Non-Invasive Imaging of Atherosclerosis Regression With Magnetic Resonance to Guide Drug Development

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Abstract

Slowing of progression and inducing the regression of atherosclerosis with medical therapy have been shown to be associated with an extensive reduction in risk of cardiovascular events. This proof of concept was obtained with invasive angiographic studies but these are, for obvious reasons, impractical for sequential investigations. Non-invasive imaging has henceforth replaced the more cumbersome invasive studies and has proven extremely valuable in numerous occasions. Because of excellent reproducibility and no radiation exposure, magnetic resonance imaging (MRI) has become the non-invasive method of choice to assess the efficacy of anti-atherosclerotic drugs. The very high accuracy of this technology is particularly helpful in rare diseases where the small number of affected patients makes the conduct of outcome-trials in large cohorts impractical. With MRI it is possible to assess the extent, as well as the composition, of atherosclerotic plaques and this further enhances the utility of this technology.
Introduction

Drug discovery and development follow a complex and long pathway that often does not lead to a commercially viable product. As the cost of drug development burgeoned to prohibitive levels over the past few decades, investigators and industry have looked for ways to curb expenses and increase efficiency minimizing possible failures. The development of new drugs to treat atherosclerosis is often met with the requirement to conduct lengthy outcome trials at extraordinary costs. To limit the possibility of failing to attain the desired outcome after having conducted a phase-3 trial, investigators have utilized surrogate targets that provide information on the burden and composition of atherosclerotic plaques.\textsuperscript{1,2,3} Particularly challenging is the development of drugs for rare diseases, where conducting randomized outcome trials is hampered by the limited number of patients affected by the condition under study. In this light, atherosclerosis imaging has provided intermediate goals to test effectiveness of novel treatments.\textsuperscript{4,5,6} There are indisputable advantages in using imaging endpoints. For example, while in mortality and morbidity trials the endpoint is only provided by patients who experience an event, in trials based on imaging biomarkers the endpoint is provided by every patient. This increases the statistical power of the study, thus leading to a reduction in the number of patients compared to event driven trials (tens or hundreds rather than thousands of subjects) and shorter follow-ups (6-24 months rather than 4-6 years). Given its potential impact on drug development, atherosclerosis imaging has been the focus of intense debate and growing interest among scientists, industry and regulators alike. In this paper we review the state of the art of magnetic resonance (MR) for vascular imaging, with a specific focus on its
implementation in the process of drug development. Magnetic resonance imaging can provide information on the location, extent and composition of atheromatous plaques in peripheral arterial beds and has been used in numerous trials to study regression of atherosclerosis. However, to date MRI has demonstrated no utility to image coronary artery atherosclerotic plaques.

Imaging biomarkers and their utility
Atherosclerosis is mostly a silent disease and autopsy studies revealed that it is already present in youth. Because of its silent development its first manifestation is often a sudden and unheralded event. This induced scientists and physicians to develop a number of algorithms to estimate risk of events and stimulated the development of a large array of biomarkers and imaging modalities to assess the presence of atherosclerosis and its progression. The earliest attempts at measuring atherosclerosis progression were accomplished with invasive coronary angiography. Several studies demonstrated a powerful reduction in event rates with even minimal regression of luminal narrowing with various interventions. Non-invasive imaging modalities were then tested to measure change in atherosclerotic plaque burden or composition and became rapidly popular as a means to test drug efficacy. Like any other biomarker, an imaging marker needs to meet methodological and regulatory requirements to provide acceptable outcome parameters.

Several approaches to biomarker validation have being taken. The NIH Definition Working Group defines a ‘biomarker’ as follows: 1. A biomarker is a characteristic that is objectively
measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacological responses to a therapeutic intervention. Boissel and co-workers proposed a framework to describe the scientific validity of laboratory parameters for biological outcomes. They posed three stipulations. First [availability and convenience], “although the surrogate endpoint should be easier to assess than the corresponding clinical endpoint, the most important advantageous characteristic of the biomarker is its potential to detect the disease process in its earlier stages, resulting in a higher frequency of detection of the disease than the corresponding clinical endpoint”. Consequently, validated biomarkers provide early and specific prediction of risk that allow implementation of preventive strategies. For an imaging biomarker to provide relevant data, availability of the imaging device in close proximity to study subjects is essential. Second, there should be a causal relationship between surrogate and clinical endpoint, both quantitatively and qualitatively, through epidemiological studies. Third, it should be possible to estimate the clinical benefit derived from a reduction in the incidence of the surrogate endpoint. A surrogate outcome must meet certain statistical criteria, such that it would allow mathematical modeling of a disease process and its consequences. Finally, to become an accepted outcome measure to evaluate efficacy of pharmaceutical products in clinical trials, regulatory acceptability must be met.
Agencies’ Acceptance of Markers of Disease

