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Aortic Wall Inflammation Predicts Abdominal Aortic Aneurysm Expansion, Rupture and Need for Surgical Repair

Running Title: *The MA^{3}RS Study*

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Abstract

***Background*—**Ultrasmall superparamagnetic particles of iron oxide (USPIO) detect cellular inflammation on magnetic resonance imaging (MRI). In patients with abdominal aortic aneurysm, we assessed whether USPIO-enhanced MRI can predict aneurysm growth rates and clinical outcomes.

***Methods*—**In a prospective multicentre open-label cohort study, 342 patients with abdominal aortic aneurysm (diameter ≥40 mm) were classified by the presence of USPIO enhancement and were monitored with serial ultrasound and clinical follow-up for at least 2 years. The primary endpoint was the composite of aneurysm rupture or repair.

***Results*—**Participants (85% male, 73·1±7·2 years) had baseline aneurysm diameter of 49·6±7·7 mm, and USPIO enhancement was identified in 146 (42·7%) participants, absent in 191 (55·8%) and indeterminate in 5 (1·5%). During follow-up (1005±280 days), there were 17 (5·0%) abdominal aortic aneurysm ruptures, 126 (36·8%) abdominal aortic aneurysm repairs, and 48 (14·0%) deaths. Compared to those without uptake, patients with USPIO enhancement have increased rates of aneurysm expansion (3·1±2·5 versus 2·5±2·4 mm/year, p=0·0424) although this was not independent of current smoking habit (p=0·1993). Patients with USPIO enhancement had higher rates of aneurysm rupture or repair (47·3% versus 35·6%; difference 11·7%, 95% confidence intervals 1·1 to 22·2%, p=0·0308): this was similar for each component of rupture (6.8% versus 3.7%, p=0·1857) or repair (41.8% versus 32.5%, p=0·0782). USPIO enhancement was associated with reduced event-free survival for aneurysm rupture or repair (p=0·0275), all-cause mortality (p=0·0635) and aneurysm-related mortality (p=0·0590). Baseline abdominal aortic aneurysm diameter (p<0·0001) and current smoking habit (p=0·0446) also predicted the primary outcome, and the addition of USPIO enhancement to the multivariate model did not improve event prediction (c-statistic, 0·7935 to 0·7936).

***Conclusions*—**USPIO-enhanced MRI is a novel approach to the identification of aortic wall cellular inflammation in patients with abdominal aortic aneurysms, and predicts the rate of aneurysm growth and clinical outcome. However, it does not provide independent prediction of aneurysm expansion or clinical outcomes in a model incorporating known clinical risk factors.

***Clinical Trial Registration*—**URL:http://www.isrctn.com/ Unique Identifier: ISRCTN76413758 EudraCT Number: 2012-002488-25

Key Words: abdominal aortic aneurysm; magnetic resonance imaging; clinical trial

Clinical Perspective

What is new?

- In this proof-of-concept phase 2 study, we demonstrate for the first time that functional imaging of abdominal aortic aneurysms can predict disease progression and clinical events.
- Aortic wall inflammation detected by ultrasmall superparamagnetic particles of iron oxide (USPIO)-enhanced magnetic resonance imaging (MRI) predicts the rate of aneurysm growth, and the risk of aneurysm rupture or repair as well as being associated with all-cause and aneurysm-related mortality.

What are the clinical implications?

- Multivariate analysis demonstrated that USPIO-enhanced MRI does not appear to improve risk stratification beyond current predictors of clinical outcome including ultrasound measures of aneurysm diameter.
- This technique may be a useful adjunctive imaging approach in those with high-risk or borderline aneurysm sizes, or those with larger aneurysms where the balance of risk and benefit is uncertain.
- This approach may also have utility in assessing candidate anti-inflammatory therapies targeted at reducing disease progression.

Abdominal aortic aneurysms have a prevalence of 5% in 65-74 year-old men and when ruptured, are associated with a mortality of up to 90%.[1] At a population level, ruptured aortic aneurysms are a major cause of death being the thirteenth commonest cause of death and accounting for over 150,000 deaths in 2013.[2] Pre-emptive elective open surgical or endovascular repair can be life-saving and is considered when the abdominal aortic aneurysm diameter exceeds 55 mm, is rapidly expanding (≥10 mm/year) or causes symptoms.[3-5]

Abdominal aortic aneurysms are usually associated with no symptoms and are often identified incidentally or as part of an ultrasound-based screening programme. Population screening has been established in some countries and is associated with a halving of the mortality associated with abdominal aortic aneurysms.[6,7] Continued surveillance of aneurysms is however challenging because of the non-linearity and unpredictability of expansion rates,[8] although the best current predictor of aneurysm expansion and rupture is the baseline aneurysm diameter.[1,9] Furthermore, the pathophysiological mechanisms underlying aneurysm expansion remain uncertain, and the role of cellular inflammation and macrophage infiltration has been debated. Finally, up to one fifth of ruptured abdominal aortic aneurysms are <55 mm in diameter and 40% of patients with aneurysm diameters between 70 and 100 mm do not experience aneurysm rupture.[10] There is therefore an unmet clinical need to identify more reliable methods of identifying those patients at risk of abdominal aortic aneurysm expansion and rupture,[11,12] and techniques that assess both the structure and biology of aneurysms hold considerable promise.

Ultrasmall superparamagnetic particles of iron oxide (USPIO) constitute a class of magnetic resonance imaging (MRI) contrast agent that are taken up by tissue-resident macrophages and can be used to identify cellular inflammation within tissues[13,14] including abdominal aortic aneurysms.[15,16] In a small pilot study of 29 patients with abdominal aortic

aneurysm,[15] we have previously demonstrated that USPIO enhancement on MRI is associated with macrophage infiltration of the abdominal aortic aneurysm wall and more rapid rates of abdominal aortic aneurysm expansion. We therefore aimed to validate these preliminary findings in a larger multicentre cohort of patients, and to determine whether USPIO-enhanced MRI could predict the rate of abdominal aortic aneurysm expansion, and subsequent rates of rupture or surgical repair.

