Atherosclerosis in the HIV and non-HIV setting: detecting and modifying cardiovascular risk
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Citation for published version (APA):

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Surrogate Markers for Atherosclerotic Disease

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Curr Opin Lipidol. 2005;16(4):434-41
Abstract

Purpose of review
Novel treatment modalities for cardiovascular prevention are emerging rapidly. Since it is virtually impossible to evaluate all these new compounds in long-term trials using clinical endpoints, there is an urgent need for validated surrogate markers of atherosclerosis in order to save both time and costs. Over the last decade, particularly the use of imaging markers has been widely introduced into drug development strategies. In the present review we will discuss the most commonly used techniques.

Recent findings
Whereas both testing of endothelial function assessed as flow mediated dilation and assessment of carotid intima–media thickness have been shown to predict future cardiovascular events, predominantly IMT has been successfully used as surrogate marker in intervention studies. More recently, standardization of intravascular ultrasound has also enabled reproducible assessment of coronary atheroma volume. Multi-slice computed tomography and electron beam computed tomography have proven useful in providing quantitative information on plaque burden and coronary calcium content, respectively. Although cardiovascular magnetic resonance (CMR) is continuously improving, additional technical improvements will be mandatory before this technique can be implemented in multicenter clinical studies.

Summary
The imaging modalities reviewed in this paper all provide specific information on either functionality of morphology of the vasculature. To date, the value of carotid IMT for cardiovascular risk prediction has been studied most extensively. Whereas assessment of plaque burden using IVUS appears to be the most direct way to quantify coronary changes, its predictive value for future cardiovascular events remains to be established. Awaiting further technical improvements, CMR is expected to provide the most valuable information for both quantitative and qualitative evaluation of atherosclerosis in the near future.
Introduction

Atherosclerosis is an inflammatory process that causes lesions in both large- and medium-sized arteries. The disease slowly progresses over many decades, causing clinical manifestations only at advanced stages of the atherosclerotic process. Due to this protracted time course, cardiovascular prevention trials using clinical endpoints usually require long-term follow-up and a large number of participants in order to be able to demonstrate clinical benefit of pharmaceutical interventions [1]. The corresponding studies are both expensive and time consuming [2]. One of the consequences is that innovative drugs may be withheld from patients for many years, awaiting final proof of efficacy [3]. To circumvent these issues, surrogate markers are increasingly being used in cardiovascular intervention studies [2]. This review addresses the available imaging modalities of both the arterial wall as well as the arterial lumen which are currently being used as surrogate markers.
Figure 1. Flow-Mediated Dilatation

Image frame of automated measurements of the brachial arterial lumen and the associated flow mediated dilatation curve (Brachial Analyzer, MIA vascular tools, Coralville USA). Y-axis: brachial lumen diameter (mm); X-axis: image frame numbers (obtained every third heart beat. Brachial FMD in this example is \((4.62-4.34)/4.34 \times 100 = 6.5\%\).

Figure 2. B-mode Intima-Media Thickness

High resolution 15MHz B-mode ultrasound image of the distal common carotid artery far wall in a healthy 23 year old volunteer. The vertical arrow indicates the carotid dilatation, just proximal of the carotid bulb. Intima-media thickness (IMT) is defined as the distance between the lumen-intima and the media-adventitia interfaces (upper and lower red lines). Measurements are done along a 10mm length of the wall. The average IMT of this particular wall was 0.049 (SD 0.008) mm.
Non-invasive and invasive imaging of atherosclerosis

