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REVIEW ARTICLE

Imaging Subclinical Atherosclerosis: Where Do We Stand?

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Abstract: The age of initiation and the rate of progression of atherosclerosis vary markedly among individuals and have been difficult to predict with traditional cardiovascular risk assessment models. Although these risk models provide good discrimination and calibration in certain populations, cardiovascular disease (CVD) risk may not be accurately estimated in low- and intermediate risk individuals. Therefore, imaging techniques such as Ankle-Brachial Index (ABI), Coronary Artery Calcium score (CAC), carotid Intima-Media Thickness (cIMT), flow mediated dilation (FMD) and Positron Emission Tomography (PET) have been developed and used to reclassify these individuals. In the present article we review the role of the most commonly used imaging techniques for CVD risk assessment.

Keywords: Subclinical atherosclerosis, calcium score, intima-media thickness.

INTRODUCTION

Atherosclerosis is a chronic disease of the arterial wall, and the underlying cause of the majority of cardiovascular events. This generalized inflammatory disease is characterized by an accumulation of lipids, inflammatory cells, and development of scar tissue covered by a fibrous cap build within the walls of medium and large-sized arteries. Cardiovascular disease (CVD) including coronary heart disease (CHD), as well as cerebrovascular, peripheral arterial disease and abdominal atherosclerosis affects the majority of adults over the age of 60 years. In the Framingham Heart study the lifetime risk for CHD at age 40 was 49 percent in men and 32 percent in women [1]. The age of initiation and the rate of progression of atherosclerosis vary markedly among individuals and have been difficult to predict with traditional cardiovascular risk assessment models.

Therefore, individuals with subclinical atherosclerosis should preferably be identified at an early stage, so that primary prevention measures can be initiated. Early identification of subclinical atherosclerosis in individuals at low- to intermediate cardiovascular risk has been challenging. Based upon assessment of traditional risk factors several multivariate risk models have been developed for estimating the risk of cardiovascular events in asymptomatic individuals. The currently available risk estimators have several limitations [2]. Firstly, they do not take into account the duration of risk exposure and do not provide life-time risk estimate. Moreover, they may overestimate or underestimate future CVD event in patients at low-risk, resulting in over- or under-treatment of these individuals. Risk estimates appear to be less accurate in diabetics, women, certain ethnicities (such as South Asians) or geographic areas, and different socio-economic strata. Since most risk equations have been derived from cohorts of middle-aged individuals, risk in young (<40 years of age) or elderly (>80 years of age) individuals may be underestimated. Finally, metabolic abnormalities such as metabolic syndrome or pre-diabetes are not included in the currently available risk estimators.

Although these risk models provide good discrimination and calibration in certain populations, CVD risk may be underestimated in low- and intermediate risk individuals. Therefore, imaging techniques have been developed and used to reclassify these individuals. In present article we will review the role of the most commonly used imaging techniques in CVD risk assessment.

IMAGING TECHNIQUES FOR ASSESSMENT OF SUBCLINICAL ATHEROSCLEROSIS

Atherosclerosis precedes cardiovascular events and has a prolonged asymptomatic phase during which the course of the disease can be modified by lifestyle modifications and treatment. Patients with asymptomatic CVD, diabetes, chronic kidney disease, atherosclerotic cardiovascular disease (ASCVD) risk estimate>7.5%, Framingham risk score

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(FRS) >20% or SCORE >5% are considered at high CVD risk and should be treated promptly with lifestyle modifications and statins. However, as described above there is considerable overlap in estimated risk between those who are affected by cardiovascular events and those who are at intermediate risk. Those with 5-7.5% ASCVD risk estimate over next decade or 10-year FRS between 10 and 20% or SCORE 1-5% may benefit from assessment of additional factors such as coronary artery calcium score ≥300 or >75th percentile, ankle-brachial index <0.9, or a high sensitivity C-reactive protein (hs-CRP) >2.0 mg/L [1, 2].

Imaging Modalities

The use of imaging to detect subclinical atherosclerosis has the potential to predict the risk of future cardiovascular events (Table **1**). Imaging of atherosclerosis is superior to risk equations as it directly identifies the disease, reclassifies low and intermediate risk individuals more effectively and can guide medical therapy.

a) Carotid Intima-Media Thickness

Carotid intima-media thickness (CIMT) can be measured with either ultrasound or magnetic resonance imaging. Normal common CIMT in childhood is approximately 0.4 to 0.5 mm, while in adulthood it progresses to 0.7 mm or more. CIMT measurement has excellent intra- and inter-observer variability when performed by experienced operators using validated image-analysis protocols (Table **2**). In a systematic review and meta-analysis of 14 studies with 45,828 asymptomatic individuals who underwent a single CIMT measurement and followed-up for 11 years, CIMT was associated with the risk of first myocardial infarction (MI) or stroke [3]. However, in another meta-analysis of 16 studies including 36,984 patients without known CVD who underwent serial CIMT measurement and followed for seven years there was no association between progression of CIMT and future events [4]. Baseline CIMT measurements were associated with future cardiovascular events. The addition of CIMT or carotid plaque to Framingham risk score in a 13,145 individuals from the ARIC study resulted in reclassification of 23% of all subjects and 13.5% of intermediate risk individuals into the high-risk group [5]. Overall, CIMT plus plaque model when compared with the Framingham risk score was associated with net reclassification index of 9.9% suggesting effective reclassification. These results are similar to the analysis of 2,965 individuals from the Framingham Offspring Study cohort followed for 7.2 years, which reported a significant increase in the net reclassification index after addition of CIMT to 7.6% [6]. However, the Carotid Atherosclerosis Progression Study (CAPS) did not confirm the previous findings. CIMT reclassified more patients to the lower risk than towards the high-risk group [7]. The addition of CIMT to Framingham risk score reclassified only 8.1% individuals with a non-significant net reclassification index of 21%. The meta-analysis of single measurement CIMT reported only a modest net reclassification improvement in all subjects of 0.8 percent, and in subjects at intermediate risk of 3.6 percent [3].

