. Plaques in the aortic arch along with atrial fibrillation and carotid atherosclerosis were shown to be important causes of peripheral emboli and iatrogenic stroke\(^7\).

Atherosclerosis of the thoracic aorta is also common (43.7%)\(^7\), especially in patients with significant CAD (75.9%)\(^5\). Aortic plaque seen on transthoracic echocardiography has been correlated with a higher prevalence of CAD and the presence of significant angiographic coronary artery stenosis\(^7\). In addition, the lack of aortic plaque has also been shown to predict the absence of CAD\(^7\). Moreover, plaques in ascending aorta are an independent factor of long-term neurologic events and mortality\(^7\).

**RENAL ARTERIES**

It is known that there is a correlation between heart and kidney functioning with impairment of one organ affecting the work of the other\(^7\). Condition of coronary and renal arteries is an important factor used to evaluate the risk of adverse events in the organs that receive blood from mentioned vessels. Renal artery stenosis (RAS) is often found in patients diagnosed with CAD\(^7\). Conlon et al. reported that significant RAS, defined as at least 75% narrowing of the luminal diameter, was observed in 4.8% of cases of patients undergoing CA\(^8\). The four-year unadjusted survivals for patients with and without significant RAS were 57% and 89%, respectively (p<0.001). Another study evaluated patients, with known or suspected CAD, who underwent CA and renal arteries examination\(^8\). The prevalence of RAS of any severity among catheterized patients was 25% and among those with CAD, this figure increased to 36%. An important finding in this study was that CAD is almost invariably present in patients with even non-significant RAS and the absence of significant CAD made the likelihood of RAS of any severity extremely remote. The incidence of renal artery stenosis is high for CABG recipients as 47% of them had concomitant RAS with higher age and hypertension classified as independent factors of its occurrence\(^8\). Przewlocki et al. aimed to determine the prevalence of RAS in 1036 patients with suspected CAD\(^8\). RAS prevalence in patients with CAD was 38.3% (284/741) and its frequency increased with the severity of CAD: from 25% in patients with insignificant coronary lesions up to 36.4%, 40.2%, and 48% in 1, 2, and 3-VD, respectively. Data from a 5% random sample of the United States Medicare population demonstrated that of 5875 patients with RAS, 66.8% had concomitant CAD while CAD occurrence in patients without RAS was 24.9%\(^8\). A group of 333 consecutive patients with CAD underwent CA, followed by renal angiography\(^2\). Authors emphasized that multivessel CAD was more frequent in patients with significant RAS than with non-significant one (72.5% vs 48.1%). Imori et al. collected data from 1,734 patients with CA and renal artery Doppler US\(^14\). Among those patients with CAD, 9% were simultaneously diagnosed with RAS. The extent of CAD was related to the prevalence of RAS, most significantly expressed with the 3-vessel disease. Not only significant stenosis (>50%) of the renal artery is correlated with CAD. The examination of 1,561 hypertensive patients showed that 71 of them had RAS and 126 - arteriosclerotic plaque (ARAP) without significant stenosis\(^8\). The occurrence of CAD was higher in both groups (80%; 70%) compared to patients without any stenoses (56.5%). The 9-year follow-up revealed that RAS and ARAP are independent factors of CAD development and severity. Another study focused on the importance of non-hemodynamically significant RAS in patients with CAD\(^8\). Of the 623 enrolled patients, RAS was confirmed in 181 cases. The median 4.5-year follow-up stated that the presence of RAS was associated with more CVE compared to the group without the diagnosis (35.4% vs. 24.7%). Edwards et al. observed among 870 patients after renal artery Doppler US, during a mean follow-up of 14 months, that the presence of renovascular disease demonstrated a significant relationship with adverse coronary events (HR 1.96)\(^8\).

**COMBINED ASSESSMENT OF PAD**
A comprehensive assessment of multiple arterial beds in CAD prediction was also reviewed. This approach may better predict CVE and the likelihood of coexisting CAD. Most studies combined data from the carotid and femoral arteries. These vascular beds lie superficially, so access is easier, faster, and can yield constructive results.

Colladenanchise et al. showed that a combined assessment of femoral bifurcation and carotid MPH was the most accurate identifier of CAD in men (AUC=0.773) \(^{66}\). However, in women, the stronger indicator of CAD was achieved by a combined analysis of common femoral and carotid TPA (AUC=0.764) than height (AUC=0.659). At this value, more than half of women with false-positive stress test results were correctly identified as having no significant CAD. In another study, the authors assessed CVD risk according to the number of affected bifurcations (carotid and femoral) by ARAP \(^{89}\). The presence of two carotid plaques (OR 2.21) or even one femoral plaque (OR 2.68) was associated with an increased prevalence of CVD. However, when both carotid and femoral arteries were combined the presence of plaques in three vessels was associated with a markedly increased prevalence of CVD (OR 6.48), and the presence of plaques in four vessels was associated with an even higher prevalence of CVD (OR 9.07).