Acceptance of surrogate markers (whether “biomarkers” or others) has long been hotly debated and opinions have swayed both in favor and against (some examples are change in CD4 cell count in HIV infected patients, change in PSA levels in prostate cancer and blood pressure measurements in cardiovascular health). In many cases there has been deep disagreement regarding the relevance of a surrogate endpoint. Progression free survival in oncology is hotly debated and it is not clear if the answer is a simple dichotomous “yes or no” but, rather, it might be cancer-specific. It is likely that surrogacy might also be drug-specific and the mechanism of action of one therapy to treat a particular disease might allow one marker as a reliable surrogate for drug alone and not another one intended for the same disease state. Therefore, regulators have been cautious about declaring any particular marker as an accepted surrogate. There are several examples where a compromise had to be reached. In terms of safety, it is often accepted to study “only” a few thousand patients in clinical trials, even though we know that databases of this size are unlikely to identify adverse reactions (possibly severe reactions) that occur in 1 in 1000 or more patients. Similarly, in terms of efficacy, it is often accepted to “only” study treatments for up to 1 – 2 years, even though they might represent life-long treatments. Clearly, these are examples of regulators being pragmatic and recognizing that the value of making new therapies available sooner, outweighs the risk involved. Other clear examples of pragmatism are in the orphan drug space where reality often dictates the need for flexibility. Such flexibility may relate to the size of the clinical database presented for review (number of patients, duration of follow-up, number of studies, etc.) but also on choice
of endpoints. In terms of size of database, for new products entering Phase III trials from 1
January 2000, an average of 731 patients were enrolled in orphan drug trials versus 3,540 in
non-orphan drug trials.¹⁶

Clinical relevance of endpoints is important but so is the ability to study those endpoints in
small clinical development programmes. The CHMP (Committee on Medical Products for
Human Use) Guideline on Clinical Trials in Small Populations (Section 4)¹⁷ acknowledges that:
“Time to disease progression is an endpoint of intermediate level and it requires a measure of
disease severity or of disease progression. Ideally, this should be validated as a tool for use in
clinical trials, but it is recognised that there might be too few patients to use some for validating
endpoints and others for testing treatments. ... It is preferable, to be able to identify a causal
relationship between treatment and a particular (beneficial) outcome.” Hence the
acknowledgement that there is an “ideal” and “preferable” way to proceed, but it may not be
always possible.

Three questions should be considered; (1) can a study with a “highly preferred” endpoint be
conducted? (“highly preferred” might mean preferred by the regulators, and/or an obvious
clinical endpoint); (2) is such an endpoint absolutely necessary in order to determine the clinical
value of a therapy? and (3) is it actually desirable to use the “highly preferred” endpoint, or
would a more efficient trial better serve the public health interest? To this end, intravascular
ultrasound (IVUS) and MRI studies offer the opportunity to pursue more efficient endpoints (i.e.
smaller trial sizes, with shorter duration and good level of assurance over the results) than
more traditional “established clinical endpoints”. At the same time they may provide enough
information to inform a decision to pursue larger clinical trials or whether such trials should be stopped.\textsuperscript{18}

