($\rightarrow$ = +0·56, p = 0·003 and $\rightarrow$ = +0·38, p < 0·0·001, respectively). RCF had an independent inverse correlation with bk-PWV ($\rightarrow$ = −0·01, p = 0·01). Systolic blood pressure showed an independent positive correlation with ba-PWV only after adjustment for other biomarkers ($\rightarrow$ = +0·1, p = 0·04). Cholesterol/HDL had an independent inverse correlation with ABPI ($\rightarrow$ = −0·08, p = 0·046). There was no significant association between the other biomarkers and ABPI or PWV.

Conclusion: Hypercholesterolaemia and hypertension need aggressive treatment in this population. Plasma Hcy and RCF levels correlated well with severity of PAD. They are easily measured markers of disease and provide possible targets for further risk factor modification.

The cerebrovascular response to hypercarbia does not support vasoparesis as a mechanism for increases in middle cerebral artery blood flow velocity after carotid endarterectomy

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Objective: It has been proposed that hyperperfusion following carotid endarterectomy (CEA) is due to vasoparesis of maximally vasodilated vessels distal to a carotid stenosis which persists into the postoperative period. We tested this hypothesis by examining the association between the percentage change in mean middle cerebral artery blood flow velocity (mean MCAv) and pre-operative and postoperative cerebrovascular reactivity to hypercarbia.

Method: In patients undergoing carotid endarterectomy (CEA), ipsilateral mean MCAv was recorded using transcranial Doppler (TCD) on the day before and the day after surgery. Hypercarbia was induced by rebreathing and end-tidal CO_2 measured with a side-stream capnograph. Vascular reactivity was quantified as the percentage change in mean MCAv per kPa change in end-tidal CO_2 concentration. The association between vascular reactivity was examined using Spearman's rank correlation coefficient.

Results: Thirty-four patients (27 male), median age 71 (52–83) years, were studied. The median (range) change in mean MCAv post-CEA was 18·4(−26·0 to 208·6)%. The median (range) pre-operative cerebrovascular reactivity to hypercarbia was 18·7(−0·2 to 45·3)% kPa-1, and the postoperative reactivity was 18·5(1·4 to 26·1)% kPa-1. The rank correlation coefficient for the association between the percentage change in mean MCAv and pre-operative cerebrovascular reactivity was −0·08 (p = 0·68) and that for postoperative cerebrovascular reactivity was −0·17 (p = 0·37).

Conclusion: These data do not support an association between vasoparesis as identified by poor CO_2 reactivity and the magnitude of the change in post-CEA mean MCA velocity.

A randomised double-blind placebo-controlled trial of the impact of high-dose statins on the ischaemia-reperfusion injury in elective AAA repair

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Objective: Ischaemia-reperfusion injury (IRI) significantly contributes to AAA-related morbidity and mortality. We performed a double-blind RCT to analyse the impact of high-dose pre-operative statins on IRI following open AAA repair.

Method: Forty patients (36 men), median age 76 (IQR 68–80) years, were randomised into placebo (n = 20) or atorvastatin 80mg o.d. (n = 20) groups, 3 weeks prior to open AAA repair. Blood and urine samples were collected at induction, 5 minutes, 6 and 24 hours following clamp release. Venous blood was analysed (ELISA method) for interleukin 10, sE selectin, sP selectin, soluble intercellular adhesion molecule-1 (sICAM-1), soluble vascular cell adhesion molecule-1 (sVCAM-1) and malondialdehyde (MDA). Arterial blood was analysed for a lactate and alveolar/arterial gradient. Urine was analysed for an albumin/creatinine ratio (ACR).

Results: Intra-group. The placebo group was associated with a significant increase from baseline in: i) IL 10 at 6 hours (p = 0·027); ii) ACR at 5 minutes (p = 0·004), 6 hours (p = 0·001) and 24 hours (p = 0·043); iii) lactate at 5 minutes (p = 0·000). The statin group was associated with a significant increase from baseline in: i) IL 10 at 6 hours (p = 0·000) and 24 hours (p = 0·001); ii) sVCAM at 24 hours (p = 0·043); iii) ACR at 5 minutes (p = 0·000) and 6 hours (p = 0·012); iv) lactate at 5 minutes (p = 0·000). Inter-group. The statin group demonstrated a significant increase in sICAM at baseline (p = 0·04) and 24 hours (p = 0·01) in comparison with placebo.

Conclusion: sICAM and sVCAM elevation, associated with pre-operative statin loading, attenuates IRI-associated end organ damage.

Atorvastatin Therapy: Effects on Reduction Of Macrophage Activity (ATHEROMA). Evaluation using USPIO-enhanced magnetic resonance imaging in carotid disease

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Objective: This randomised double-blind study investigated the effects of low-dose (10mg) and high-dose (80mg) atorvastatin on macrophage activity in carotid atherosclerotic plaques using serial ultra-small super-paramagnetic iron oxide (USPIO)-enhanced MRI. The hypothesis was that treatment with 80mg atorvastatin would demonstrate quantifiable changes in USPIO-enhanced MRI defined inflammation within 12 weeks of therapy.