Methods

Study Design

The Magnetic resonance imaging using ultrasmall superparamagnetic particles of iron oxide in patients under surveillance for Abdominal Aortic Aneurysm to predict Rupture or Surgical repair (MA^{3}RS) study was a prospective multi-centre observational open-label cohort study of patients under routine ultrasound surveillance for abdominal aortic aneurysm. The research design and protocol has been described previously (ISRCTN76413758).[17] The study was approved by the local research ethics committee (12/ES/0068) and the use of ferumoxytol was given Clinical Trial Authorisation by the Medicines and Healthcare products Regulatory Authority (MHRA) of the United Kingdom (EudraCT Number 2012-002488-25).

Study Population

Consecutive patients were recruited from three centres in Scotland, UK (Royal Infirmary of Edinburgh, Western Infirmary of Glasgow and Forth Valley Royal Hospital in Larbert) between 8th November 2012 and 5th December 2014. Inclusion criteria were age >40 years, maximum anteroposterior abdominal aortic aneurysm diameter ≥40 mm by abdominal ultrasound, and under ultrasound surveillance as part of routine clinical care. Exclusion criteria included patients

with planned repair of abdominal aortic aneurysm, known inflammatory aneurysm, aneurysm arising from a connective tissue disorder, women of child-bearing potential, renal failure (estimated glomerular filtration rate ≤30 mL/min/1.73 m^2) and contraindication to MRI or ferumoxytol. All participants gave written informed consent to participate in the study.

Study Protocol

Participants attended for a baseline assessment within 6 weeks of the screening abdominal ultrasound. Participant characterisation comprised of full clinical assessment, USPIO-enhanced MRI and computed tomography aortography. The scanning protocols and image analysis techniques have been described previously.[15,17] In brief, patients underwent a baseline 3T MRI (Magnetom Verio 3T, Siemens Healthcare, Erlangen, Germany) before receiving an intravenous infusion of a weight-adjusted dose of USPIO (4 mg/kg of ferumoxytol; Rienso®, Takeda Italia, Italy). A second MRI scan was performed 24-36 hours after USPIO administration. Two trained observers performed image analysis using bespoke software that compared pre- and post-contrast images using semi-automatic registration. To calculate the degree of USPIO enhancement, colour maps were generated to depict the percentage change in T2* which is the decay constant for the exponential decay of signal over time. Using the pre-defined threshold of ≥71% change in T2*, each colour map was independently classified by two trained observers into patients with or without USPIO enhancement (≥10 contiguous voxels[15]) within the wall of the abdominal aortic aneurysm (Figure 1). Discordant classifications were resolved by consensus.

Clinical Follow Up

Patients were reviewed every 6 months in the research clinic for a minimum of 24 months. Structured follow up data were collected on abdominal aortic aneurysm events, hospital admissions and other relevant clinical data. Clinical events were verified independently using

electronic health records and public registry data as described previously.[18,19] Serial maximum anteroposterior diameters were obtained by ultrasound in dedicated abdominal aortic aneurysm surveillance clinics performed by trained specialist vascular practitioners who were blinded to USPIO-enhanced MRI findings. We have previously reported interobserver coefficient of variation of aortic diameter measurements of 3.5%.[20] Participants unable to attend for subsequent research visits were followed-up through electronic health records as described previously.[18,19]

Clinical Endpoints and Adjudication

Clinical data from clinic visits, research database, electronic health records, primary care contacts and General Register Office were reviewed and clinical endpoints adjudicated by an independent Clinical Endpoint Committee. The committee members were blinded to the MRI findings. Follow-up was censored at 21st November 2016 or at the time of event.

Statistical Analysis

The primary endpoint was the composite of abdominal aortic aneurysm rupture or repair. We estimated that 130 events would be required to have adequate sensitivity to determine the added value of USPIO-enhanced MRI to predict the occurrence of the primary endpoint. Previous data from the United Kingdom have suggested a two-year event rate of 41% in patients under surveillance for abdominal aortic aneurysm.[21] We therefore aimed to recruit approximately 350 patients, with an expected drop-out rate of 10%, resulting in a minimum of 317 patients with 130 events to be included in the final analysis.

Categorical data are presented using counts and percentages, continuous variables presented using mean±standard deviation and absolute differences with 95% confidence intervals. Comparisons in baseline characteristics were made using either a binomial test for proportions in the case of categorical data or by two-sample *t*-test for continuous data. Aneurysm

growth rate was determined from serial ultrasound measurements using a linear regression model that was fitted to all available data and the slope used to determine the aneurysm growth rate per year. The primary and clinical event endpoints were assessed by log-rank test and are presented as Kaplan-Meier curves. Cox proportional hazards models were generated to include the baseline covariates of sex, smoking, systolic blood pressure and baseline aneurysm diameter determined by ultrasound. The additional value of USPIO enhancement was assessed by the c-statistic and net reclassification index.[22-24] Statistical significance was taken as two-sided p<0·05.

Role of the Funder

The funder played no role in developing the study design, the collection, analysis, and interpretation of data, in the writing of the report, or in the decision to submit the paper for publication.

Results

We screened approximately two thousand patients attending the out-patient vascular clinics of the study centres and identified 741 potentially eligible patients of whom ultimately 361 (48·7%) were recruited into the study (Figure 2). Nineteen patients were subsequently withdrawn predominantly because they were unable to undergo repeated magnetic resonance imaging due to claustrophobia. The final study population comprised of 342 participants who were predominantly elderly male current or ex-smokers with hypercholesterolaemia and hypertension (Table 1). There were no serious adverse events or reactions to intravenous ferumoxytol administration which was generally well tolerated by all participants. Mild asymptomatic hypotension that was possibly related to ferumoxytol was noted in one subject but required no action or intervention.