Flow Mediated Dilatation

The crucial role of the vascular endothelium as first line defense mechanism against atherogenic insults has been generally acknowledged. All known cardiovascular risk factors, such as hypertension [4], smoking [5], hypercholesterolemia and diabetes mellitus [6] have been shown to contribute to onset of endothelial dysfunction. In line, endothelial dysfunction is one of the earliest stages of atherogenesis, preceding the occurrence of atherosclerotic lesion formation [7]. More recently, endothelial dysfunction has also been shown to have predictive value for cardiovascular events [8;9]. Besides invasive techniques to measure endothelial function using intra-arterial infusion of selective endothelial agonists, the introduction of flow mediated dilation to test endothelial function has paved the way for wider application [10;11]. The basic principle of this measurement pertains to the induction of increased blood flow in the brachial artery, following deflation of an occluding forearm cuff. The ensuing reactive hyperemia causes increased shear stress at the level of the endothelium of the brachial artery, which induces production of nitric oxide (NO) resulting in relaxation of vascular smooth muscle cells [12]. The ensuing diameter increase of the brachial artery can be measured using ultrasound diameter measurements. The advantages of this technique are its non-invasive and readily applicable nature. However, substantial variation in reproducibility has been described, due to both differences in technical protocols as well as the impact of physiological factors on FMD [10]. Careful standardization of the protocol, including the implementation of automated real-time vessel boundary detection, has contributed significantly to reduce the variability (Figure 1). Yet, FMD values in healthy middle-aged subjects may still vary extensively, ranging from 5\% to 21\% [13]. The large interindividual variation limits the use of FMD as an individual cardiovascular risk marker. In spite of these shortcomings, FMD has proven to be a valuable parameter to evaluate changes in endothelial function at a group level [14].

B-mode ultrasound carotid intima-media thickness

High-resolution B-mode ultrasonography of the carotid arterial far-wall enables visualization of the distance between the lumen-intima interface and media-adventitia interface, reflecting the carotid intima-media thickness (CIMT) (Figure 2). This non-invasive technique allows for real-time in vivo imaging of all stages of atherosclerosis, going from the normal arterial wall to complete arterial occlusion. Accordingly, arterial wall thickness can be measured as a continuous variable from childhood to old age, in patients as well as in healthy controls [15]. The great variability in measurement...
protocols which could affect clinical trial outcomes obviates the need for standardization of these protocols in order to permit reliable comparison of study results. Nevertheless, under standardized conditions, the technique of CIMT offers good reproducibility. This makes it suitable to apply in relatively small, comparative studies investigating vascular pathophysiology, as well as in large, multicenter clinical trials. Three large observational studies utilizing IMT as a surrogate marker for CVD are the Atherosclerosis Risk in Communities (ARIC) Study [16], the Cardiovascular Health Study (CHS) [17], and the Rotterdam Study [18;19]. In the ARIC study (n=12841), IMT was able to assess all stages of atherosclerosis and proved an independent predictor of coronary artery disease. These findings could be confirmed in the subsequent CHS (n= 5858) and the Rotterdam Study (n=8000). In addition, statin intervention trials such as ASAP [20], REGRESS [21;22] and ARBITER-I [23], have underscored the value of CIMT as an efficient parameter to assess efficacy of lipid treatment. Both ASAP and ARBITER-I showed that aggressive lipid lowering with 80 mg of atorvastatin was associated with a decrease in carotid IMT as opposed to no change or progression in the comparative low-dose statin arms. Various studies have shown the strong correlation between IMT with cardiovascular risk factors such as LDL-C [24-27], HDL-C [28;29] and blood pressure [30]. Collectively, carotid IMT has proven to be a well standardized and validated surrogate marker for CVD and is particularly closely correlated with CAD and incidence of cardiovascular events such as myocardial infarction and stroke [17;18;31-33].

**Quantitative coronary angiography**

In patients with coronary atherosclerosis, angiographically determined progression of the disease is one of the major factors determining clinical prognosis[34-36]. This makes serial angiography a ‘validated’ technique as surrogate marker for cardiovascular risk, which has been used successfully used in many multicenter trials [21;36]. Coronary atherosclerosis is a complex process that is not limited to focal areas of the coronary artery tree [37]. Therefore, to assess the effect of an intervention on progression or regression of coronary atherosclerosis, both focal (minimal lumen/obstruction diameter in mm) and diffuse (mean lumen diameter) changes should be measured [36]. Visual interpretation of coronary angiograms has its limitations because assessment of stenosis severity is associated with: a) a large intra- and inter-observer grading variability (8-37%) b) only relative stenosis measurements are provided and c) severity of diffuse atherosclerosis is difficult to estimate. Therefore, Quantitative Coronary Angiography (QCA) providing absolute diameters in mm is now the established standard [38] (Figure 3). Of note, early stages of coronary atherosclerosis are associated with remodeling of the coronary artery [39], resulting in preservation of the lumen cross sectional area. Consequently, early stage coronary atherosclerosis is angiographically undetectable [40]. This often causes underestimation of the severity and extent of coronary atherosclerosis when compared to
post-mortem pathological studies [41]. Despite the limitations, standardized QCA has proven itself as a worthwhile technique, carrying important prognostic information.