Although, the previous ACC/AHA guidelines for the assessment of CVD risk in asymptomatic individuals made a level IIa recommendation for CIMT in intermediate risk individuals, the most recent risk assessment ACC/AHA recommended against the routine measurement of CIMT due to only modest net reclassification improvement with the use of this method [8, 9]. CIMT measured by MRI is currently being studied. It exhibits lower measurement variability and correlates well with the ultrasound measurements suggesting similar predictive capacity [10].

b) Coronary Artery Calcium Score

Evidence of CAC on coronary angiography is a well-known marker associated with severity of CAD and survival [11]. CAC is present before the development of clinically significant coronary stenosis. Advances in CT technology allowed imaging of the heart without motion artifacts and thus quantitative assessment of CAC. The most widely used and established measure of CAC is the Agatston score [12]. In most studies CAC scores<100 signify mild disease while score >400 indicate severe CAD [13]. However, due to the fact that only few asymptomatic individuals have scores>400, the use of CAC percentiles according to age and gender, appears a more effective stratification method [14]. Intra- and inter- scan variability of Agatston score by non-contrast CT is low [15]. The presence and extent of CAC detect calcified plaques with high accuracy when compared to intra-coronary ultrasound and correlate well with the presence and extend of CAD rather than the severity of stenosis [16, 17]. The absence of CAC is highly predictive of the absence of significant coronary artery stenosis. In a study of 1,764 patients with suspected CAD those with no CAC had <1% probability of significant coronary stenosis [18]. Among individuals with CAC 0, conversion to CAC score>0 occurred in 25%, was associated with age, diabetes and smoking and was more frequent after the fourth year of follow up [19].

Table 1. Available imaging techniques assessing vascular function.

Coronary circulation	Peripheral circulation	Subclinical atherosclerosis
Coronary angiography	Strain-gauge plethysmography	Arterial stiffness
Intravascular ultrasonography	Flow mediated vasodilation	Pulse wave velocity
MRI	Laser Doppler flowmetry	Carotid intima-media thickness
PET	ABI	Coronary Artery Calcium

Abbreviations: MRI; magnetic resonance imaging, PET; positron emission tomography, ABI; ankle-brachial index.

Table 2. Studies measuring intima-media thickness and carotid plaque in asymptomatic patients.

Study	Technique	Population	Number	Follow up	Endpoint	C-statistic without/with IMT
Anderson *et al*. [62]	cIMT	Asymptomatic men	1,574	7.2 years	CV events	0.75/0.75
Folsom *et al*. [63]	cIMT	Asymptomatic subjects	6,698	5.3 years	CV events	0.77/0.78
Price *et al*. [64]	cIMT	Asymptomatic men	1,007	12 years	CV events	0.61/0.62
Lorenz *et al*. [65]	cIMT	Asymptomatic subjects	4,909	10 years	CV events	0.72/0.72
Nambi *et al*. [66]	cIMT	Asymptomatic subjects	13,145	15.1 years	CV events	0.74/0.75
Cao *et al*. [67]	Carotid plaque	Asymptomatic subjects	5,020	8 years	CV events	0.72/0.73
Stork *et al*. [68]	Carotid plaque	Asymptomatic subjects	403	4 years	CV events	0.67/0.72
Plichart *et al*. [69]	Carotid plaque	Asymptomatic subjects	5.895	5.4 years	CV events	0.75/0.76

Abbreviations: HR: hazard ratio, CV: cardiovascular, cIMT: carotid intima-media thickness.

CAC score is associated with cardiac event in low- to intermediate- risk individuals with incremental prognostic information in addition to age and other risk factors as shown in a study of 8,855 asymptomatic adults screened for CAC (Table **3**). Also, the extent of CAC correlates with the magnitude of the risk in middle-aged and elderly individuals [20-22].

CAC score provided independent prognostic information to that determined by the Framingham risk score across different ethnicities. As shown in a Multiethnic study of atherosclerosis (MESA) study sub-analysis, CAC>300 was found in one fourth of those with a Framingham risk score of 15-20% [23]. Additionally, based on the results of large observational studies CAC score predicted all-cause mortality independent of and more accurately than Framingham risk score. A German cohort of asymptomatic individuals showed that CAC reclassified 21.7% of intermediate-risk patients into the low-risk group and 30.6% into the high-risk category and resulted in significant increase of c-statistic 0.75 when added to Framingham risk score or ATPIII risk model [24-26]. Similarly, in MESA the addition of CAC to traditional risk factors resulted in reclassification of 26 percent of the cohort [27]. Although, both CAC and hs-CRP are independently associated with CVD events, the net reclassification improvement appears to be higher for CAC (23.8%) compared to hs-CRP (10.5%) [28]. In MESA, CAC score stratified better patients with hs-CRP>2mg/l and improved reclassification compared to hsCRP, CIMT, ABI, brachial FMD, and family history [29, 30]. Importantly, after adjustment for traditional risk factors hs-CRP did not correlate with CAC in the Dallas Heart study, suggesting weak association with the atherosclerotic burden [31]. Finally, studies in asymptomatic individuals have shown that progression of CAC was associated with increased risk of CAD events [32]. Overall, the absence of CAC in asymptomatic individuals signifies absence of CAD while the presence enhances risk prediction when added to currently available risk models particularly in intermediate-risk individuals.

However, it may be prudent at this point to note some limitations in its use. CAC score may not give accurate risk estimates in specific subgroups such as uremic subjects and it is sensible not be used as a test in isolation in the risk stratification of these patients. Another obvious disadvantage is the use of CT and concomitant radiation exposure with doses up to 21.4 mSv compared to a mean of 5.6 mSv for diagnostic catheter angiographies [1].