USPIO enhancement of the abdominal aortic aneurysm wall was identified in 146 (42·7%) participants, was absent in 191 (55·8%) and was indeterminate in 5 (1·5%). USPIO enhancement was strongly associated with current smoking status as well as baseline abdominal aortic aneurysm diameter and the presence of a common iliac aneurysm (Table 1).

Aneurysm Growth Rate

On ultrasound, baseline maximum abdominal aortic aneurysm diameter was 49·6±7·7 mm and was slightly larger in patients with USPIO enhancement (Table 1). The abdominal aortic aneurysm growth rate during the trial was 2·8±2·4 mm/year (n=279) and was greater in patients with USPIO enhancement (3·1±2·5 versus 2·5±2·4 mm/year; difference 0·6 [95% confidence intervals (CI), 0·02 to 1·2] mm/year, p=0·0424). Current smoking status (p=0·0305), but not aneurysm diameter (p=0·1853), baseline systolic blood pressure (p=0.6994) or USPIO enhancement (p=0·1993), was an independent predictor of aneurysm growth rate.

Clinical Follow-up

All participants were followed up for a mean of 1005±280 days. Overall, the primary endpoint occurred in 140 (40·9%) subjects with 17 abdominal aortic aneurysm ruptures and 126 abdominal aortic aneurysm repairs (Table 2): 3 subjects underwent repair after rupture. There were 48 (14·0%) deaths of which a third was abdominal aortic aneurysm related (17 [35·4%]) and a quarter was due to other cardiovascular causes (12 [25·0%]).

Rupture or Repair

The primary endpoint occurred more frequently in participants with USPIO enhancement of abdominal aortic aneurysm (69/146=47·3% versus 68/191=35·6%; difference 11·7%, 95% CI 1·1 to 22·2%, p=0·0308) and was associated with a reduced event-free survival (p=0·0275; Figure 3). This was consistent for both components of the endpoint (Table 2). In contrast to

female sex (hazards ratio 0·952, 95% confidence intervals 0·589 to 1·540; p=0·8413) and systolic blood pressure (hazards ratio 0·997, 95% confidence intervals 0·988 to 1·005; p=0·4492), baseline abdominal aortic aneurysm diameter (hazards ratio 1·077, 95% confidence intervals 1·061 to 1·094; p<0·0001) and current smoking habit (hazards ratio 1·464, 95% confidence intervals 1·001 to 2·120; p=0·0433) were the main predictors of the primary endpoint. The addition of USPIO enhancement to the model (hazards ratio 1·003, 95% confidence intervals 0·700 to 1·439; p=0·9849) did not improve the prediction of events (c-statistic, 0·7924 to 0·7926) or the unconditional net reclassification (-13·5%, 95% confidence intervals -36·4% to 9·3%). This was true for both components of the endpoint: (a) aneurysm rupture, c-statistic, 0·6317 to 0·6304 and net reclassification 29·9% (95% confidence intervals, -22·0% to 81·9%), and (b) aneurysm repair, c-statistic, 0·8000 to 0·7996 and net reclassification -9·9% (95% confidence intervals, -33·4% to 13·7%).

All-cause and abdominal aortic aneurysm-related death appeared to be more frequent in participants with USPIO enhancement of the abdominal aortic aneurysm (Table 2 and Figure 3) but fell short of statistical significance.

In post-hoc analysis, we explored whether USPIO enhancement varied according to aneurysm size. We dichotomised the population at the mean diameter into smaller (diameter 40-49 mm; n=187) and larger (diameter ≥50 mm; n=155) aneurysms. The rate of USPIO enhancement was lower in patients with smaller aneurysms: 65 (35·1%) versus 81 (53·3%) in those with larger aneurysms, difference 18·2% (95% confidence interval, 7·7 to 28·9; p=0·0008). However, in patients with smaller aneurysms, USPIO enhancement was associated with a doubling in the rate of repair or rupture without an effect on mortality (Table 3) whereas

in those with larger aneurysms, it was the reverse with a more than doubling of mortality but no effect on the primary endpoint (Table 4).

Discussion

In a prospective multicentre observational cohort study, we have demonstrated that USPIO-enhanced MRI not only predicts the rate of aneurysm expansion but also the future risk of abdominal aortic aneurysm rupture or repair. This is the largest prospective clinical study of magnetic resonance imaging in patients with abdominal aortic aneurysms, and is the first report of an imaging technique that not only identifies cellular inflammation, but also predicts disease progression and outcome. This suggests a central role of cellular inflammation in the pathophysiology, progression and outcome of abdominal aortic aneurysm disease.

Abdominal aortic aneurysm expansion is driven by several potential pathogenetic mechanisms that are associated with inflammation and tissue degradation.[1,11] Macrophages are central to many of these processes[25] and their depletion appears to prevent aneurysm formation or progression in preclinical models of abdominal aortic aneurysm.[26] Non-invasive *in vivo* imaging of tissue-resident macrophages would therefore seem an intuitive and promising approach in patients with abdominal aortic aneurysm but until now has not been prospectively tested in large clinical cohorts.[11,12,27] We here report the first study in a large clinical cohort to image tissue-resident macrophages with USPIO-enhanced MRI, and demonstrate that USPIO enhancement is associated with more rapid abdominal aortic aneurysm growth rates and adverse clinical outcomes. This provides strong support for the concept that imaging the biology of abdominal aortic aneurysm may be a promising new approach to risk stratify and manage patients with this disease.[11]

The rate of abdominal aortic aneurysm growth has previously been shown to be predicted by smoking status, aneurysm size and the presence of common iliac aneurysms.[9,28] Indeed, smoking habit is the principal modifiable risk factor for abdominal aortic aneurysm progression and rupture, and is the main focus of lifestyle modification in these patients. We here demonstrate that USPIO-enhanced MRI is associated with all of these three risk factors. In particular, current smoking was an independent risk factor for abdominal aortic aneurysm growth and intriguingly, USPIO enhancement was twice as frequent in current smokers. We know that smoking promotes inflammation, macrophage-mediated injury and vascular dysfunction.[29-31] This suggests a potential mechanistic link between smoking and macrophage-driven abdominal aortic aneurysm inflammation. Indeed, components of cigarette smoke, such as 3,4-benzopyrene, promote macrophage infiltration of abdominal aortic aneurysm leading to increased matrix metalloproteinase expression and vascular smooth muscle apoptosis.[32] Using adoptive transfer experiments, Jin and colleagues have further shown that *in vivo* exposure of leukocytes to smoke can accelerate the progression of aneurysm disease in smoke-free animals.[33] In this context, our USPIO data suggest that macrophage-mediated inflammation may be the mechanistic link to explain the association between smoking and disease progression in patients with abdominal aortic aneurysm.