\textbf{Atherosclerosis Imaging for Plaque Regression: a Historical Perspective}

Invasive and non-invasive imaging have been used extensively to study progression of atherosclerosis. A few pivotal principles govern sequential imaging of atherosclerosis to assess its temporal changes.\textsuperscript{1} First, the test-to-test variability should be smaller than the change detected with sequential imaging. Second, the measured change should be clinically relevant and associated with meaningful outcomes. Atherosclerosis imaging began with quantitative invasive coronary angiography (QCA).\textsuperscript{7-10} Although QCA is not an atherosclerosis imaging technique per se, as it assesses the degree of luminal stenosis but not plaque volume and composition, it demonstrated that even minimal regression or slowing of progression of intraluminal coronary artery disease are associated with a large reduction in event rates.\textsuperscript{11} Despite its success, QCA is limited by its invasive nature, the need to use iodinated contrast media and the exposure of patients to ionizing radiation and is therefore not fit for population studies. This stimulated and facilitated the development of non-invasive imaging modalities to detect atherosclerosis and study its progression. Pignoli et al\textsuperscript{19} were the first to demonstrate that the thickness of the arterial wall comprising the intima and media layers (IMT) of the femoral arteries was closely associated with atherosclerosis of the aorta. Given the greater ease and convenience of measurement, carotid IMT (cIMT) quickly replaced measurement of femoral IMT (Figure 1). Several epidemiological studies later showed that cIMT is an independent predictor of stroke and cardiovascular events in the general population.\textsuperscript{20} As proof
of concept, over the last two decades, many investigators have employed cIMT as primary endpoint in clinical trials designed to identify populations at risk and assess the effectiveness of anti-atherosclerotic drugs.21

Although successfully employed to study the effect of cardiovascular drugs in large population trials,22,23,24 in several cases randomized clinical trials using the same drugs that regressed cIMT gave inconclusive or negative results. cIMT has several distinct disadvantages when used to evaluate the efficacy of drugs on regression and progression of atherosclerotic plaques. The main limitations of cIMT are the high degree of technical expertise required to perform accurate measurements and the high test-to-test measurement variability. As a consequence, large numbers of patients are typically needed to demonstrate treatment efficacy due to the small arterial wall changes. In addition, cIMT is measured in two-dimensional longitudinal images, while atherosclerosis is a three-dimensional, eccentric and irregular disease. Finally, the precision of cIMT measurement may be affected by vessel wall calcification (that causes “shadowing”) and the technique does not provide information on plaque composition or risk of plaque rupture. It is therefore virtually impossible to determine whether a change in cIMT actually reflects a change in atherosclerosis plaque burden. Modern ultrasound techniques measuring plaque volume rather than a mere bi-dimensional IMT have improved the reproducibility of carotid atherosclerosis imaging and given a better appreciation of plaque volume changes,25,26 but have not been extensively employed for sequential imaging in randomized trials.27,28
The high reproducibility of plaque imaging demonstrated by magnetic resonance imaging (MRI)\textsuperscript{29,30} rendered this technique the most advanced and reliable non-invasive tool to conduct atherosclerosis imaging. Its low scan-to-scan variability allows investigators to utilize a smaller number of patients to demonstrate the efficacy of interventions on plaque size and composition.\textsuperscript{31} These characteristics of high-resolution MRI imaging are particularly desirable when research is focused on mechanistic plaque studies of innovative compounds in patients with rare diseases who are difficult to discover and enroll in clinical trials.

As indicated in the previous paragraphs, the value of surrogate biomarkers is embedded in their ability to identify a disease state and its change prior to the outbreak of symptomatic disease. These properties are crucial when studying rare diseases, as the population size is limited and may be geographically widespread. According to the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) group, the average prevalence threshold for a rare disease ranges from 5 to 76 cases/100,000 people, with a global average of 40 cases/100,000 people.\textsuperscript{32} With such a small prevalence, the inclusion of thousands (or even only hundreds) of patients in a study becomes virtually impossible, thus making essential the identification of sensitive imaging biomarkers that allow the designing of studies with sufficient statistical power despite the availability of only a few dozens of patients.

**Magnetic Resonance Imaging in Clinical Trials**

Magnetic Resonance Imaging (MRI) has become one of the leading non-invasive in-vivo imaging modalities for quantification and characterization of atherosclerosis. Like ultrasound, MRI does
not expose patients to ionizing radiation and can be repeated as often as required: it enables measurement of plaque burden (area and volume), luminal narrowing and plaque characteristics.\textsuperscript{33,34} Additionally, with MRI it is possible to assess the thickness of the fibrous-cap covering a plaque\textsuperscript{35} and the extent of the lipid-rich necrotic core (LRNC),\textsuperscript{36} (\textbf{Figure 2}) as well as adventitial neovascularization\textsuperscript{37} and intra-plaque haemorrhage.\textsuperscript{30} Image acquisition in MRI requires a high degree of expertise although most measurements are fairly operator independent. Additionally, MRI imaging provides multi-planar 3D data with sub-millimeter spatial resolution.\textsuperscript{30} Most of the MR vascular imaging work has been performed on 1.5T (Tesla) MR scanners. However, more modern imaging at 3T provides a higher signal-to-noise ratio with better resolution compared to 1.5T. The imaging protocols have matured and sequences have been optimized enough at 3T that it is recommendable that future clinical studies be conducted with 3T scanners.