c) Arterial Stiffness

Progressive alteration of arterial structure and function including hypertrophy and hyperplasia of smooth muscle cells within the arterial wall, coupled with deposition of collagen, calcium and loss of elastic matrix leads to impaired reduced vascular compliance and increased vascular stiffness, which play a pivotal role in the initiation and progression of atherosclerosis [33]. Arterial stiffness may be assessed by a variety of noninvasive, reproducible, and relatively inexpensive methods [34], and has been linked to increased risk for the development of atherosclerosis, as well as been utilized as a prognostic marker beyond standard risk factor stratification (Table **4**) [35]. The physiologic marker of aortic stiffness that is most easily evaluated is the measurement of the pulse pressure. Increased pulse pressure has been associated with an increased incidence of CVD [36]. However, the most useful clinical marker of arterial stiffness is pulse wave velocity (PWV), which represents the time required for the pressure wave to travel between two regions in the vasculature. PWV has been demonstrated to be an independent predictor of CVD events after adjustment for traditional risk factors in hypertensive's and elderly individuals [37, 38]. In a meta-analysis of 17 studies that included over 15,000 patients in whom aortic PWV between the carotid and femoral arteries had been correlated to clinical outcome, the pooled relative risks for total cardiovascular events, cardiovascular mortality, and all-cause mortality were significantly increased comparing high versus low aortic PWV groups [39]. The additive value of PWV above and beyond traditional risk factors has been quantified by 3 separate studies. In asymptomatic hypertensive patient, Framingham risk score and PWV had similar predictive value (c-statistic), and when combined the c-statistic significantly increased to 0.76 [40]. The predictive ability of PWV was confirmed in the asymptomatic middle-aged and elderly individuals [41, 42]. PWV but not augmentation index or central pulse pressure has also been demonstrated to improve

Table 3. Studies measuring coronary artery calcium score in asymptomatic patients.

Study	Technique	Population	Number	Follow up	Endpoint	C-statistic without/with CAC
Polonski *et al*. [27]	CAC	Asymptomatic subjects	5,878	5.8 years	CV events	0.76/0.81
Erbel *et al*. [26]	CAC	Asymptomatic subjects	4,129	5 years	CV events	0.68/0.75
Folsom *et al*. [63]	CAC	Asymptomatic subjects	6,698	5.3 years	CV events	0.77/0.81
Elias-Smale [70]	CAC	Asymptomatic subjects	2,028	9.2 years	CV events	0.72/0.76
Greenland *et al*. [5]	CAC	Asymptomatic subjects	1,312	7 years	CV events	0.63/0.69

Abbreviations: CV: cardiovascular, CAC: coronary artery calcium.

Table 4. Pulse wave velocity and prognostic information.

Study	Population	Number	Follow up	Endpoint	Comments
Meaume *et al*. [71]	Geriatric subjects	141	2.5 years	CV events	PWV is a strong, independent predictor of CV death
Boutouyrie *et al*. [72]	Essential hypertensive patients	1,045	5.7 years	CV events	PWV was significantly associated with the occurrence of coronary event after adjustment either of Framingham score or classic risk factors
Mattace-Raso *et al*. [73]	Community-based adults	2,835	4.1 years	CV events	PWV is an independent predictor of coronary heart disease and stroke
Mitchell *et al*. [74]	Community-dwelling sample	2,232	7.8	CV events	PWV is an independent predictor of CV events
Laurent *et al*. [75]	Essential hypertensive patients	1,980	9.3 years	CV events	PWV was significantly associated with all-cause and cardiovascular mortality, independent of previous cardiovascular diseases, age, and diabetes
Cruickshank *et al*. [76]	Patients with Diabetes Mellitus	394	10.7 years	CV events	The addition of PWV independently predicted all-cause and CV mortality
Shoji *et al*. [77]	End-stage renal disease patients	265	5.3 years	CV events	PWV was a significant predictor for CV and overall mortality but not for non-CV death
Shokawa *et al*. [78]	Japanese-Americans subjects	492	10 years	CV events	PWV is an independent predictor of CVD
Sutton-Tyrrell *et al*. [79]	Community-dwelling sample of older adults	2,488	4.6 years	CV events	PWV associated with higher CV mortality, CHD, and stroke
Zoungas *et al*. [80]	Patients with chronic kidney disease	315	3.6 years	CV events	PWV was an independent predictor of CV events
Wang *et al*. [81]	Community-dwelling sample	1,272	15 years	CV events	PWV predicted all-cause and CV mortality in both men and women

Abbreviations: PWV: Pulse wave velocity, CV: cardiovascular.

reclassification. In the Framingham study, 15.7% of patients at intermediate risk were reclassified into higher (14.3%) or lower (1.4%) risk group [43]. Finally, in a recent meta-analysis, 19% and 22% of intermediate risk individuals were reclassified into higher-risk and 22% into lower- cardiovascular risk [44]. Based on the above, arterial stiffness assessed with PWV is a strong predictor of CVD events that could enhance predictive ability of traditional risk models.

d) Ankle-Brachial Index

The ankle-brachial index (ABI), namely the ratio of systolic blood pressure at the ankle to the blood pressure in the upper arm is a relatively simple and inexpensive method to confirm the clinical suspicion of peripheral arterial disease. ABI is also a strong predictor of CVD events. Low ABI<0.9 is associated with a higher risk of CHD, stroke, transient ischemic attack, progressive renal insufficiency, and all-cause mortality (Table **5**) [45-47]. In a meta-analysis comprising 48,294 subjects, a low ABI (<0.9) compared to a normal ABI (1.1–1.4) was related to a 2–3-fold increase in both 10-year major coronary events and cardiovascular mortality independent of the Framingham risk score [48]. The addition of ABI to Framingham risk score resulted in reclassification of risk in 1 in 5 men and 1 in 3 women mainly from intermediate towards the high risk-group [48]. Finally,

Table 5. Ankle brachial index and CV risk.

Study	Population	Number	Endpoint	Comments
McDermott *et al*. [82]	Subjects free of clinically evident CVD	6,570	Subclinical cardiac and carotid atherosclerosis	Excess coronary and carotid atherosclerosis at ABI values below 1.10 (men) and 1.00 (women)
Hasimu *et al*. [83]	Patients at high CV risk	5,646	Subclinical atherosclerosis	A lower ABI was associated with generalized atherosclerosis
Menke *et al*. [84]	Representative sample of United States population	4,895	CV events	A low-normal ABI was associated with a 10-year risk of CHD of ≥20%
Matsushita *et al*. [85]	Participants ages 45-84 years without prior CVD	6,553	CV events	ABI was independently associated with cardiovascular outcomes HR, 1.20; 95% CI, 1.08 to 1.32
Li *et al*. [86]	Inpatients at high risk of atherosclerosis	3,210	All-cause and CV mortality	Low ABI is related to a higher all-cause and CV mortality
Li *et al*. [87]	Patients with type 2 DM	1,647	All-cause and CV mortality	Low ABI was independently associated with a high risk of all-cause and CVD mortality
Ramos *et al*. [88]	Subjects aged 35-79 (general population)	6,262	CV events	Adding ABI measurement to CHD-risk screening better identifies moderate-to-high cardiovascular risk patients
Poredos *et al*. [89]	Patients at high CV risk, or with evidence of CAD or CVD	952	CV events	Abnormal ABI was strongly associated with CAD and CVD