The primary endpoint of the study was the rate of abdominal aortic aneurysm rupture or repair and although this was higher in patients with USPIO-enhancement on MRI, it was not independent of known predictors of outcome including baseline abdominal aortic aneurysm diameter and smoking habit. Indeed, incorporation of USPIO-enhanced MRI did not improve the discrimination of a model incorporating these known clinical risk factors. This likely reflects the mutual interdependence and potential causal association of these factors, namely that USPIO-

enhancement highlights areas of smoking induced cellular inflammation within the aneurysm which causes more rapid expansion and increase in the aneurysm diameter leading to aneurysm rupture or triggering of the threshold for repair.

Ultrasound measurements of abdominal aortic aneurysm diameter are the mainstay of clinical management and the principal determinant of the timing of elective surgical repair. Their dominant effect on the primary endpoint is therefore perhaps not surprising, especially as most events were due to elective surgical repair. Given that the clinicians were blind to the results of the USPIO-enhanced MRI, it would be challenging to demonstrate that it could lead to any changes in the rate of elective surgical repair. We therefore explored other measures of outcome that were independent of elective surgical repair. We found that USPIO enhancement appeared to be greater in those with emergent abdominal aortic aneurysm-related events including abdominal aortic aneurysm rupture and abdominal aortic aneurysm-related mortality although the absolute number of events was small and fell just short of achieving statistical significance. Given the small number of emergent events, our study did not have sufficient power to determine whether USPIO enhancement could provide clinically useful information that could independently predict emergent events. However, post-hoc analyses did suggest that USPIO-enhanced MRI did predict overall mortality in patients with larger aneurysms.

Although USPIO-enhanced MRI was not an independent predictor of outcome across the whole study population, it did identify aneurysm disease activity, correlate with rates of aneurysm expansion and appear to predict clinical outcome including rupture and death. If future studies confirm the utility of USPIO-enhanced MRI, how would it be applied in the clinic? For some patients, treatment decisions are not straight forward. For example, abdominal pain in a patient with an aortic aneurysm may be due to other abdominal pathology and not the aneurysm

itself. Urgent repair may be unhelpful in such circumstances and associated with considerable risk. Furthermore, decisions to undertake surgical repair can be challenging in those with high-risk or morphologically atypical aneurysms below 55 mm, those with borderline aneurysm sizes of 50-55 mm (especially in women), or those with larger aneurysms where the balance of risk and benefit is uncertain. Additional information regarding disease activity that is tied to disease progression and adverse clinical outcome may be helpful in guiding such decisions. The value of USPIO-enhanced MRI may also differ according to aneurysm size with the prediction of future aneurysm repair greater in patients with smaller aneurysms, and the future mortality risk more marked in those with larger aneurysms. Although not directly tested here, USPIO-enhanced MRI may assist the clinician in making these difficult management decisions that are associated with significant potential benefits and hazards. This requires further investigation.

There are no definitive medical treatments that can impact on disease progression in this serious and potentially fatal condition. Novel anti-inflammatory or other disease modifying therapies are potential interventions that could address this unmet clinical need. USPIO-enhanced MRI would provide a very useful surrogate biomarker of efficacy in such early proof-of-concept clinical trials. Reduction in USPIO enhancement would be predicted to correlate with reduced cellular inflammation within the aneurysm and consequently reduced rates of expansion. This merits further investigation.

Our study has a number of strengths. It was a multicentre prospective observational cohort study that ensured blinding of the USPIO-enhanced MRI findings from the patients, vascular technicians and attending clinicians, and was therefore independent of clinical decision making. It was an adequately sized phase 2 proof-of-concept trial that was ~10-fold larger than previous studies in this area.[15,34] The study also achieved its predicted event rates and met its

primary endpoint although not independent of known clinical predictors. However, the inclusion of elective surgical repair in the primary endpoint generates some challenges in interpretation because of the ultrasound and diameter-guided decision making for elective surgical repair. The prediction of emergent events appears promising but will require a much larger study with greater power to confirm these findings. Finally, USPIO-enhanced MRI is resource intensive and was not possible in a small number of patients due to contraindications or claustrophobia. However, it was a feasible, safe and deliverable clinical technique that was well tolerated in the vast majority of patients with no serious adverse effects of the MRI or contrast medium. Moreover, we have demonstrated its applicability across multiple sites, and have developed robust computer algorithms and image analysis techniques than enables automated reporting of USPIO enhancement, lending itself to immediate clinical application.

In conclusion, in a multicentre prospective observational cohort study, we have demonstrated that USPIO-enhanced MRI predicts the rate of aneurysm expansion, and the risk of abdominal aortic aneurysm rupture and repair. Although it does not provide independent prediction of aneurysm expansion or clinical outcomes in a model incorporating known clinical risk factors, this is the first demonstration of a cellular imaging technique that can predict clinical events in patients with abdominal aortic aneurysm. Whether clinical outcomes can be improved by treatment decisions based on this novel imaging approach remains to be established.

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Declaration of interests

A patent (US 9275432 B2) held by the University of Edinburgh has been filed relating to the registration of medical images which were generated as part of this study.

Contribution to Manuscript

The MA^{3}RS Study Investigators contributed to the conception or design of the work, or the acquisition, analysis, or interpretation of data for the work. ROF and DEN wrote the first draft of the manuscript. The MA^{3}RS Study Investigators were involved in drafting the manuscript and revising it, and have given final approval of the version to be published. The MA^{3}RS Study Investigators are accountable for the work.