The presence of plaques also in the iliac, femoral, and/or carotid arteries were shown to correlate with the presence and severity of cardiovascular disease (CVD). In 323 hypertensive patients carotid artery intima-media thickness (CCA-IMT) and carotid and/or iliofemoral (C/IF) plaques were compared according to the presence or absence of CVD\(^{90}\). Only C/IF plaques but not CCA-IMT, showed a positive correlation to the presence of CVD (coronary artery disease, peripheral vascular disease, cerebrovascular disease, renal artery stenosis, abdominal aortic aneurysm). C/IF plaques presented significantly greater diagnostic value than CCA-IMT for the presence of CVD (AUC, 0.78 versus 0.64) but not for 10-year risk according to Framingham equations. Khoury et al. in CAD prediction tested a combined analysis not only of the femoral and carotid arteries but also of aortic atherosclerosis\(^{9}\). They found the best sensitivity in combining aortic and femoral plaques (sensitivity 74%, specificity 79%, AUC 0.75) and the best specificity in combining aortic and carotid and femoral plaques (respectively: 59%, 84%, 0.7), both better than combing femoral and carotid plaques (respectively: 59%, 71%, 0.71).

Kafetzakis et al. in their study also assessed ultrasonic biopsy (UB) but included in this index the presence of atherosclerotic plaque in both carotid and femoral artery bifurcations\(^{63}\). Carotid atherosclerotic lesions were grouped into classes according to the UB scale: I - normal intima-media thickness, II - intima degenerative changes, III - early (< 2 mm), IV - homogeneous (> 2 mm), V - heterogeneous (> 2 mm), VI - multiple atherosclerotic plaque, VII - total artery occlusion. Univariate analysis showed that UB had significantly higher values in patients with obstructive CAD than in control subjects (3.94 vs. 2.65, p<0.001). ROC analysis showed that indexes yielded a significant area under the ROC curve (0.77) with a sensitivity of 69%, specificity of 70%, and cut-off value 3.25. However, IMTC was superior to UB (respectively; 0.81, 74%, 76%, 0.88).

Because of the continuing need to find the most effective method to use in clinical practice, a new Atherosclerosis Burden Score was proposed (ABS) \(^{91}\). It includes the sum of the number of bifurcations of the carotid and femoral arteries with atherosclerotic plaques assessed in the US, which is similar to what was used in their study by Griffin et al. \(^{89}\). ABS was highly accurate in detecting CAD (AUC=0.79) in 203 patients undergoing coronary angiography. It is superior in predictive efficacy to CCA IMT, mean/maximum carotid artery thickness, and carotid and femoral artery plaque scores in detecting CAD. CAD incidence increased from 11 % in subjects with ABS=0 to 87 % in subjects with ABS=4. By contrast, standardized C-IMT was only weakly correlated with CAD (R=0.164; P=0.02), with a 55 % occurrence in quartile 1 and 74.5 % in quartile. Table 3 summarizes the studies that showed the most significant effect of the combined PAD score on the prediction of CAD and CVD.

In their study, Lehrke et al. demonstrated potential Whole-body magnetic resonance angiography (WB-MRA) for the noninvasive assessment of almost the entire arterial vasculature within one examination\(^{92}\). They used the Atherosclerosis Score Index (ASI), which was generated as the ratio of summed scores to analyzable segments. The ASI was higher in patients with significant (>50% stenosis) CAD compared to
patients without CAD (1.56 vs. 1.28, p=0.004). The ASI correlated with the PROCAM (R = 0.57, p < 0.001) and Framingham (R = 0.36, p = 0.01) risk scores as estimates of the 10-year risk of coronary events. A ROC-based ASI > 1.54 predicted significant CAD with a sensitivity of 59%, a specificity of 86%, and a positive predictive value of 84%.

**SUMMARY**

In this review, we have shown how the US assessment of multiple arterial beds offers a promising perspective in clinical practice. The results of these studies highlight the benefits of peripheral artery testing when CAD is suspected. The location and size of the coronary arteries make imaging them more challenging compared to the more superficial carotid and femoral arteries. The analysis of the renal arteries, abdominal aorta, and iliac arteries, although more difficult to assess, may be a good alternative to other non-invasive imaging studies with risks associated with exposure to ionizing radiation and administration of contrast.

These findings highlight the benefits of US examination, especially of carotid and femoral arteries whenever CAD is suspected and precisely CV risk assessments are needed. Detecting asymptomatic atherosclerotic plaques can aid in prevention and treatment strategies. An excellent illustration of this is the study by Dodge et al. demonstrated that routine abdominal aortic screening during echocardiography can enhance statin prophylaxis in patients with asymptomatic atherosclerosis, at no extra expense, and detect some AAAs. 93.