Abbreviations: ABI: Ankle brachial index, CVD: Cardiovascular disease, HR: Hazard ratio, DM: Diabetes mellitus, CAD: Coronary artery disease.

in an analysis of 18 cohorts which included 24,375 asymptomatic men and 20,377 asymptomatic women, ABI in addition to Framingham risk score led to an improvement in reclassification mainly in women [49]. Although, ABI improves performance of the risk models when measured in the intermediate risk individuals [49], it appears to be inferior in reclassifying intermediate risk individuals compared to CAC as demonstrated in the Rotterdam and MESA studies [50, 51].

e) Flow-Mediated Dilation (FMD)

Inflation of a blood pressure cuff to supasystolic pressure for five minutes and subsequent release of pressure leads to endothelial-dependent FMD of the brachial artery. The percentage of change of end-diastolic diameter of the artery from baseline is a surrogate marker of endothelial function [52]. A meta-analysis of fourteen cohorts including 5,547 asymptomatic individuals showed that FMD is associated with future CVD beyond traditional risk factors [53]. Data from the MESA cohort suggest that FMD is a predictor of CVD events in asymptomatic individuals, and correctly reclassifies 29% of these individuals without a significant improvement in discrimination when added to FRS [54]. Although, FMD correlates well with future events, it does not add significantly to risk stratification as shown by a more recent robust meta-analysis of different imaging modalities [55] (Table **6**). The use and application of vascular reactivity techniques such as FMD has been limited by the fact that several factors, such as environmental (time, light, temperature), patient-related (caffeinated beverage, food intake, smoking, menstrual cycle, antihypertensive and lipid-lowering medications) and operator-related (intra- and inter-observer variability, technique, equipment) may affect the validity and accuracy of the measurements.

POSITRON EMISSION TOMOGRAPHY (PET)

In contrast to the aforementioned modalities, PET can evaluate dynamic intraplaque activity such as inflammation, active plaque calcification, and other biologic processes [56, 57]. For example inflammatory process of the unstable plaque can be imaged and quantified with fluorine-18 (F-18) fluorodeoxyglucose (FDG). FDG has also become established in diagnosing and monitoring large vessel vasculitis and has now entered routine practice [58].

Macrophages have high metabolic rates and require an equally abundant energy supply while they potentiate localized inflammatory responses and are fundamental mediators of atherosclerosis. Radiolabelled FDG may then serve as a marker of metabolic activity within the plaque and an inflamed high-risk lesion. Of note, in patients with symptomatic carotid atherosclerosis imaged with 18FDG-PET, FDG was found to localize to macrophage-rich regions [59]. Moreover, while the degree of vascular stenosis evaluated with angiography is related to FDG uptake, Davies et al have suggested that angiography may not always identify the culprit lesion [60]. Patients with recent transient ischemic attack who had a severe stenosis in the ipsilateral carotid artery, and were awaiting carotid endarterectomy underwent FDG-PET and high resolution magnetic resonance imaging (HRMRI) scanning. It was demonstrated that combined FDG-PET and HRMRI can assess the degree of inflammation in stenotic and even nonstenotic plaques and could potentially be used

Table 6. Flow-mediated dilatation and prognostic information.

Study	Population	Number	Follow up	Endpoint	Comments
Gokce *et al*. [90]	Patients with peripheral arterial disease	199	1.2 years	CV events	Risk was approximately nine-fold higher in patients with FMD <8.1% (lower two tertiles) compared with those in the upper tertile
Frick *et al*. [91]	Patients admitted for invasive evaluation of chest pain	398	4.5 years	CV events	No difference in CV events was found
Huang *et al*. [92]	Patients with peripheral arterial disease	267	0.8 years	CV events	FMD independently predicted CV events
Hu *et al*. [93]	Patients admitted for invasive evaluation of chest pain	279	1.3 years	CV events	FMD independently predicted CV events
Suessenbacher *et al*. [94]	Patients admitted for invasive evaluation of chest pain	396	11.8 years	CV events	No difference in CV events was found
Brevetti *et al*. [95]	Patients with peripheral arterial disease	131	1.9 years	CV events	FMD independently predicted CV events
Chan *et al*. [96]	Patients with coronary artery disease	152	2.8 years	CV events	FMD independently predicted CV events
Fathi *et al*. [97]	Patients at risk of CV events	444	2 years	CV events	No difference in CV events was found
Modena *et al*. [98]	Post-menopausal and hypertensive women	400	5.6 years	CV events	After 6 months of treatment subjects without improvement of FMD exhibited increased event rate

Abbreviations: FMD: Flow mediated dilatation, CV: cardiovascular.

Table 7. Studies measuring atherosclerotic plaque inflammation with 18FDG-PET.

Study	Technique	Population	Number	Endpoint	Comments
Rudd *et al*. [59]	18FDG-PET	Symptomatic carotid atherosclerosis	8	Atherosclerotic plaque inflammation	Unstable plaques accumulate more 18FDG than asymptomatic lesions
Davies *et al*. [60]	18FDG-PET HRMRI	Recent transient ischemic attack	12	Atherosclerotic plaque inflammation	Combined FDG-PET and HRMRI can assess the degree of inflammation
Khalil *et al*. [61]	18FDG-PET	3 healthy subjects, 3 patients with hypercholesterolemia and 2 patients with stable angina pectoris	8	Atherosclerotic plaque inflammation	After 12-month follow-up period, non-calcified arteries showed a significant increase of (18)F-FDG uptake in both healthy, hypercholesterolemic and stable angina patients

Abbreviations: 18FDG-PET: 18F fluorodeoxyglucose positron (FDG)-emission tomography (PET), HRMRI: high-resolution magnetic resonance imaging.

to identify lesions responsible for embolic events. Therefore, FDG imaging of atherosclerotic lesions may be of incremental benefit when performed in conjunction with other modalities to identify culprit lesions at high risk of rupture [60]. Moreover, according to a recent study, the usefulness of 18FDG measurement to localize and quantify arterial inflammation in each artery segments and as a result of the CVD risk factors was confirmed [61]. Current trials will contribute toward validating and establishing FDG PET, as well as developing other biomarkers using a multimodality approach to characterize aspects of atherosclerosis biology, disease burden, and identifying high-risk plaques [57] (Table **7**).