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Table 1. Baseline characteristics of participants

	All Participants n=342	Indeterminant USPIO Enhancement n=5	No USPIO Enhancement n=191	USPIO Enhancement n=146	Difference (95% CI)	P-value
Characteristic						
Age (years)	73·1±7·2	75·0±7·0	73·4±7·5	72·8±6·8	-0·6 (-2·2 to 0·9)	0·4330
Male	292 (85·4)	5 (100)	166 (86·9)	121 (82·9)	-4·0 (-11·8 to 3·7)	0·3019
Blood pressure - systolic (mmHg)	139·6±21·2	151·6±5·3	140·3±21·3	138·2±21·3	-2·1 (-6·8 to 2·5)	0·3610
Blood pressure - diastolic (mmHg)	81·4 ±10·8	87·0±10·7	80·5±10·3	82·3±11·3	1·9 (-0·4 to 4·2)	0·1101
Heart rate (/min)	70·7±10·1	71·6±12·1	70·0±10·1	71·5±10·0	1·5 (-0·7 to 3·7)	0·1779
Body-mass index (kg/m^2)	27·6±4·2	25·0±3·1	28·0±4·2	27·2±4·2	-0·8 (-1·7 to 0·1)	0·0729
Creatinine (µmol/L)	89·9±23·4	76·2±9·7	90·0±21·1	90·3±26·5	0·4 (-4·9 to 5·7)	0·8912
Cholesterol (mmol/L)	4·5±1·0	5·0±1·9	4·5±1·0	4·5±1·0	0·0 (-0·2 to 0·3)	0·7732
Smoking: Current smoker	101 (29·5)	4 (80)	40 (20·9)	57 (39·0)	18·1 (8·3 to 27·9)*	0·0003*
Ex-smoker	195 (57.0)	1 (20)	120 (62.8)	74 (50.7)		
Never smoker	46 (13.5)	0 (0)	31 (16.2)	15 (10.3)		
Aneurysm						
AAA diameter (mm)	49·6±7·7	54·4±12·3	48·2±6·6	51·4±8·4	3·2 (1·5 to 4·8)	0·0002
Concurrent iliac artery aneurysm	66 (19·3)	1 (20)	29 (15·2)	36 (24·7)	9·5 (0·8 to 18·1)	0·0289
Past Medical History						
Hypertension	246 (71·9)	3 (60)	143 (74·9)	100 (68·5)	-6·4 (-16·1 to 3·4)	0·1959
Hypercholesterolaemia	257 (75·1)	2 (40)	146 (76·4)	109 (74·7)	-1·8 (-11·1 to 7·5)	0·7056
Diabetes Mellitus	47 (13·7)	0 (0)	31 (16·2)	16 (11·0)	-5·3 (-12·6 to 2·0)	0·1663
Family history of AAA	61 (17·8)	0 (0)	32 (16·8)	29 (19·9)	3·1 (-5·3 to 11·5)	0·4626
Ischaemic heart disease	125 (36·5)	1 (20)	69 (36·1)	55 (37·7)	1·6 (-8·9 to 12·0)	0·7706
Peripheral vascular disease	66 (19·3)	1 (20)	34 (17·8)	31 (21·2)	3·4 (-5·1 to 12·0)	0·4288
Cerebrovascular disease	46 (13·5)	0 (0)	22 (11·5)	24 (16·4)	4·9 (-2·6 to 12·5)	0·1924
Baseline Medication						
Anti-platelet therapy	224 (65·5)	2 (40)	127 (66·5)	95 (65·1)	-1·4 (-11·7 to 8·8)	0·7847
Statin therapy	270 (78·9)	4 (80)	151 (79·1)	115 (78·8)	-0·3 (-9·1 to 8·5)	0·9483
Anti-coagulant therapy	25 (7·3)	0 (0)	16 (8·4)	9 (6·2)	-2·2 (-7·8 to 3·3)	0·4425
Beta blocker therapy	120 (35·1)	1 (20)	72 (37·7)	47 (32·2)	-5·5 (-15·7 to 4·7)	0·2948

Mean±SD or n (%).

*Current smoker versus combined ex-smoker and never smokers.

CI, confidence intervals; USPIO, ultrasmall superparagemagnetic particles of iron oxide; AAA, abdominal aortic aneurysm; ACE, angiotensin-converting enzyme.

Table 2. Clinical Outcome Events in All Patients

	All Participants n=342	Indeterminant USPIO Enhancement n=5	No USPIO Enhancement n=191	USPIO Enhancement n=146	Difference (95% CI)	P-value
Abdominal Aortic Aneurysm Event						
Rupture/repair	140 (40·9)	3 (60)	68 (35·6)	69 (47·3)	11·7 (1·1 to 22·2)	0·0308
Rupture	17 (5·0)	0 (0)	7 (3·7)	10 (6·8)	3·2 (-1·7 to 8·1)	0·1857
Repair	26 (36·8)	3 (60)	62 (32·5)	61 (41·8)	9·3 (-1·1 to 19·7)	0·0782
Type of repair: EVAR	53 (15·5)	1 (20)	29 (15·2)	23 (15·8)		
Open	73 (21·3)	2 (40)	33 (17·3)	38 (26·0)		
Type of surgery: Elective	120 (35·1)	3 (60)	58 (30·4)	59 (40·4)		
Emergency	6 (1·8)	0 (0)	4 (2·1)	2 (1·4)		
Death						
All cause	48 (14·0)	1 (20)	21 (11·0)	26 (17·8)	6·8 (-0·8 to 14·4)	0·0736
Cardiovascular - AAA related	17 (5·0)	0 (0)	6 (3·1)	11 (7·5)	4·4 (-0·6 to 9·3)	0·0679
Cardiovascular – non-AAA related	12 (3·5)	0 (0)	8 (4·2)	4 (2·7)		
Stroke	2 (0·6)	0 (0)	2 (1·0)	0 (0)		
Myocardial infarction	8 (2·3)	0 (0)	4 (2·1)	4 (2·7)		
Other cardiovascular	2 (0·6)	0 (0)	2 (1·0)	0 (0)		
Non-cardiovascular	19 (5·6)	1 (20)	7 (3·7)	11 (7·5)		
Malignancy	12 (3·5)	1 (20)	4 (2·1)	7 (4·8)		
Other	7 (2·0)	0 (0)	3 (1·6)	4 (2·7)		

n (%).

