MRI screening for lipid-rich necrotic core in multicenter clinical trials of lipid-lowering therapy

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Introduction: The lipid rich necrotic core (LRNC) is one of the primary imaging targets for drug therapies aimed at reducing carotid atherosclerotic plaque burden. Magnetic resonance imaging (MRI) can more accurately measure LRNC size [1] than competing modalities such as ultrasound and may provide a more sensitive measure of treatment effect in studies of lipid-lowering therapy. Screening for subjects with LRNC using MRI, can be cost prohibitive when the prevalence of LRNC is low in the target study population. A tiered screening approach of Ultrasound (US) followed by MRI may reduce cost while improving patient recruitment. We describe the first MRI based multicenter study (clinicaltrials.gov #NCT00851500) using LRNC as the primary study endpoint in which patients were screened-in based on visible plaque on B-mode ultrasound and the presence of LRNC on a subsequent screening MRI scan. Although US cannot measure LRNC size, it can be used to measure vessel wall thickness. Utilization of max wall thickness (maxWT) during US screening may improve the specificity for LRNC identification in early atherosclerosis and reduce the number of negative MRI scans.

Aims: 1) To describe the sensitivity and specificity of maxWT for identifying subjects with LRNC. 2) To identify whether addition of maxWT to the ultrasound assessment can reduce imaging cost in clinical trials.

Materials and Methods: As part of a multicenter MRI study, subjects with 16-79% stenosis by duplex ultrasound were recruited from 24 clinical sites and scanned at 13 North American imaging centers with either 3T GE or 3T Philips MRI scanners. A screening B-mode ultrasound was used to select patients with visible plaque. Qualifying subjects were then screened by carotid MRI with dedicated carotid coils (GE 6 channel phased array or Philips 8 channel phased array) and dedicated black-blood carotid MRI (T1: TR/TE 800/10, T2: TR/TE 4800/50, 3D-TOF TR/TE 24/5, CE-T1 TR/TE 800/10, resolution 0.63x0.63x2mm). Trained reviewers at a central lab identified the presence of LRNC based on decreased uptake of Gadolinium contrast (Magnevist) by LRNC relative to adjacent muscle. Presence of extensive calcification (extCA) defined as calcification >50% of plaque by visual inspection, was also noted since such plaques do not respond to lipid-lowering therapy. Subjects were designated as screened-out or SO group if they had no LRNC or if they had extCA. The remaining subjects with LRNC and no extCA were designated as screened-in or SI group. Lumen and outerwall contours were drawn using custom designed software. MaxWT was calculated from the contours in all SI subjects and 50 randomly selected SO subjects. A modified US screening procedure was considered where maxWT was required to be greater than a particular threshold as an additional inclusion criterion. To study the effect of adding maxWT to the screening procedure, a probabilistic model for average total imaging costs was constructed. The total cost of imaging was derived as $C_{total} \propto (R + 1/p_{12})/p_3$, where R is the fixed per scan cost ratio between MR and US scans, p12 is the probability of being qualified by US as a function of the maxWT threshold, and p3 is the probability of being qualified by MR given prior qualification by US, also a function of the maxWT threshold. The parameters p_{12} and p_3 can be expressed entirely as functions of the sensitivity and specificity of maxWT for detecting qualified subjects, the probability of passing the initial US criteria, and the overall probability of being qualified by MR after passing the initial US criteria. Empirical estimates were derived accordingly from the study samples.

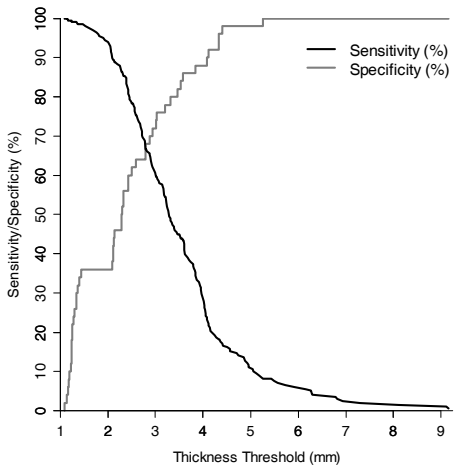

Figure 1: Sensitivity and specificity curves of max wall thickness (max WT) threshold in identifying subjects with LRNC and without extensive calcification

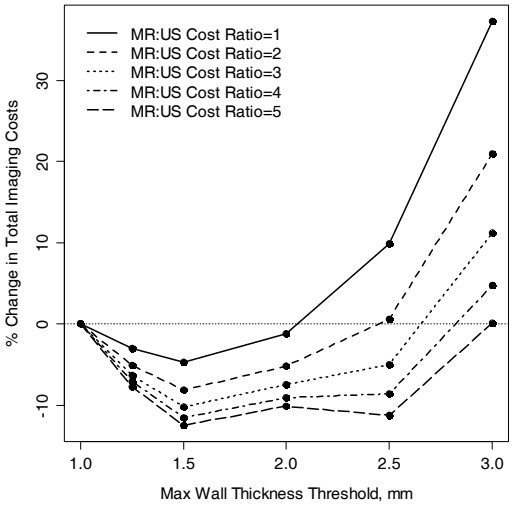

Figure 2: Percent change in total imaging cost by adding max wall thickness (max WT) based screening before MRI, compared with no additional screening.

Results: 531 of 1051 (51%) subjects were qualified by US as having a visible plaque and 509 of these subjects subsequently underwent carotid MRI. Ten (2%) had insufficient MR image quality for interpretation and of the remaining 499, 240 (48%) had LRNC and were not extensively calcified. Of the 240, 198 successfully completed the study and were fully analyzed (the SI group). The average max WT was greater in the SI group than the SO group (3.5 ± 1.3 vs. 2.4 ± 1.1 mm, Δ=1.1 [0.8, 1.5], $p < 0.001$). Figure 1 shows the sensitivity and specificity of using a max WT threshold for detecting qualified subjects. Up to a threshold of about 1.5 mm, the specificity increased rapidly while the sensitivity fell only slightly. The theoretical change in average total imaging costs were estimated based on the observed data and assuming a range of per scan cost ratios between MR and US (Figure 2). Regardless of the cost ratio from 1 to 5, a threshold of 1.5 mm performed well by lowering the average total cost between 5 and 13%. When the cost ratio was larger (4 or 5), higher thresholds (up to 2.5 mm) also provided approximately 10% savings but at lower sensitivity.

Discussion and Conclusions: Adding a maxWT criterion by US for selecting patients into the MRI study can reduce study expenses by 10% when the cost ratio between MR and ultrasound is four-fold or higher. Setting a higher threshold of 2.5-3mm can reduce costs at typical MR-ultrasound cost ratios but may require more subjects to be screened to meet study requirements. When patient recruitment is a concern, a screening max WT threshold of 1.5mm is suggested since it works for all cost ratios while still saving 10% in imaging costs.

References: [1] Saam ATVB 2005; 25(1):234-9