However, it should be clearly noted that FDG imaging of vasculature is a relatively new area which suffers from several limitations. For example, direct evidence demonstrating that FDG is taken up directly into macrophage cells is still lacking. Also, imaging coronary vasculature with FDG continues to be affected by myocardial motion and myocardial FDG uptake. Besides, there are other limitations such as patient preparation and diets which may lower myocardial FDG uptake [57].

CONCLUSIONS

It has become evident that monitoring or treating subclinical atherosclerosis remains an issue under debate. Over the last decade, there is increasing use of imaging techniques. Data from studies using CAC, ABI, cIMT and FMD appear to be encouraging, but large-scale studies with cost-

effectiveness analysis in low- to intermediate- risk individuals have not yet been completed. The best available strategy to improve outcomes is primary prevention based on risk estimation and screening for subclinical atherosclerosis. Individuals with diabetes, advanced chronic kidney disease, or classified as high-risk according to the various risk models should be aggressively treated. In the intermediate risk individuals the addition of imaging modalities-mainly CAC- or ABI, enhances the predictive capacity of traditional risk models and better predict CVD events. However, further studies are needed to examine whether treatment based on re-classification with imaging modalities and risk scores results in meaningful improvement of cardiovascular outcomes.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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REFERENCES

[1] Lloyd-Jones DM, Larson MG, Beiser A, *et al*. Lifetime risk of developing coronary heart disease. Lancet 1999; 353: 89-92.

[2] Kavousi M, Leening MJ, Nanchen D, *et al*. Comparison of application of the ACC/AHA guidelines, Adult Treatment Panel III guidelines, and European Society of Cardiology guidelines for cardiovascular disease prevention in a European cohort. JAMA 2014; 311: 1416-23.

[3] Den Ruijter HM, Peters SA, Anderson TJ, *et al*. Common carotid intima-media thickness measurements in cardiovascular risk prediction: a meta-analysis. JAMA 2012; 308: 796-803.

[4] Lorenz MW, Polak JF, Kavousi M, *et al*, PROG-IMT Study Group. Carotid intima-media thickness progression to predict cardiovascular events in the general population (the PROG-IMT collaborative project): a meta-analysis of individual participant data. Lancet 2012; 379(9831): 2053-62.

[5] Nambi V, Chambless L, Folsom AR, *et al*. Carotid intimamedia thickness and presence or absence of plaque improves prediction of coronary heart disease risk the ARIC (Atherosclerosis Risk In Communities) study. J Am Coll Cardiol 2010; 55: 1600-7.

[6] Polak JF, Pencina MJ, Pencina KM, *et al*. Carotid-wall intima-media thickness and cardiovascular events. N Engl J Med 2011; 365: 213-21.

[7] Lorenz MW, Schaefer C, Steinmetz H, Sitzer M. Is carotid intima media thickness useful for individual prediction of cardiovascular risk? Ten-year results from the Carotid Atherosclerosis Progression Study (CAPS). Eur Heart J 2010; 31: 2041-8.

[8] Greenland P, Alpert JS, Beller GA, *et al*, American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. 2010 ACCF/AHA guideline for assessment of cardiovascular risk in asymptomatic adults: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation 2010; 122: 2748-64.

[9] Goff DC Jr, Lloyd-Jones DM, Bennett G, *et al*. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 2014; 129(25 Suppl 2): S49-73.

[10] Duivenvoorden R, de Groot E, Elsen BM, *et al*. In vivo quantification of carotid artery wall dimensions: 3.0-Tesla MRI versus B-mode ultrasound imaging. Circ Cardiovasc Imaging 2009; 2: 235-42.

[11] Margolis JR, Chen JT, Kong Y, *et al*. The diagnostic and prognostic significance of coronary artery calcification. A report of 800 cases. Radiology 1980; 137(3): 609-16.

[12] Agatston AS, Janowitz WR, Hildner FJ, *et al*. Quantification of coronary artery calcium using ultrafast computed tomography. J Am Coll Cardiol 1990; 15: 827-32.

[13] Pletcher MJ, Tice JA, Pignone M, Browner WS. Using the coronary artery calcium score to predict coronary heart disease events: a systematic review and meta-analysis. Arch Intern Med 2004; 164: 1285-92.

[14] Raggi P, Callister TQ, Cooil B, *et al*. Identification of patients at increased risk of first unheralded acute myocardial infarction by electron-beam computed tomography. Circulation 2000; 101: 850-5.

[15] Ghadri JR, Goetti R, Fiechter M, *et al*. Inter-scan variability of coronary artery calcium scoring assessed on 64-multidetector computed tomography vs. dual-source computed tomography: a head-to-head comparison. Eur Heart J 2011; 32: 1865-74.

[16] Baumgart D, Schmermund A, Goerge G, *et al*. Comparison of electron beam computed tomography with intracoronary ultrasound and coronary angiography for detection of coronary atherosclerosis. J Am Coll Cardiol 1997; 30: 57-64.

[17] Nallamothu BK, Saint S, Bielak LF, *et al*. Electron-beam computed tomography in the diagnosis of coronary artery disease: a meta-analysis. Arch Intern Med 2001; 161: 833-8.

[18] Haberl R, Becker A, Leber A, *et al*. Correlation of coronary calcification and angiographically documented stenoses in patients with suspected coronary artery disease: results of 1,764 patients. J Am Coll Cardiol 2001; 37: 451-7.

[19] Min JK, Lin FY, Gidseg DS, *et al*. Determinants of coronary calcium conversion among patients with a normal coronary calcium scan: what is the "warranty period" for remaining normal? J Am Coll Cardiol 2010; 55: 1110-7.

