The time has come for clinical cardiovascular trials with plaque characterization as an endpoint

Zahi A. Fayad1,2, Venkatesh Mani1,2, and Valentin Fuster2,3*

1Translational and Molecular Imaging Institute, Mount Sinai School of Medicine, New York, NY, USA; 2Zena and Michael A. Weiner Cardiovascular Institute and Marie-Josée and Henry R. Kravis Cardiovascular Health Center, Mount Sinai Medical Center, New York, NY, USA; and 3Centro Nacional de Investigaciones Cardiovasculares (CNIC), Madrid, Spain

Online publish-ahead-of-print 28 August 2011

This editorial refers to ‘Determinants of magnetic resonance imaging detected carotid plaque components: the Rotterdam Study’1, by Q.J.A. van den Bouwhuijsen et al., on page 221

Atherosclerosis and its clinical sequelae are responsible for coronary artery disease, cerebrovascular complications, and peripheral arterial disease, a leading cause of mortality and morbidity. At the heart of the atherosclerotic disease cascade is the atherosclerotic plaque. For many years, pathology and post-mortem studies were the only method to evaluate the manifestation of atherosclerosis. The vulnerability of atherosclerotic plaques to rupture and cause cardiovascular and cerebrovascular events has long been associated with the presence of a thin fibrous cap with a large lipid core, endothelial denudation with platelet aggregation, presence of active inflammation, calcification, intraplaque haemorrhage, endothelial dysfunction, outward remodeling, and the presence of fissures. It has been well established that conventional cardiovascular disease risk factors and the use of the Framingham risk score do not fully explain the level of coronary or cerebrovascular events in asymptomatic individuals. Therefore, current research has focused on improving risk stratification using new methodologies to identify subjects at higher risk that can benefit from aggressive treatment.

Over the last decade or two, atherosclerotic plaque imaging using magnetic resonance (MR) has made significant strides and is quickly becoming the preferred methodology for non-invasive evaluation of atherosclerotic plaques in vivo. It allows classification of carotid plaques into high-risk and low-risk lesion types (I–VIII). MR plaque imaging typically involves acquisition of several contrasts, i.e. black blood proton density-weighted, T1-weighted, and T2-weighted for vessel wall evaluation, along with an angiography sequence for accurate lumen delineation. Based on signal intensities on the various imaging contrasts acquired, plaque components are characterized. A contrast-enhanced T1-weighted scan is often used to better delineate the fibrous cap and define a lipid-rich necrotic core (LRNC). Calcification is typically hypointense on all acquisitions, fresh hemorrhage is bright on T1, whereas lipid pools are also bright on T1 and proton density images, but lose signal on T2 sequences, and haemorrhage-related methaemoglobin remains bright on T2 images.

The Multi-Ethnic Study of Atherosclerosis (MESA) was the first epidemiology study that used MR imaging (Figure 1) to evaluate relationships between imaging and cardiovascular events. In a substudy of MESA involving carotid MRI in individuals with the highest carotid intima media thickness (IMT), total cholesterol was associated with the presence of LRNCs. Other studies in literature, such as the atherosclerosis risk in communities (ARIC) carotid MRI study, have also observed a strong correlation between carotid wall thickness and the presence of plaque features such as LRNCs and intraplaque haemorrhage.

van Bouwhuijsen et al. have now examined the determinants of MRI-detected components of plaque (Figure 1) as part of the Rotterdam Study in a large cohort of > 1000 patients. They investigate associations between cardiovascular risk factors and atherosclerotic lesion composition determined by MRI in asymptomatic individuals with ultrasound-derived carotid wall thickness > 2.5mm. In agreement with the MESA study, their results indicate that individuals with hypercholesterolaemia were more likely to exhibit LRNCs. They also found that patients with hypertension were more likely to exhibit calcification and intraplaque haemorrhage; and smoking was correlated with intraplaque haemorrhage. Interestingly, and contradicting previous studies, they found that diabetes was not associated with high-risk lesion types based on composition. Gender was also an important determinant of plaque size as well as prevalence of intraplaque haemorrhage. Limitations of this study include the fact that the methodologies used for plaque classification were not standard and hence only partially validated previously. Additionally, reliability of detection of LRNCs was limited as no contrast-enhanced imaging was used. Furthermore, only the
prevalence of high-risk plaque features was examined, and no quantification was performed.

As plaque imaging gains popularity and clinical trials that use imaging as an endpoint become more frequent, the need to select individuals with certain plaque characteristics as study subjects will exist. This study provides valuable data with regard to the traditional risk factors that determine plaque features that may be the target for intervention in such future clinical trials. Results of this study will help screen patients as candidates for early therapies and clinical trials that use imaging as an endpoint.

Funding

Supported by the National Heart, Lung, and Blood Institute at the National Institutes of Health R01 HL071021 and R01 HL078667 (to Z.A.F.).

Conflict of interest: none declared.

References