A standardized and well-proven US method is necessary for the safe, accurate, and efficient assessment of atherosclerosis severity to be incorporated into guidelines.

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Table 1 Noninvasive modalities for the diagnosis and assessment of coronary artery disease

<table>
<thead>
<tr>
<th>modality</th>
<th>advantages</th>
<th>limitations and disadvantages</th>
<th>ESC guidelines class</th>
<th>definitions of high event risk in patients with established chronic CAD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exercise ECG</td>
<td>widely available, does not require intravenous access or radiation exposure, relatively inexpensive, widely validated</td>
<td>some patients are unable to exercise, some may have certain baseline ECG abnormalities that make the ECG uninterpretable during stress, certain medications can cause false positive ST changes</td>
<td>IIbB</td>
<td>cardiovascular mortality &gt;3% per year according to Duke Treadmill Score</td>
</tr>
<tr>
<td>CT coronary angiography</td>
<td>rich evidence, high accuracy, identification and quantification of calcification and plaque volume</td>
<td>usage of iodinated contrast material, exposure to radiation, lacks the ability to predict the functional significance of stenoses</td>
<td>IB</td>
<td>three-vessel disease with proximal stenoses, LM disease, or proximal anterior descending disease</td>
</tr>
<tr>
<td>modality</td>
<td>advantages</td>
<td>limitations and disadvantages</td>
<td>ESC guidelines class</td>
<td>definitions of high event risk in patients with established chronic CAD</td>
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<tr>
<td>SPECT or PET perfusion imaging</td>
<td>high image quality</td>
<td>susceptible to technical and acquisition issues, use of ionizing radiation, dependent on operator expertise, limited availability and a relatively high cost</td>
<td>IB</td>
<td>area of ischaemia &gt;=10% of the left ventricle myocardium</td>
</tr>
<tr>
<td>Stress echocardiography</td>
<td>versatile/patient-friendly, lack of ionizing radiation, Inexpensive</td>
<td>dependent on image quality due to body habitus or pulmonary disease, technical challenges, operator dependent expensive and low availability, complex training required</td>
<td>IB</td>
<td>&gt;=3 of 16 segments with stress-induced hypokinesia or akinesia</td>
</tr>
<tr>
<td>Stress CMR</td>
<td>high resolution and reproducibility, identification of plaque ulceration and intraplaque hemorrhage</td>
<td></td>
<td>IB</td>
<td>&gt;=2 of 16 segments with stress perfusion defects or &gt;=3 dobutamine-induced dysfunctional segments</td>
</tr>
</tbody>
</table>

CAD – coronary artery disease, CMR – coronary magnetic resonance, CT – computed tomography, ECG – electrocardiogram, ESC – European Society of Cardiology, LM – left main, PET – positron emission tomography, SPECT – single-photon emission computed tomography

Table 2 Studies summarizing the impact of carotid atherosclerosis assessment on the prediction of coronary artery disease
<table>
<thead>
<tr>
<th>research</th>
<th>n</th>
<th>CAD</th>
<th>significance</th>
<th>p</th>
<th>compared parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steinvil 2014</td>
<td>1391</td>
<td>CA</td>
<td>HR₁=3.17</td>
<td>p₁&lt;0.01 p₂&lt;0.07</td>
<td>Relationship between carotid artery stenosis (p₁); carotid atherosclerosis (p₂) and an increased risk of the composite major adverse cardiovascular event end point among patients without CAD.</td>
</tr>
<tr>
<td>Drozd 2003</td>
<td>150</td>
<td>CA</td>
<td>R=0.41</td>
<td>p&lt;0.0001</td>
<td>The higher the number of stenosed coronary arteries, the higher the value of the UB index.</td>
</tr>
<tr>
<td>Vranic 2017</td>
<td>100</td>
<td>CA</td>
<td>ND</td>
<td></td>
<td>The value of stenosis are significantly higher in coronary patients: right CCA (p₁); right ICA (p₂); left CCA (p₄); left ICA (p₅). Correlation between total maximum carotid artery plaque and number of coronary stenosis.</td>
</tr>
<tr>
<td>He 2018</td>
<td>388</td>
<td>CA/ CCT</td>
<td>R=0.245</td>
<td>p&lt;0.001</td>
<td>Relationship between CAD disease and plaque burden.</td>
</tr>
<tr>
<td>Ye Zhu 2021</td>
<td>480</td>
<td>CA/ CCT</td>
<td>OR=0.457</td>
<td>P=0.048</td>
<td>Relationship between CAD and plaque burden.</td>
</tr>
<tr>
<td>Morito 2007</td>
<td>116</td>
<td>CA</td>
<td>ND</td>
<td></td>
<td>Relationship between PS (p₁); PN (p₂) and severity of CAD.</td>
</tr>
<tr>
<td>research</td>
<td>n</td>
<td>CAD</td>
<td>significance</td>
<td>p</td>
<td>compared parameters</td>
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<tr>
<td>Kanadasi 2006</td>
<td>143</td>
<td>CA</td>
<td>R=0.42</td>
<td>p&lt;0.001</td>
<td>Correlation between CAD and CCA wall morphology</td>
</tr>
<tr>
<td>Brook 2006 32</td>
<td>42</td>
<td>CCT</td>
<td>R=0.43</td>
<td>p=0.006</td>
<td>^ Relationship between carotid plaque area and the Framingham Risk Score PS as an independent factor associated with the presence of CAD</td>
</tr>
<tr>
<td>Ikeda 2012 33</td>
<td>501</td>
<td>CA</td>
<td>OR=1.22</td>
<td>p&lt;0.001</td>
<td>^Correlation between plaque area and the incidence of CAD (1&lt;60yo, 2&gt;=60yo)</td>
</tr>
<tr>
<td>Chang 2013 34</td>
<td>120</td>
<td>CCT</td>
<td>OR1=5.36, OR2=14.91</td>
<td>p1=0.06, p2=0.45</td>
<td>Correlation between plaque and the incidence of CAD (1&lt;60yo, 2&gt;=60yo)</td>
</tr>
<tr>
<td>Akazawa 2016 35</td>
<td>332</td>
<td>CCT</td>
<td>R1=0.436, R2=0.470</td>
<td>p1&lt;0.001, p2&lt;0.001</td>
<td>Correlation between CAD and plaque sum (1) and maximum thickness of plaque (2) among asymptomatic patients with DM2</td>
</tr>
<tr>
<td>Chung 2017 36</td>
<td>170</td>
<td>CA</td>
<td>OR=1.15</td>
<td>p&lt;0.001</td>
<td>PS as an independent predictor of CAD</td>
</tr>
</tbody>
</table>