[20] Kondos GT, Hoff JA, Sevrukov A, *et al*. Electron-beam tomography coronary artery calcium and cardiac events: a 37-month follow-up of 5,635 initially asymptomatic low- to intermediate-risk adults. Circulation 2003; 107: 2571-6.

[21] Arad Y, Goodman KJ, Roth M, *et al*. Coronary calcification, coronary disease risk factors, C-reactive protein, and atherosclerotic cardiovascular disease events: the St. Francis Heart Study. J Am Coll Cardiol 2005; 46: 158-65.

[22] Vliegenthart R, Oudkerk M, Hofman A, *et al*. Coronary calcification improves cardiovascular risk prediction in the elderly. Circulation 2005; 112: 572-7.

[23] Okwuosa TM, Greenland P, Ning H, *et al*. Distribution of coronary artery calcium scores by Framingham 10-year risk strata in the MESA (Multi-Ethnic Study of Atherosclerosis) potential implications for coronary risk assessment. J Am Coll Cardiol 2011; 57: 1838-45.

[24] Shaw LJ, Raggi P, Schisterman E, Berman DS, Callister TQ. Prognostic value of cardiac risk factors and coronary artery calcium screening for all-cause mortality. Radiology 2003; 228: 826-33.

[25] Budoff MJ, Shaw LJ, Liu ST, *et al*. Long-term prognosis associated with coronary calcification: observations from a registry of 25,253 patients. J Am Coll Cardiol 2007; 49: 1860-70.

[26] Erbel R, Möhlenkamp S, Moebus S, *et al*, Heinz Nixdorf Recall Study Investigative Group. Coronary risk stratification, discrimination, and reclassification improvement based on quantification of subclinical coronary atherosclerosis: the Heinz Nixdorf Recall study. J Am Coll Cardiol 2010; 56: 1397-406.

[27] Polonsky TS, McClelland RL, Jorgensen NW, *et al*. Coronary artery calcium score and risk classification for coronary heart disease prediction. JAMA 2010; 303: 1610-6.

[28] Möhlenkamp S, Lehmann N, Moebus S, *et al*, Heinz Nixdorf Recall Study Investigators. Quantification of coronary atherosclerosis and inflammation to predict coronary events and all-cause mortality. J Am Coll Cardiol 2011; 57: 1455-64.

[29] Blaha MJ, Budoff MJ, DeFilippis AP, *et al*. Associations between C-reactive protein, coronary artery calcium, and cardiovascular events: implications for the JUPITER population from MESA, a population-based cohort study. Lancet 2011; 378: 684-92.

[30] Yeboah J, McClelland RL, Polonsky TS, *et al*. Comparison of novel risk markers for improvement in cardiovascular risk assessment in intermediate-risk individuals. JAMA 2012; 308: 788-95.

[31] Khera A, de Lemos JA, Peshock RM, *et al*. Relationship between C-reactive protein and subclinical atherosclerosis: the Dallas Heart Study. Circulation 2006; 113: 38-43.

[32] Budoff MJ, Young R, Lopez VA, *et al*. Progression of coronary calcium and incident coronary heart disease events: MESA (Multi-

Ethnic Study of Atherosclerosis). J Am Coll Cardiol 2013; 61: 1231-9.

[33] Zieman SJ, Melenovsky V, Kass DA. Mechanisms, pathophysiology, and therapy of arterial stiffness. Arterioscler Thromb Vasc Biol 2005; 25: 932-43.

[34] Laurent S, Cockcroft J, Van Bortel L, *et al*. European Network for Non-invasive Investigation of Large Arteries. Expert consensus document on arterial stiffness: methodological issues and clinical applications. Eur Heart J 2006; 27: 2588-605.

[35] Kullo IJ, Malik AR. Arterial ultrasonography and tonometry as adjuncts to cardiovascular risk stratification. J Am Coll Cardiol 2007; 49: 1413-26.

[36] Agabiti-Rosei E, Mancia G, O'Rourke MF, *et al*. Central blood pressure measurements and antihypertensive therapy: a consensus document. Hypertension 2007; 50: 154-60.

[37] Blacher J, Asmar R, Djane S, *et al*. Aortic pulse wave velocity as a marker of cardiovascular risk in hypertensive patients. Hypertension 1999; 33: 1111-7.

[38] Meaume S, Benetos A, Henry OF, Rudnichi A, Safar ME. Aortic pulse wave velocity predicts cardiovascular mortality in subjects >70 years of age. Arterioscler Thromb Vasc Biol 2001; 21: 2046-50.

[39] Vlachopoulos C, Aznaouridis K, Stefanadis C. Prediction of cardiovascular events and all-cause mortality with arterial stiffness: a systematic review and meta-analysis. J Am Coll Cardiol 2010; 55: 1318-27.

[40] Boutouyrie P, Tropeano AI, Asmar R, *et al*. Aortic stiffness is an independent predictor of primary coronary events in hypertensive patients: a longitudinal study. Hypertension 2002; 39: 10-5.

[41] Sehestedt T, Jeppesen J, Hansen TW, *et al*. Risk stratification with the risk chart from the European Society of Hypertension compared with SCORE in the general population. J Hypertens 2009; 27: 2351-7.

[42] Mattace-Raso FU, van der Cammen TJ, Hofman A, *et al*. Arterial stiffness and risk of coronary heart disease and stroke: the Rotterdam Study. Circulation 2006; 113: 657-63.

[43] Mitchell GF, Hwang SJ, Vasan RD, *et al*. Arterial stiffness and cardiovascular events: the Framingham Heart Study. Circulation 2010; 121: 505-11.

[44] Ben Schlomo Y, Spears M, Boustred C, *et al*. Predictive value of pulse wave velocity for cardiovascular events in 15,220 subjects: an individual participant meta-analysis on behalf of the PWV collaborative group. J Hypertens 2010; 28(suppl A): E446.

[45] Resnick HE, Lindsay RS, McDermott MM, *et al*. Relationship of high and low ankle brachial index to all-cause and cardiovascular disease mortality: the Strong Heart Study. Circulation 2004; 109: 733-9.