Figure 3. Quantitative Coronary Angiography

An example of a coronary bifurcation analysis with QVA-CMS® V6.0

The bifurcation analysis output shows the arterial contours of the proximal and two distal artery segments of the bifurcation as one. For each of the three artery segments (each including its central part of the bifurcation) separate reference contours and reference diameter functions (graphs) are created. Some major advantages of this technique are: 1) A proper determination of the reference diameter function for each individual artery segment in combination with its central part of the bifurcation, resulting in the correct estimation of the reference diameter and percentage diameter stenosis. 2) A proper determination of the obstruction length (see Distal1) and better positioning of the obstruction marker when the lesion is overlapping with or close to the central part of the bifurcation. This is due to the presence of the elongated arterial- and reference contours.

**CT coronary imaging**

Non-invasive visualization of the coronary arteries puts any diagnostic technique to the test, because the coronaries are small, tortuous, and respiratory motion and the continuous cardiac motion distorts the image. Thus, high temporal resolution is required to “freeze” the heart to produce a sharp image. Despite these hurdles CT (Computed Tomography)-scanners are able to visualize the coronary arteries.
**Electron Beam Computed Tomography**

Electron-beam Computed Tomography (EBCT) can accurately and reproducibly quantify the presence of coronary calcium in the coronary tree. Whereas the ‘coronary calcification score’ correlates well with total atherosclerotic plaque burden, it only reflects the presence of advanced lesions. Several studies have shown that coronary artery calcium (CAC) is a marker of increased risk for adverse coronary events[42], independently from other CV risk factors [43;44]. To date, only few studies are available, reporting decreased progression of CAC during active treatment [45].

**Multidetector CT**

Multidetector CT coronary imaging represents cross-sectional imaging of the coronary lumen and wall which allows quantification of coronary plaques as well as the artery wall[46;47]. In addition, valuable information with respect to the composition of the plaque can be obtained based on the differences of the CT-density values [48;49] (Figure 4). Based on the presence or distribution of plaques (1,2,3 vessel disease) and stenosis severity (> 50% diameter stenosis) one can establish the plaque burden of the coronary tree [50]. However, it remains to be established whether the CT-assessment of the coronary plaque burden is accurate in stratifying cardiac risk. In addition, further studies are needed to further explore the ability of MD-CT to assess disease progression, stabilization or even regression following specific therapy.

Figure 4. MSCT Coronary Plaque Imaging

![Image of plaque imaging with HU values](image)

The density values expressed as Hounsfield Units (HU) are shown for atheroma, calcific plaque, fibrotic plaque and a plaque complicated by thrombus formation.

Shown are the axial images and for each lesion a cross-sectional image (inlays).
Cardiovascular magnetic resonance

Cardiovascular magnetic resonance (CMR) is a relatively new technique in the assessment of atherosclerosis. New sequences allow the vessel wall to be imaged such that either its area (2D technique) or volume (3D technique) can be measured and followed over time (Figure 5). The 3D technique has the merit of being less dependent on slice positioning in longitudinal studies, and is a more sensitive test, because the area of many slices is added in order to generate a vessel wall volume [51]. Most work has been performed in the carotid artery because it can be imaged in high resolution as it is near the surface. The 3D technique samples about 3cm either side of the carotid bifurcation and has an interstudy reproducibility of 4.4% [52]. The vessel wall volume is the difference between the external wall volume and the luminal volume, and semi-automated software is now available to make these measurements reliably and quickly (Atheroma-Tools, CVIS, London, UK).

A number of studies in humans have assessed CMR in the longitudinal measurement of atheroma. Mohiaddin showed atheroma progression in untreated aortic plaque area over 2 years [53]. Corti showed that simvastatin caused regression of aortic and carotid artery atheroma area over 12 [54], and 24 months [55]. Lima showed that simvastatin could induce regression of aortic plaque volume after only 6 months of treatment [56]. Yonemura showed regression of aortic plaque area after 12 months of simvastatin treatment [57]. In conclusion, atheroma CMR is beginning to be used for longitudinal follow-up of patients to investigate atheroma progression and regression. The good reproducibility has allowed current trials to be conducted in small samples sizes (~40 patients) over reasonable time periods (12 months) to show statistically significant effects.