The superior reproducibility of MR resulted in the ability to conduct limited size studies to demonstrate a proof of concept. In fact, several studies have shown that significant changes in carotid atherosclerosis (area or volume) can be detected with moderate sample sizes (less than 40 patients per arm) within the first months or year of intervention (\textbf{Table 1 and Figure 3}). Lee et al,\textsuperscript{38} observed plaque regression within 3 months of starting statins in 24 treatment naïve patients with coronary artery disease. Saam et al\textsuperscript{39} calculated that a study with only 14 subjects per arm is sufficient to assess a 5% treatment effect if the plaque volume is used as an endpoint. In a case-control study, eight cases and eight control subjects were sufficient to demonstrate that prolonged intensive lipid-lowering therapy is associated with a decrease in
lipid-rich necrotic core. The power of MRI in showing reduction in atherosclerosis burden in rare diseases was clearly demonstrated in two trials employing a new HDL-mimetic drug containing recombinant human apoA1 (CER-001). In the MODE trial after 12 biweekly infusions of CER-001 in 23 patients affected by homozygous familial hypercholesterolemia, MR imaging showed a significant reduction in carotid plaque area (P=0.008). Similar results were obtained in the SAMBA trial; in this study of 7 patients affected by familial primary hypoalphalipoproteinemia, the mean carotid plaque area was significantly reduced after 9 biweekly infusions of CER-001 (25 mm² to 22.8 mm²; P=0.043). Numerous other trials have been conducted to evaluate the efficacy of lipid-lowering therapies and their ability to induce atherosclerotic plaque regression as summarized in Table 1. In the first ever trial, Corti et al administered simvastatin to 18 asymptomatic hypercholesterolemic patients with documented atherosclerotic plaques in the carotid arteries and/or the aorta. The statin treatment induced an 8% regression of the aortic plaque area at 12 months (p<0.001) and the carotid plaque area regressed by 15% (p<0.001). Corresponding changes were also seen in vessel wall thickness. Subsequent studies assessed the comparative ability of different doses of statins to achieve plaque regression and overall showed that the more aggressive the treatment the greater the benefit as far as reduction in plaque area or volume. (Table 1)

Atherosclerotic Plaque Imaging With Magnetic Resonance

Several observational and case-control studies have reported the ability of MRI to identify components of the atherosclerotic plaque that might be of interest as goals of therapy. It is
however important to note that none of these parameters has been linked with an outcome of interest to date. The excellent soft tissue contrast generated from differences in relaxation times (T1 and T2) and proton density enables the use of MR imaging to obtain detailed information about atherosclerotic plaque composition besides accurate plaque area and volume measurements. Histopathological studies have demonstrated that ruptured plaques causing acute vascular events are inflamed, contain microcalcifications, a large necrotic core, a thin fibrous cap covering the core, intraplaque neo-angiogenesis and hemorrhage, and they demonstrate outward (positive) remodeling. Each of these characteristics represents a potential imaging target for identifying high-risk plaques with an increased risk of rupture. Many of these plaque characteristics can be accurately identified on MR imaging of large vessels.

**Necrotic Core.** The lipid rich necrotic core can be identified in the carotid arteries and aorta using multi-contrast weighted plus post-contrast T1-weighted imaging. In combination these techniques can be used to identify and quantify the lipid rich necrotic core burden (LRNC) a potentially more sensitive biomarker with which to assess the therapeutic effects of lipid lowering therapies. In the ORION trial\(^2\) the investigators assessed the effect of rosuvastatin on carotid plaque volume and composition. Forty-three patients with hypercholesterolemia and carotid plaques were randomized to low (5mg daily) or high (40mg daily) rosuvastatin doses. Of interest, at 24 months the plaque volume remained unchanged but there was a reduction in the percentage LRNC.
*Positive Remodeling.* The same *black-blood* imaging technique used to measure plaque burden can be used to identify positive remodeling. The presence of positive remodeling of the aorta and carotids on MR imaging has been shown to identify patients with an increased risk of future cardiovascular events.43