[46] Murabito JM, Evans JC, Larson MG, *et al*, Framingham Study. The ankle-brachial index in the elderly and risk of stroke, coronary disease, and death: the Framingham Study. Arch Intern Med 2003; 163: 1939-42.

[47] O'Hare AM, Rodriguez RA, Bacchetti P. Low ankle-brachial index associated with rise in creatinine level over time: results from the atherosclerosis risk in communities study. Arch Intern Med 2005; 165: 1481-5.

[48] Ankle Brachial Index Collaboration. Ankle brachial index combined with Framingham Risk Score to predict cardiovascular events and mortality. A meta-analysis. JAMA 2008; 300: 197-208.

[49] Fowkes FG, Murray GD, Butcher I, *et al*, Ankle Brachial Index Collaboration. Development and validation of an ankle brachial index risk model for the prediction of cardiovascular events. Eur J Prev Cardiol 2014; 21: 310-20.

[50] Kavousi M, Elias-Smale S, Rutten JHW, *et al*. Evaluation of newer risk markers for coronary heart disease risk classification. A cohort study. Ann Intern Med 2012; 156: 438-44.

[51] Rodondi N, Marques-Vidal P, Butler J, *et al*. Health, Aging, and Body Composition Study. Markers of atherosclerosis and inflammation for prediction of coronary heart disease in older adults. Am J Epidemiol 2010; 171: 540-9.

[52] Tousoulis D, Antoniades C, Vlachopoulos C, Stefanadis C. Flow mediated dilation and carotid intima media thickness: clinical markers or just research tools? Int J Cardiol 2013; 163(3): 226-8.

[53] Inaba Y, Chen JA, Bergmann SR. Prediction of future cardiovascular outcomes by flow-mediated vasodilatation of brachial artery: a meta-analysis. Int J Cardiovasc Imaging 2010; 26(6): 631-40.

[54] Yeboah J, Folsom AR, Burke GL, *et al*. Predictive value of brachial flow-mediated dilation for incident cardiovascular events in a population-based study: the multi-ethnic study of atherosclerosis. Circulation 2009; 120(6): 502-9.

[55] Peters SA, den Ruijter HM, Bots ML, Moons KG. Improvements in risk stratification for the occurrence of cardiovascular disease by imaging subclinical atherosclerosis: a systematic review. Heart 2012; 98(3): 177-84.

[56] Phelps ME. Positron emission tomography provides molecular imaging of biological processes. Proc Natl Acad Sci U S A 2000; 97: 9226-33.

[57] Cocker MS, Mc Ardle B, Spence JD, *et al*. Imaging atherosclerosis with hybrid [18F]fluorodeoxyglucose positron emission tomography/computed tomography imaging: what Leonardo da Vinci could not see. J Nucl Cardiol 2012; 19: 1211-25.

[58] Buscombe JR. Exploring the nature of atheroma and cardiovascular inflammation in-vivo using Positron emission Tomography (PET). Br J Radiol 2015; 20140648. [Epub ahead of print].

[59] Rudd JH, Warburton EA, Fryer TD, *et al*. Imaging atherosclerotic plaque inflammation with [18F]-fluorodeoxyglucose positron emission tomography. Circulation 2002; 105: 2708-11.

[60] Davies JR, Rudd JH, Fryer TD, *et al*. Identification of culprit lesions after transient ischemic attack by combined 18F fluorodeoxyglucose positron-emission tomography and high-resolution magnetic resonance imaging. Stroke 2005; 36: 2642-7.

[61] Khalil A, Orellana MR, Fulop T, *et al*. Positron emission tomography imaging for vascular inflammation evaluation in elderly subjects with different risk factors for cardiovascular diseases. Am J Nucl Med Mol Imaging 2014; 4: 283-92.

[62] Anderson TJ, Charbonneau F, Title LM, *et al*. Microvascular function predicts cardiovascular events in primary prevention: long-term results from the Firefighters and Their Endothelium (FATE) study. Circulation 2011; 123: 163-9.

[63] Folsom AR, Kronmal RA, Detrano RC, *et al*. Coronary artery calcification compared with carotid intima-media thickness in the prediction of cardiovascular disease incidence: the Multi-Ethnic Study of Atherosclerosis (MESA). Arch Intern Med 2008; 168: 1333-9.

[64] Price JF, Tzoulaki I, Lee AJ, Fowkes FG. Ankle brachial index and intima media thickness predict cardiovascular events similarly and increased prediction when combined. J Clin Epidemiol 2007; 60: 1067-75.

[65] Lorenz MW, Schaefer C, Steinmetz H, *et al*. Is carotid intima media thickness useful for individual prediction of cardiovascular risk? Ten-year results from the Carotid Atherosclerosis Progression Study (CAPS). Eur Heart J 2010; 31: 2041-8.

[66] Nambi V, Chambless L, He M, *et al*. Common carotid artery intima-media thickness is as good as carotid intima-media thickness of all carotid artery segments in improving prediction of coronary heart disease risk in the Atherosclerosis Risk in Communities (ARIC) study. Eur Heart J 2012; 33: 183-90.

[67] Cao JJ, Arnold AM, Manolio TA, *et al*. Association of carotid artery intima-media thickness, plaques, and C-reactive protein with future cardiovascular disease and all-cause mortality: the Cardiovascular Health Study. Circulation 2007; 116: 32-8.

[68] Stork S, Feelders RA, van den Beld AW, *et al*. Prediction of mortality risk in the elderly. Am J Med 2006; 119: 519-25.

[69] Plichart M, Celermajer DS, Zureik M, *et al*. Carotid intima-media thickness in plaque-free site, carotid plaques and coronary heart disease risk prediction in older adults. The Three-City Study. Atherosclerosis 2011; 219: 917-24.

[70] Elias-Smale SE, Kavousi M, Verwoert GC, *et al*. Common carotid intima-media thickness in cardiovascular risk stratification of older people: the Rotterdam Study. Eur J Prev Cardiol 2012; 19: 698-705.

[71] Meaume S, Benetos A, Henry OF, *et al*. Aortic pulse wave velocity predicts cardiovascular mortality in subjects >70 years of age. Arterioscler Thromb Vasc Biol 2001; 21: 2046-50.