Intravascular Ultrasound

Intravascular ultrasound (IVUS) is performed during cardiac catheterization using small, intracoronary catheters. The strong ultrasound signal reflected from the intima and external elastic membrane (EEM) allows real-time intraluminal imaging of the vessel wall and measurement of the atheroma (intima-media area) [58,59]. Initial quantitative IVUS studies examined the progression of plaque area at diseased lesion sites [60]. However, the reproducibility of this analysis approach was limited by the difficulties to exactly match individual sites. Accordingly volumetric analysis approaches integrate consecutive plaque area measurements at 0.5-1mm intervals along long vessel segments (Figure 6). Because the segment rather than individual sites are matched at baseline and follow-up, assessment of small percent changes in atheroma volume is possible with considerable statistical power [61-66]. In a recent randomized trial, intraobserver variability was analyzed in 1177 images from 18 patients [64]. The mean [SD] differences were negligible for both EEM (~0.16 [0.68] mm²) and lumen areas (~0.02 [0.75] mm²).
3D reconstruction of CMR of a carotid artery on the left for a normal subject, and on the right a patient with carotid artery atherosclerosis. The inner and outer borders of the carotid artery have been analysed semi-automatically with specialized software (Atheroma-Tools, www.CMRtools.com) and the total wall volume has been calculated from the difference. This is a sensitive measure of atherosclerosis burden which is highly reproducible allowing longitudinal changes in atheroma to be followed, especially with drug interventions, in small sample sizes. The total wall volume for the normal subject (left) is considerably lower than that of the patient with carotid atherosclerosis (right) and the arrows indicate a particular area of wall thickening at the carotid bulb.
Linear regression analysis showed close correlations between the original and re-analysis ($r = 0.99$ and $0.98$ for EEM and lumen areas). Interobserver variability was evaluated in 2151 images from 30 patients. The mean [SD] differences were negligible for both EEM ($-0.07 \pm 0.93$ mm$^2$) and lumen areas ($-0.07 \pm 0.93$ mm$^2$). Regression analysis showed close correlations between the original and re-analysis ($r = 0.99$ and $0.98$ for EEM and lumen areas).

Results from randomized, serial IVUS studies collectively demonstrate either arrest of progression or actual regression during intensive lipid-modifying therapies [61-66]. Sub-studies have also demonstrated the independent role of the inflammatory marker CRP [67]. The comparison of these IVUS trials with outcome studies using similar pharmacological interventions provide indirect data correlating plaque burden to clinical outcomes [64;67-69]. Collectively, these studies underscore the validity of volumetric plaque burden as endpoint for the assessment of atherosclerosis progression/regression.

Figure 6. Intravascular Ultrasound

For volumetric analysis of plaque burden, a segment of interest is selected between two characteristic fiduciary points. Evenly spaced frames are selected at 0.5-1.0 mm intervals. For each of the selected frames, the lumen and EEM cross sectional areas are measured. The Simpson equation is applied to calculate plaque volume by multiplying plaque area and distance between adjacent images.

Conclusion

At present, the use of IMT as surrogate marker has several advantages compared to other imaging techniques: it is easy to use, non-invasive, has a good reproducibility and has the capacity to identify atherosclerosis progression and regression. At the same time, the validity of the method is supported by a large number of clinical trials. Whereas FMD also has predictive value for future CVD, this method is of limited use due to a large interindividual variation. Coronary angiography has traditionally been the ‘gold-standard’ imaging modality to assess coronary atherosclerosis progression and regression. However, this technique identifies only the arterial lumen and fails to identify early stages of the disease. Electron beam CT reliably quantifies calcium content in the coronary arteries. However, EBCT solely identifies advanced plaques. Cardiovascular MR has rapidly evolved as a means to assess carotid and coronary plaque area and volume. Further data are awaited to evaluate its reliability as a surrogate marker for CAD. IVUS permits assessment of plaque burden in vivo. Whereas changes in plaque burden as measured by IVUS may well be the most direct way to evaluate the effect of an anti-atherosclerotic agent, its predictive value for future CV events remains to be established. In summary, ultrasound IMT of the carotid arteries is considered the predominant non-invasive surrogate marker for CVD, albeit in a non-coronary vessel, whereas IVUS is the preferred tool for invasive assessment of atherosclerotic disease where it is most relevant, i.e. in the coronary arteries.
References


