# Evaluation of USPIO uptake to assess the risk of future cerebrovascular and cardiovascular events: long-term follow-up of the ATHEROMA trial

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**Introduction**

There is a clinical need for diagnostic tools capable of identifying high risk atheromatous plaques. Ultrasmall superparamagnetic iron oxides (USPIO) may be used to detect inflammation within the carotid artery.[1,2] The ATHEROMA study demonstrated USPIO-enhancement changed with high-dose atorvastatin therapy.[3] We retrospectively sought to assess whether baseline USPIO-indicated inflammation was predictive of subsequent vascular events. In 2006-2007, the ATHEROMA trial (Atorvastatin THerapy: Effects on Reduction of Macrophage Activity) (NCT00368589) assessed differences in USPIO-related signal change in patients with moderate carotid stenosis. The study randomly assigned patients into two treatment arms, low- (10 mg) and high-dose (80 mg) atorvastatin therapy, over 12 weeks and assessed dose-response interaction. The purpose of this long-term follow-up study is to assess and report on the ability of initial USPIO-enhanced MR imaging to predict subsequent cerebrovascular and cardiovascular morbidity and mortality events.

**Methods**

In total n=62 patients (56 male and 6 female) were initially recruited and imaged with USPIO (Ferumoxtran-10, Guerbet, Aulnay sos Bois, France) and followed up through electronic medical records and general practitioner notes. All patients had both their left and right carotids imaged on a 1.5T whole body clinical machine (Signa HDx, GE Healthcare, Waukesha, WI) using a four-channel phased-array carotid coil (MachNet BV, Eelde, The Netherlands). USPIO-enhanced MR imaging was performed pre- and post-infusion. The USPIO contrast agent Ferumoxtran-10 was diluted in normal saline and administered as a slow infusion through an indwelling large-bore intravenous cannula over 30 minutes with a total dose of 2.6 mg/kg. The post-infusion scan was acquired 36 hours after the contrast administration. A quadruple inversion recovery 2D ECG-triggered $T_2$*-weighted spiral sequence was performed with the following scan parameters (FOV: 12cm, NEX: 2, TE: 2.6ms, TR: 1 R-R, flip angle: 60º). The spiral trajectory consisted of 4092 data points sampled on 22 separate arms. Multiple slices were prescribed to encompass the extent of the plaque with 3mm thickness and no inter-slice gaps. Figure 1 depicts a representative example of slice matched pre- and post-USPIO contrast images. Image analysis involved placing a horizontal line through the lumen center and a perpendicular line placed in the midpoint of the artery to divide the plaque into quadrants. Using these defined regions of interest (ROI) the mean signal changes between pre- and post-USPIO infusion was calculated for each quadrant following signal normalization to that of the adjacent sternocleidomastoid muscle. The rational for this approach follows USPIO uptake being localized and could be averaged out on a per slice basis. As USPIO uptake causes a loss of signal intensity due to its paramagnetic effects, we report the percentage signal intensity decrease as a relative measure of USPIO uptake. A Cox proportional hazard regression model was performed where the predictive variable was defined as the quadrant with maximum signal intensity change. The models outcome variable was defined as 'true' if patients experienced myocardial infarctions, transient ischemic attacks or strokes, which resulted in either morbidity or mortality. Alternatively the outcome variable was defined as 'false'. Time to event was defined based on the time which elapsed following the baseline MRI examination. For those patients that did not experience an event the 1st of January 2011 was defined for censorship. In addition, USPIO uptake was subjectively assessed by generating Kaplan-Meier survival curves. The predictive variable, maximum percentage change within a quadrant, was stratified in two groups: 'USPIO positive' and 'USPIO negative' were the threshold was defined by the median value of the patient cohort.

**Results**

The study demographic included (n=62) patients (56 males; median age 68.5 [IQs 61.3-74.0] years). The median carotid stenosis was 60% [IQs 50-65%]). The median follow-up period was 4.0 [IQs 3.9 – 4.4] years. In total 17 patients reported subsequent events; there were a total of 8 myocardial infarctions (3 fatal), 6 transient ischemic attacks, and 5 strokes (3 fatal) over the follow-up period. The timing of these events is graphically illustrated in Fig 2. The Cox proportional hazard regression model found that the variable maximum percentage change within a quadrant was predictive of outcome (b=0.01134, se(b)=0.00626) with a p-value of 0.07.

**Discussion**

While there may be an association between USPIO-indicated plaque inflammation seen as signal loss on MRI and risk of vascular events, our study failed to demonstrate a statistically-significant association but this is likely confounded by an inadequately sized study population and low incident rates. Further studies exploring the utility of USPIO agents in larger cohorts should consider modeling sample sizes based on survival analysis statistics,[4] as establishing utility based on hard clinical outcomes is ultimately required to establish efficacy.

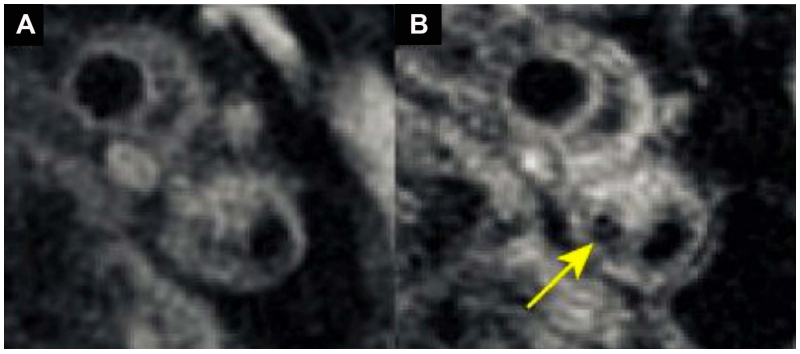


**Figure 1: The $T_2$* effect of USPIO as seen on QIR Spiral Acquisition. Pre (A) and post-USPIO (B) MR imaging of a symptomatic carotid plaque. Focal USPIO uptake is evident (yellow arrow head)**

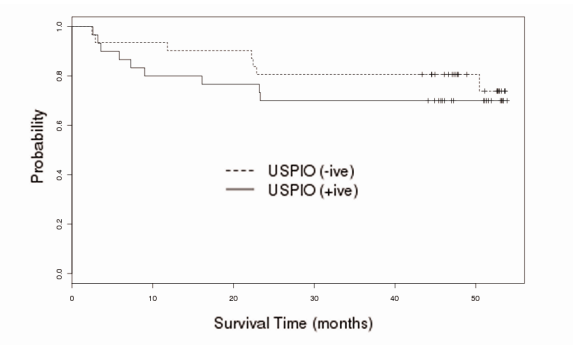


**Fig 2 Kaplan-Meier survival curves showing subsequent cerebrovascular and cardiovascular morbidity and mortality events**

**References** [1] Kooi ME, et al. Circulation 2003;107(19):2453-2458 [2] Tang TY, et al. J Neurol Neurosurg Psychiatry 2007;78(12):1337-1343 [3] Tang TY, et al. J Am Coll Cardiol 2009;53 [4] Hsieh FY, Lavori PW. Control Clin Trials 2000; 21(6):552-60