*Neovascularization, Plaque Hemorrhage & Luminal Thrombus.* Vasa-vasorum proliferate and penetrate from the adventitia toward the subintimal space in growing atherosclerotic plaques. Since these vessels are particularly fragile they may cause intralabelional hemorrhage that promotes plaque expansion.44 Dynamic contrast-enhanced MR imaging allows to indirectly estimate the extent of vasa-vasorum proliferation via the calculation of a transfer constant: *K-trans*, i.e the transit of contrast from the adventitia through the vessel wall.45 Using this technique, Dong et al46 were able to demonstrate that intensive lipid lowering therapy for one year induced a 21% reduction in *K-trans*, suggesting an inhibitory effect on vasa-vasorum.

Methemoglobin is an intermediate breakdown product of hemoglobin formed 12-72 hours following hemorrhage. It is therefore a key component of acute thrombus and can be detected as regions of high signal on non-contrast T1-weighted echo gradient sequences. This has been used to detect both plaque rupture and intra-plaque hemorrhage in the carotid arteries. In particular, high signal can be observed in the culprit plaques of patients who have suffered a recent stroke.47,48 In a recent study the presence of such high-intensity
carotid plaque in stable coronary artery disease patients predicted future cardiovascular events, outperforming carotid intimal medial thickness and traditional cardiovascular risk factors.49

_Late gadolinium enhancement_ detects regions of extracellular expansion within carotid plaques corresponding to areas of inflammation and angiogenesis on histology,30 and localizing to the culprit lesions of patients who suffered a stroke. Late gadolinium enhancement also allows assessment of the thickness of the fibrous cap in a carotid atherosclerotic plaque31 as well as identification of carotid plaque rupture or ulceration that may or may not be clinically apparent.32,33

Alternative MRI techniques have also been explored as efficacy end-points in clinical trials. Ultra-small particles of iron oxide (USPIO) have superparamagnetic properties on T2* weighted sequences. They have been used to measure vascular inflammation, since these particles are removed from the circulation by the reticuloendothelial system and accumulate in macrophages present in atherosclerotic plaques. In the Atheroma study50 the investigators randomized 47 patients with carotid stenosis >40% and high USPIO uptake on baseline scans, to either 10mg or 80mg of Atorvastatin daily for 12 weeks. A significant decrease in the carotid plaque USPIO uptake was observed in the high-dose cohort but not the low-dose group.
Taken together, these data show that MRI allows an accurate assessment of the effects of treatment on atherosclerotic plaque burden and composition with very small sample sizes and during short follow-up times. These characteristics make MRI a very efficient tool for a variety of clinical trials but especially those involving patients affected by rare diseases for which large sample sizes are unavailable. The ability of MRI to detect changes in atherosclerosis burden in rare diseases will be tested again in the recently announced TANGO trial (https://clinicaltrials.gov/ct2/show/NCT02697136?term=TANGO&rank=6). In this phase III multi-center trial, 30 patients with familial primary hypoalphalipoproteinemia on optimal lipid lowering medical therapy, will be randomized to treatment with an HDL mimetic compound or placebo. The primary end-point of the trial will be change in carotid mean plaque area measured by 3T MRI after 24 weeks of treatment. Given the small number of individuals recruitable with such a rare disease and the difficulty to assess efficacy, MR appears to be the perfect tool to provide the answer to this difficult question.

In summary, in a substantial and growing number of cases the scientific, clinical and pharmaceutical communities have embraced non-invasive cardiovascular imaging to evaluate changes in human atherosclerosis as a desirable method to assess therapeutic efficacy of novel and innovative drugs. Development of pharmaceutical agents designed to slow or prevent atherosclerotic disease and improve cardiovascular health can benefit from these imaging markers. The available evidence shows that MRI allows an accurate assessment of the effects of treatment on atherosclerotic plaque burden and composition with very small sample sizes and
short follow-up times. Like cIMT and other imaging modalities, however, to date there have been no reports of prospective clinical studies linking MRI-measured atherosclerosis with incident clinical events, and these data will need to be actively collected in future trials.
Table 1. Effect of lipid modifying drugs on carotid atherosclerosis assessed by magnetic resonance imaging

