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 undertreatment of these individuals. Risk estimates appear to be less accurate in diabetics, women, certain ethnicities (such as South Asians) or geographic areas, and different socioeconomic 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
(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 7 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 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.
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 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.
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,

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**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.  | CAC       | Asymptomatic subjects       | 5,878  | 5.8 years | CV events| 0.76/0.81                   |
| Erbel et al.     | CAC       | Asymptomatic subjects       | 4,129  | 5 years   | CV events| 0.68/0.75                   |
| Folsom et al.    | CAC       | Asymptomatic subjects       | 6,698  | 5.3 years | CV events| 0.77/0.81                   |
| Elias-Smale     | CAC       | Asymptomatic subjects       | 2,028  | 9.2 years | CV events| 0.72/0.76                   |
| Greenland et al. | 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.      | Geriatric subjects              | 141    | 2.5 years | CV events| PWV is a strong, independent predictor of CV death                        |
| Boutouyrie et al.  | 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.| Community-based adults          | 2,835  | 4.1 years | CV events| PWV is an independent predictor of coronary heart disease and stroke     |
| Mitchell et al.    | Community-dwelling sample       | 2,232  | 7.8       | CV events| PWV is an independent predictor of CV events                              |
| Laurent et al.     | 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. | Patients with Diabetes Mellitus | 394    | 10.7 years| CV events| The addition of PWV independently predicted all-cause and CV mortality   |
| Shoji et al.       | 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.     | Japanese-Americans subjects     | 492    | 10 years  | CV events| PWV is an independent predictor of CVD                                   |
| Sutton-Tyrrell et al. | 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.     | Patients with chronic kidney disease | 315 | 3.6 years | CV events| PWV was an independent predictor of CV events                             |
| Wang et al.        | 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.
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 local-ized 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 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.
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-

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          | Recent transient ischemic attack                | 12     | Atherosclerotic plaque inflammation | Combined FDG-PET and HRMRI can assess the degree of inflammation       |
|           | HRMRI               |                                                  |        |                           |                                                                         |
| 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.
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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