[72] Laurent S, Boutouyrie P, Asmar R, *et al*. Aortic stiffness is an independent predictor of all-cause and cardiovascular mortality in hypertensive patients. Hypertension 2001; 37: 1236-41.

[73] Mattace-Raso FU, van Popele N, Vliegenthart R, *et al*. Aortic stiffness is associated with atherosclerosis of the coronary arteries in older adults: the Rotterdam Study. J Hypertens 2006; 24: 2371-6.

[74] Mitchell GF, Hwang SJ, Vasan RS, *et al*. Arterial stiffness and cardiovascular events: the Framingham Heart Study. Circulation 2010; 121: 505-11.

[75] Laurent S, Boutouyrie P, Asmar R, *et al*. Aortic stiffness is an independent predictor of all-cause and cardiovascular mortality in hypertensive patients. Hypertension 2001; 37: 1236-41.

[76] Cruickshank K, Riste L, Anderson SG, Wright JS, Dunn G, Gosling RG. Aortic pulse-wave velocity and its relationship to mortality in diabetes and glucose intolerance: an integrated index of vascular function? Circulation 2002; 106: 2085-90.

[77] Shoji T, Emoto M, Shinohara K, *et al*. Diabetes mellitus, aortic stiffness, and cardiovascular mortality in end-stage renal disease. J Am Soc Nephrol 2001; 12: 2117-24.

[78] Shokawa T, Imazu M, Yamamoto H, *et al*. Pulse wave velocity predicts cardiovascular mortality: findings from the Hawaii-Los Angeles-Hiroshima study. Circ J 2005; 69: 259-64.

[79] Sutton-Tyrrell K, Najjar SS, Boudreau RM, *et al*; Health ABC Study. Elevated aortic pulse wave velocity, a marker of arterial stiffness, predicts cardiovascular events in well-functioning older adults. Circulation 2005; 111: 3384-90.

[80] Zoungas S, Cameron JD, Kerr PG, *et al*. Association of carotid intima-medial thickness and indices of arterial stiffness with cardiovascular disease outcomes in CKD. Am J Kidney Dis 2007; 50: 622-30.

[81] Wang KL, Cheng HM, Sung SH, *et al*. Wave reflection and arterial stiffness in the prediction of 15-year all-cause and cardiovascular mortalities: a community-based study. Hypertension 2010; 55: 799-805.

[82] McDermott MM, Liu K, Criqui MH, *et al*. Ankle-brachial index and subclinical cardiac and carotid disease: the multi-ethnic study of atherosclerosis. Am J Epidemiol 2005; 162: 33-41.

[83] Hasimu B, Li J, Nakayama T, *et al*. Ankle brachial index as a marker of atherosclerosis in Chinese patients with high cardiovascular risk. Hypertens Res 2006; 29: 23-8.

[84] Menke A, Muntner P, Wildman RP, *et al*. Relation of borderline peripheral arterial disease to cardiovascular disease risk. Am J Cardiol 2006; 98: 1226-30.

[85] Matsushita K, Sang Y, Ballew SH, *et al*. Subclinical atherosclerosis measures for cardiovascular prediction in CKD. J Am Soc Nephrol 2015; 26: 439-47.

[86] Li X, Luo Y, Xu Y, *et al*. Relationship of ankle-brachial index with all-cause mortality and cardiovascular mortality after a 3-year follow-up: the China ankle-brxachial index cohort study. J Hum Hypertens 2010; 24: 111-6.

[87] Li J, Luo Y, Xu Y, *et al*. Risk factors of peripheral arterial disease and relationship between low ankle - brachial index and mortality from all-cause and cardiovascular disease in Chinese patients with type 2 diabetes. Circ J 2007; 71: 377-81.

[88] Ramos R, Quesada M, Solanas P, *et al*; REGICOR Investigators. Prevalence of symptomatic and asymptomatic peripheral arterial disease and the value of the ankle-brachial index to stratify cardiovascular risk. Eur J Vasc Endovasc Surg 2009; 38: 305-11.

[89] Poredos P, Jug B. The prevalence of peripheral arterial disease in high risk subjects and coronary or cerebrovascular patients. Angiology 2007; 58: 309-15.

[90] Gokce N, Keaney JF Jr, Hunter LM, *et al*. Predictive value of noninvasively determined endothelial dysfunction for long-term cardiovascular events in patients with peripheral vascular disease. J Am Coll Cardiol 2003; 41: 1769- 75.

[91] Frick M, Suessenbacher A, Alber HF, *et al*. Prognostic value of brachial artery endothelial function and wall thickness. J Am Coll Cardiol 2005; 46: 1006-10.

[92] Huang AL, Silver AE, Shvenke E, *et al*. Predictive value of reactive hyperemia for cardiovascular events in patients with peripheral arterial disease undergoing vascular surgery. Arterioscler Thromb Vasc Biol 2007; 27: 2113-9.

[93] Hu R, Wang WQ, Lau CP, *et al*. Gender differences on brachial flowmediated dilation and carotid intima-media thickness for prediction of spontaneous cardiovascular events. Clin Cardiol 2008; 31: 525-30.

[94] Suessenbacher A, Frick M, Alber HF, *et al*. Association of improvement of brachial artery flow-mediated vasodilation with cardiovascular events. Vasc Med 2006; 11: 239-44.

[95] Brevetti G, Silvestro A, Schiano V, *et al*. Endothelial dysfunction and cardiovascular risk prediction in peripheral arterial disease: additive value of flowmediated dilation to ankle-brachial pressure index. Circulation 2003; 108: 2093-8.

[96] Chan SY, Mancini GB, Kuramoto L, *et al*. The prognostic importance of endothelial dysfunction and carotid atheroma burden in patients with coronary artery disease. J Am Coll Cardiol 2003; 42: 1037-43.

[97] Fathi R, Haluska B, Isbel N, *et al*. The relative importance of vascularstructure and function in predicting cardiovascular events. J Am Coll Cardiol 2004; 43: 616-23.

[98] Modena MG, Bonetti L, Coppi F, *et al*. Prognostic role of reversible endothelial dysfunction in hypertensive postmenopausal women. J Am Coll Cardiol 2002; 40: 505-10.