<table>
<thead>
<tr>
<th>First Author’s Name</th>
<th>Number of subjects</th>
<th>MRI parameter</th>
<th>Study Drug</th>
<th>Baseline and change in LDL (mg/dl)</th>
<th>Change in MRI parameter from baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corti 2001³⁷</td>
<td>18 (25 plaques)</td>
<td>Vessel wall area</td>
<td>Simvastatin</td>
<td>159±32 -38%</td>
<td>-15% (12 months)</td>
</tr>
<tr>
<td>Corti 2002⁵¹</td>
<td>21 (32 plaques)</td>
<td>Vessel wall area</td>
<td>Simvastatin</td>
<td>159±32 -38%</td>
<td>-18% (24 months)</td>
</tr>
<tr>
<td>Corti 2005⁵²</td>
<td>29 (20mg) 22 (80mg)</td>
<td>Vessel wall area</td>
<td>Simvastatin 20mg Simvastatin 80mg</td>
<td>154±31 and 173±33 -26% and -46%</td>
<td>-14% (12months) -18% (24months)</td>
</tr>
<tr>
<td>Yonemura 2005⁵³</td>
<td>21 (5mg) 19 (20mg)</td>
<td>Vessel wall area</td>
<td>Atorvastatin 5mg Atorvastatin 20mg</td>
<td>200±30 and 201±46 -34% and -47%</td>
<td>+4±16% (5mg 12 months) -18±10% (20mg, 12 months)</td>
</tr>
<tr>
<td>Study</td>
<td>Participants</td>
<td>Interventions</td>
<td>Outcomes</td>
<td>Summary</td>
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<tr>
<td>Lee JM 2008</td>
<td>24</td>
<td>Normalized wall index (wall area/total area)</td>
<td>Simvastatin 40mg (n=15) Simvastatin 10-20mg (n=5) Atorvastatin (n=4)</td>
<td>Overall mean baseline 112±39 -29%</td>
<td>-7% (12 months)</td>
</tr>
<tr>
<td>Underhill 2008</td>
<td>18 with LRNC</td>
<td>Lipid-Rich Necrotic Core</td>
<td>Rosuvastatin 5mg Rosuvastatin 40mg</td>
<td>Overall mean baseline 148±27 and 153±31 -38% and -60%</td>
<td>-41% (24 months)</td>
</tr>
<tr>
<td>Tang 2009</td>
<td>47</td>
<td>USPIO uptake on T2* imaging</td>
<td>Atorvastatin 10mg Atorvastatin 80mg</td>
<td>Overall mean baseline 88 and 97 +5% and -22%</td>
<td>-6.2% (12 weeks)</td>
</tr>
<tr>
<td>Zhao 2011</td>
<td>33 with LRNC</td>
<td>Lipid-Rich Necrotic Core</td>
<td>Atorvastatin ± coveselam ± niacin</td>
<td>Overall mean baseline 148±29 -52%</td>
<td>-38% (36 months)</td>
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<tr>
<td>Sibley 2013</td>
<td>73</td>
<td>Carotid Wall</td>
<td>Multiple statin doses</td>
<td>Overall mean baseline 171</td>
<td>-6%</td>
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<tr>
<td></td>
<td>Volume</td>
<td>± niacin</td>
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<tr>
<td>Hovingh 2015⁴</td>
<td>23 with FH</td>
<td>Vessel wall area</td>
<td>CER-001</td>
<td>214±81</td>
<td>N/A</td>
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<tr>
<td>Kootte 2015⁵</td>
<td>7 with FPHA</td>
<td>Vessel wall area</td>
<td>CER-001</td>
<td>77±54</td>
<td>N/A</td>
</tr>
</tbody>
</table>

**Legend:** CER-001: recombinant human apolipoprotein A-1 containing HDL-mimetic particle

Figure legends

**Figure 1:** Longitudinal bi-dimensional image of the right common carotid artery showing a very thick intima-media layer of the far wall (solid arrows) and mild thickening of the near wall (arrow phantoms).

**Figure 2:** Cross sectional high-resolution black blood image of the left carotid bulb showing a lipid rich atheromatous plaque with a thick fibrous cap. The inset shows an enlargement of the plaque encircled by the broken line. The lipid core is indicated by the white arrow (courtesy of Dr. Richard Coulden, Department of Diagnostic Imaging, University of Alberta, AB, Canada).

**Figure 3:** Cross sectional high-resolution black blood image of the left internal carotid artery at baseline (A) and after 6 months (B) showing increase in wall thickness at follow-up (white arrows point to the thickened carotid wall).
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