CI, confidence intervals; USPIO, ultrasmall superparamagnetic particles of iron oxide; AAA, abdominal aortic aneurysm; EVAR, endovascular aneurysm repair.

Table 3. Clinical Outcome Events in Patients with Small Aneurysms (diameter 40-49 mm).

	All Participants n=187	Indeterminant USPIO Enhancement n=2	No USPIO Enhancement n=120	USPIO Enhancement n=65	Difference (95% CI)	P-value
Abdominal Aortic Aneurysm Event						
Rupture/repair	42 (22·5)	0 (0)	20 (16·7)	22 (33·8)	17·2 (3·9 to 30·5)	0·0077
Rupture	4 (2·1)	0 (0)	2 (1·7)	2 (3·1)	1·4 (-3·4 to 6·2)	0·6136*
Repair	38 (20·3)	0 (0)	18 (15·0)	20 (30·8)	15·8 (2·9 to 28·7)	0·0113
Type of repair: EVAR	19 (10·2)	0 (0)	9 (7·5)	10 (15·4)		
Open	19 (10·2)	0 (0)	9 (7·5)	10 (15·4)		
Type of surgery: Elective	36 (19·3)	0 (0)	16 (13·3)	20 (30·8)		
Emergency	2 (1·1)	0 (0)	2 (1·7)	0 (0)		
Death						
All cause	20 (10·7)	1 (50)	14 (11·7)	5 (7·7)	-4·0 (-12·6 to 4·7)	0·3953
Cardiovascular - AAA related	4 (2·1)	0 (0)	2 (1·7)	2 (3·1)	1·4 (-3·4 to 6·2)	0·6136*
Cardiovascular – non-AAA related	8 (4·3)	0 (0)	7 (5·8)	1 (1·5)		
Stroke	1 (0·5)	0 (0)	1 (0·8)	0(0)		
Myocardial infarction	5 (2·7)	0 (0)	4 (3·3)	1 (1·5)		
Other cardiovascular	2 (1·1)	0 (0)	2 (1·7)	0 (0)		
Non-cardiovascular	8 (4·3)	1 (50)	5 (4·2)	2 (3·1)		
Malignancy	4 (2·1)	1 (50)	3 (2·5)	0 (0)		
Other	4 (2·1)	0 (0)	2 (1·7)	0 (0)		

n (%). CI, confidence intervals; USPIO, ultrasmall superparamagnetic particles of iron oxide; AAA, abdominal aortic aneurysm; EVAR, endovascular aneurysm repair. *Fisher's exact test due to small numbers.

Table 4. Clinical Outcome Events in Patients with Large Aneurysms (diameter ≥50 mm).

	All Participants n=155	Indeterminant USPIO Enhancement n=3	No USPIO Enhancement n=71	USPIO Enhancement n=81	Difference (95% CI)	P-value
Abdominal Aortic Aneurysm Event						
Rupture/repair						
Rupture	98 (63·2)	3 (100)	48 (67·6)	47 (58·0)	-9·6 (-24·9 to 5·7)	0·2235
Repair	13 (8·4)	0 (0)	5 (7·0)	8 (9·9)	2·8 (-6·0 to 11·7)	0·5330
Type of repair: EVAR	88 (56·8)	3 (100)	44 (62·0)	41 (50·6)	-11·4 (-27·0 to 4·3)	0·1595
Open	34 (21·9)	1 (33)	20 (28·2)	13 (16·0)		
Type of surgery: Elective	54 (34·8)	2 (67)	24 (33·8)	28 (34·6)		
Emergency	84 (54·2)	3 (100)	42 (59·2)	39 (48·1)		
Death	4 (2·6)	0 (0)	2 (2·8)	2 (2·5)		
All cause						
Cardiovascular - AAA related	28 (18·1)	0 (0)	7 (9·9)	21 (25·9)	16·1 (4·3 to 27·9)	0·0108
Cardiovascular – non-AAA related	13 (8·4)	0 (0)	4 (5·6)	9 (11·1)	5·5 (-3·2 to 14·2)	0·2283
Stroke	4 (2·6)	0 (0)	1 (1·4)	3 (3·7)		
Myocardial infarction	1 (0·6)	0 (0)	1 (1·4)	0 (0)		
Other cardiovascular	3 (1·9)	0 (0)	0 (0)	3 (3·7)		
Non-cardiovascular	0 (0)	0 (0)	0 (0)	0 (0)		
Malignancy	11 (7·1)	0 (0)	2 (2·8)	9 (11·1)		
Other	8 (5·2)	0 (0)	1 (1·4)	7 (8·6)		

n (%). CI, confidence intervals; USPIO, ultrasmall superparamagnetic particles of iron oxide; AAA, abdominal aortic aneurysm; EVAR, endovascular aneurysm repair.

Figure Legends

Figure 1. Magnetic resonance imaging of abdominal aortic aneurysm. **A** - T2-weighted HASTE sequence in the sagittal plane. **B** - Cross-sectional image (dashed line panel A) using a T2-weighted fat saturated sequence to highlight intraluminal thrombus (white) within the aneurysm. **C** - T2* map (blue) overlying the T2-weighted HASTE sequence of image B, demonstrating enhancement of the posterior aneurysm wall with ultrasmall superparamagnetic particles of iron oxide (red).

Figure 2. CONSORT diagram of participant recruitment.