CA – coronary angiography, CAD – coronary artery disease, CCA – common carotid artery, CCT – coronary computed tomography, DM2 – diabetes mellitus type 2, ICA – internal carotid artery, PN – plaque number, PS – plaque score, UB – ultrasonic biopsy

Table 3 The most significant ultrasound indicators in cardiovascular disease prediction
**Table 1: Atherosclerotic Lesion Detection Using Clinical Manifestations of Cardiovascular Disease**

<table>
<thead>
<tr>
<th>Research</th>
<th>n</th>
<th>Indicator Description</th>
<th>AUC</th>
<th>Cut off Value</th>
<th>Sensitivity [%]</th>
<th>Specificity [%]</th>
<th>CVD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colledanchise 2020 *66</td>
<td>500</td>
<td>Femoral bifurcation and carotid MPH*</td>
<td>0.77</td>
<td>&gt;2.7 mm</td>
<td>87</td>
<td>53</td>
<td>&gt;1 segment of &gt;1 epicardial artery carried a &gt;30% stenosis of CA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Common femoral and carotid TPA**</td>
<td>0.76</td>
<td>&gt;42 mm²</td>
<td>86</td>
<td>53</td>
<td>clinical manifestation of CVD</td>
</tr>
<tr>
<td>Tartiere 2003 *90</td>
<td>323</td>
<td>Carotid and/or iliofemoral plaques</td>
<td>0.78</td>
<td>1 plaque</td>
<td>76</td>
<td>70</td>
<td>clinical manifestation of CVD</td>
</tr>
<tr>
<td>Yerly 2015 *91</td>
<td>203</td>
<td>ABS</td>
<td>0.79</td>
<td>3 plaques</td>
<td>78</td>
<td>71</td>
<td>&gt;1 segment of &gt;1 epicardial artery carried a &gt;30% stenosis of CA</td>
</tr>
<tr>
<td>Griffin 2009 *89</td>
<td>767</td>
<td>TPT of both carotid and femoral bifurcation</td>
<td>ND</td>
<td>&gt;5.2 mm</td>
<td>75</td>
<td>75</td>
<td>clinical manifestation of CVD</td>
</tr>
<tr>
<td>Khoury 1997 *9</td>
<td>113</td>
<td>Aortic and femoral plaques</td>
<td>0.75</td>
<td>ND</td>
<td>74</td>
<td>79</td>
<td>&gt;1 segment of &gt;1 coronary artery in CA</td>
</tr>
<tr>
<td>Kafetzakis 2005 *63</td>
<td>108</td>
<td>UB</td>
<td>0.77</td>
<td>3.25</td>
<td>69</td>
<td>70</td>
<td>&gt;1 segment of &gt;1 coronary artery in CA</td>
</tr>
</tbody>
</table>


*Figure 1 The incidence of both significant and non-significant atherosclerotic lesions in peripheral arteries in patients with coronary artery disease*