Figure 3. Abdominal aortic aneurysm rupture or repair (primary endpoint; A), all-cause mortality (B) and aneurysm-related mortality (C) in participants with (red) and without (blue) ultrasmall superparamagnetic particles of iron oxide (USPIO) enhancement of the aneurysm wall. Cross-hairs represent individual censoring.

Figure 1

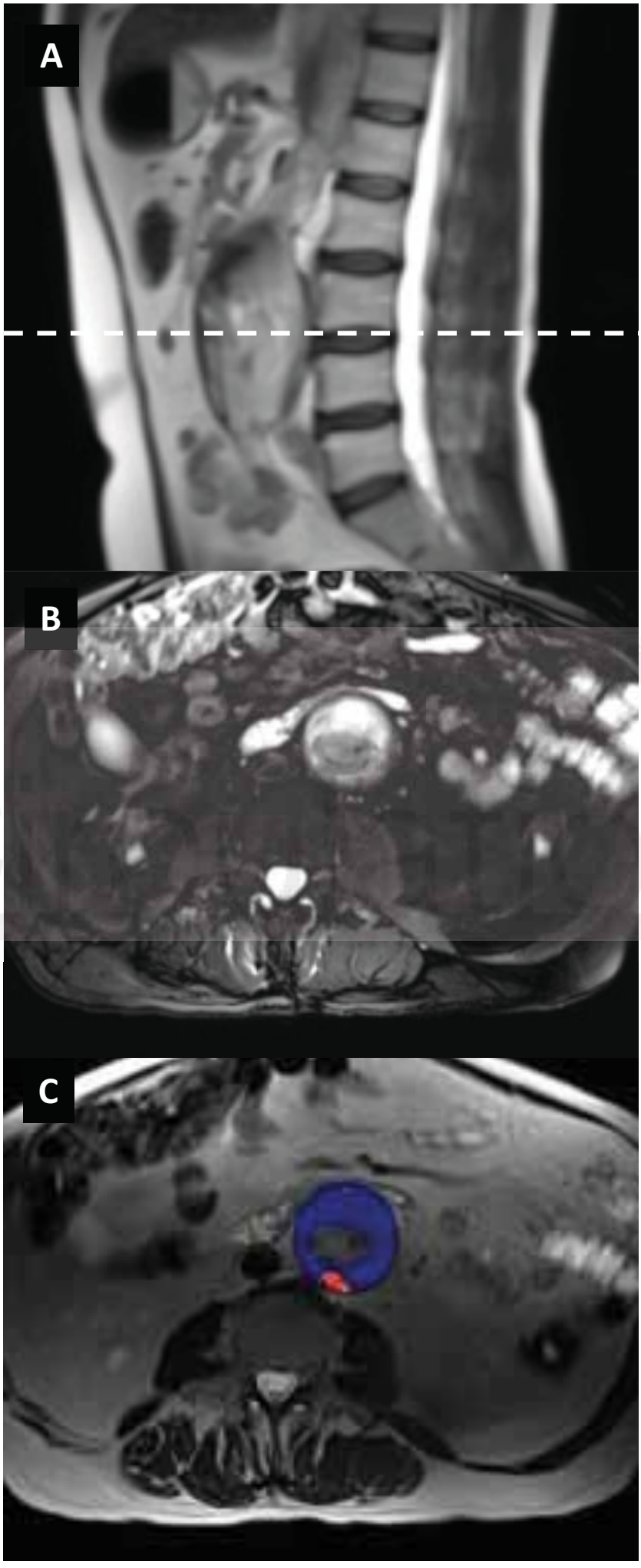


Figure 2

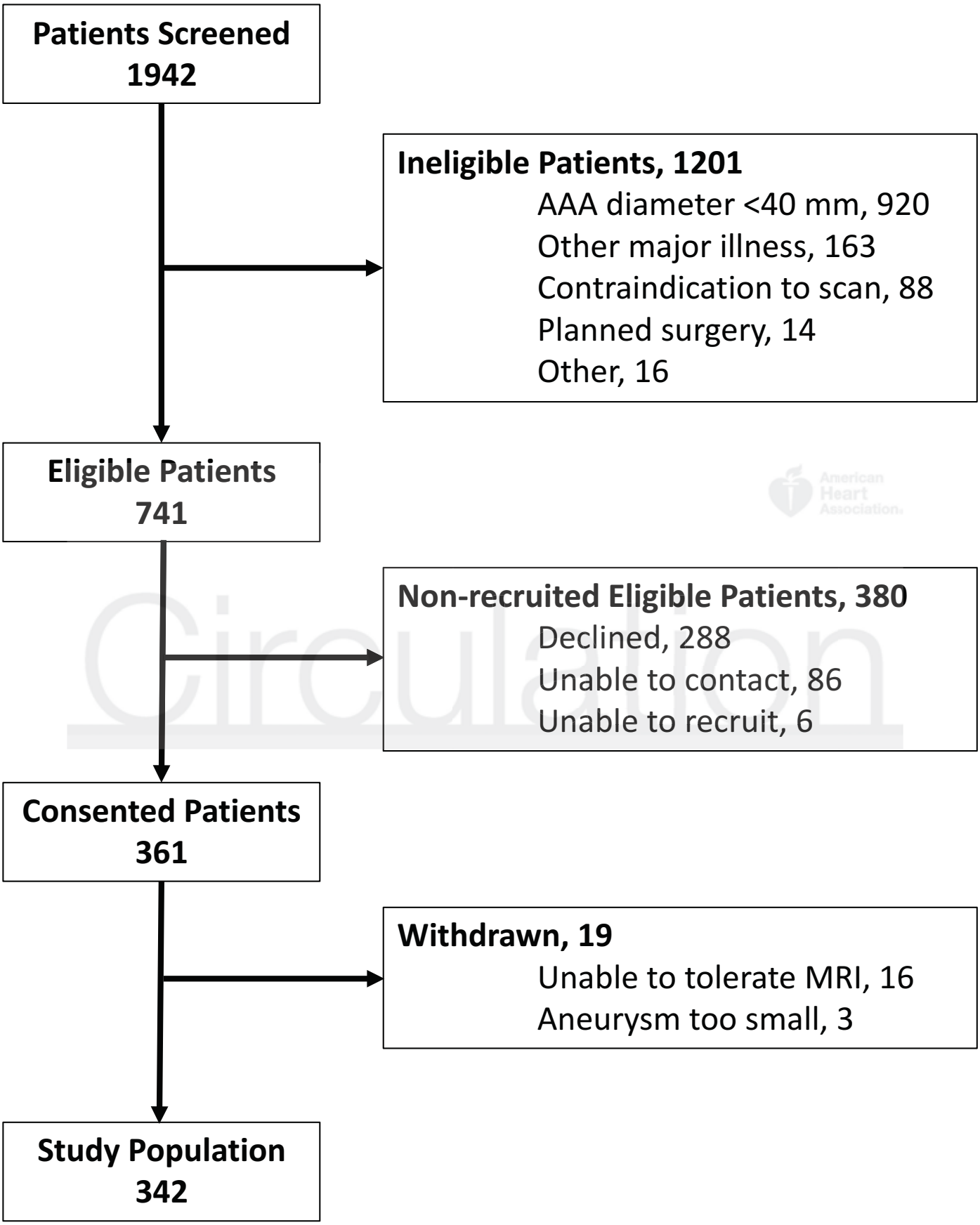
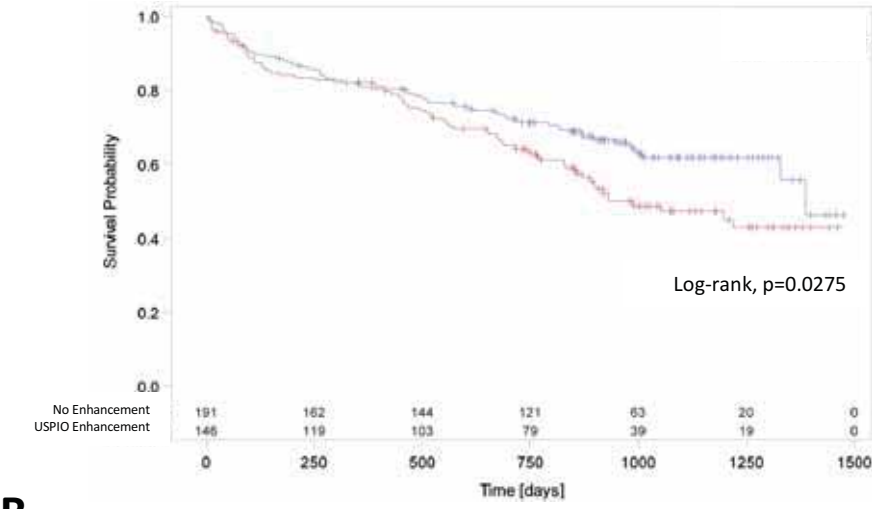


Figure 3

A



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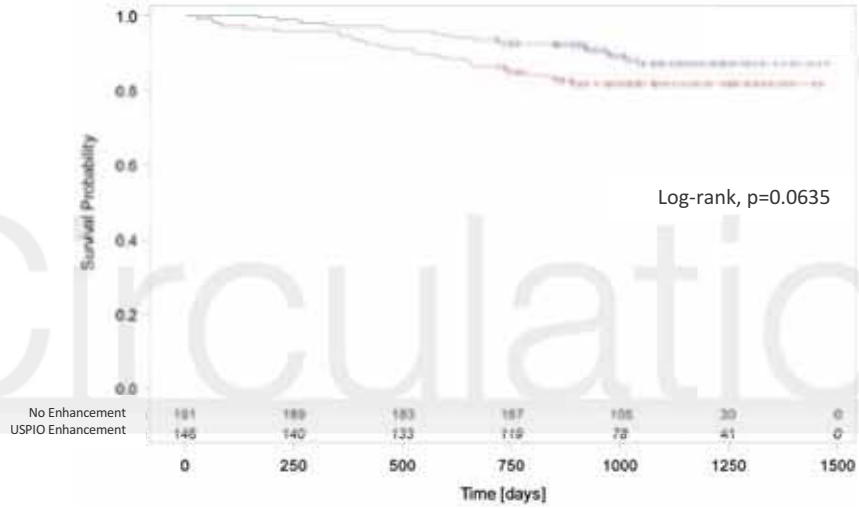
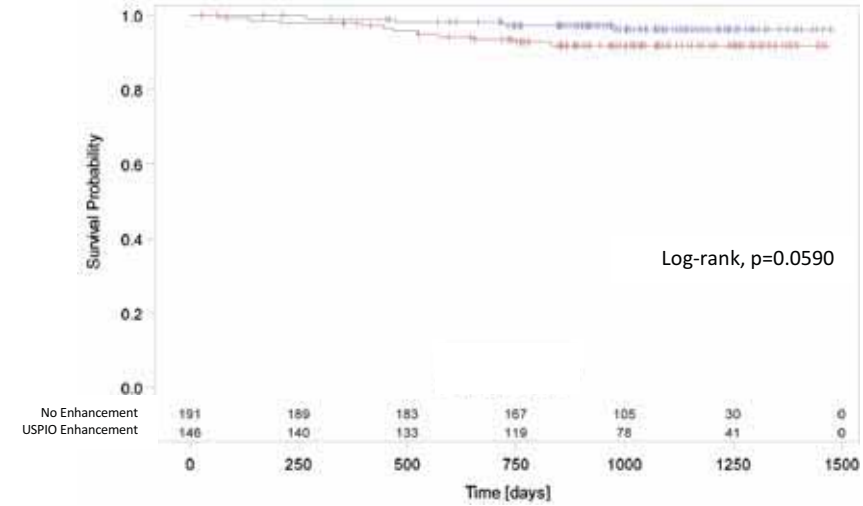


C



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The MA³RS Study Investigators

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