Method: Forty-seven patients with carotid stenosis >40% on ultrasonography and who demonstrated intraplaque accumulation of USPIO on MRI at baseline were randomised to either 10mg or 80mg atorvastatin daily for 12 weeks. The primary endpoint was change from baseline in signal intensity (ΔSI) on USPIO-enhanced MRI in carotid plaque at 6 and 12 weeks. Transcranial Doppler (TCD) monitoring was also performed for clinical correlation.

Results: Twenty patients completed 12 weeks of treatment in each group. A significant reduction from baseline in USPIO-defined inflammation was observed in the 80mg group at 6 weeks (ΔSI 0·13; p = 0·0003) and 12 weeks (ΔSI 0·20; p < 0·0001). In parallel, there were reductions in cerebral emboli count at 6 weeks (71%; p < 0·0001) and 12 weeks (91%; p < 0·0001) in the high-dose group on TCD. 80mg atorvastatin significantly reduced low-density lipoprotein cholesterol by 29% (p < 0·0001) at 12 weeks.

Conclusion: Aggressive lipid-lowering therapy over a 12-week period is associated with a significant reduction in USPIO-defined inflammation and associated emboli counts. USPIO-enhanced MRI methodology may be a useful imaging biomarker for the screening and assessment of therapeutic response to 'anti-inflammatory' interventions in patients with carotid atherosclerotic lesions.

Activated platelets and coagulation in patients on haemodialysis

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Objective: Patients on haemodialysis (HD) have an increased risk of cardiac events. Controversy exists as to whether these patients have a pro-thrombotic state. We aimed to determine markers of platelet activation and coagulation in patients on HD compared with healthy volunteers.

Method: Platelet function was assessed in 78 patients pre-HD and 78 volunteers by: i) Ultegra rapid platelet function assay using the agonists thrombin receptor activating peptide (TRAP) and arachidonic acid (ASA); ii) flow cytometry of P-selectin expression and fibrinogen binding with/without ADP stimulation; and iii) measuring plasma soluble P-selectin. Coagulation and fibrinolysis were assessed by ELISA determination of thrombin-antithrombin (TAT) and D-dimer, respectively.

Results: ASA-stimulated platelet aggregation was significantly reduced in HD patients, of whom 50 (64%) were on aspirin therapy (median [IQR] 555 [355–671] *versus* 649 [385–675], p < 0·001). TRAP-mediated aggregation was similar in both groups. Unstimulated fibrinogen binding was significantly increased in patients (2·02 [1·48–2·62] *versus* 1·46 [1·15–1·94], p < 0·001) but stimulated fibrinogen was decreased (40·75 [26·7–50·3] *versus* 50·05 [40·6–59·9], p < 0·001). Unstimulated P-selectin was significantly decreased in patients

(0·82 [0·52–1·46] *versus* 1·62 [0·86–2·34], p < 0·001, yet soluble P-selectin was significantly increased (43·26 [13·88–86·7] *versus* 24·67 [13·41–43·32], p = 0·039). Stimulated P-selectin was similar in both groups. Markers of coagulation were significantly increased in patients on HD: TAT 4·59 (2·67–6·04) *versus* 2·84 (1·81–3·82), p < 0·001 and D-dimer 876·5 (434·2–1338·5) *versus* 265·5 (175·0–401·51), p < 0·001.

Conclusion: Patients on HD have a pro-thrombotic state with chronically activated platelets and elevated markers of coagulation. Drug therapy to counteract this pro-thrombotic state should be considered with the aim of preventing both cardiac events and vascular access thrombosis.

Dual antiplatelet therapy in surgery for critical limb ischaemia

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Objective: Patients with critical limb ischaemia have a peri-operative cardiovascular morbidity comparable to patients with an acute coronary syndrome. We hypothesised that peri-operative dual antiplatelet therapy would improve biomarkers of atherothrombosis without causing unacceptable bleeding in patients undergoing surgery for critical limb ischaemia.

Method: In a prospective double-blind randomised controlled trial, 108 patients undergoing infra-inguinal revascularisation or amputation for critical limb ischaemia were maintained on aspirin (75mg daily) and randomised to clopidogrel (600mg prior to surgery, and 75mg daily for 3 days; n = 50) or matched placebo (n = 58). Platelet activation and myocardial injury were assessed by flow cytometry and plasma troponin concentrations, respectively.

Results: Clopidogrel caused a reduction in platelet-monocyte aggregation (30% *versus* 38%; p = 0·007) that was sustained in the postoperative period (p = 0·002). There were 18 troponin-positive events (8 clopidogrel *versus* 10 placebo; OR 0·91; p = 0·863) with clopidogrel causing a greater decline in troponin concentrations (p < 0·001). Clopidogrel did not increase major life-threatening bleeding (7 clopidogrel *versus* 6 placebo; OR 1·4; p = 0·56), or minor bleeding (17 *versus* 12; OR 1·9; p = 0·12). However, blood transfusions were increased (11 *versus* 4; OR 2·8; p = 0·037).

Conclusion: In patients with critical limb ischaemia, peri-operative dual antiplatelet therapy reduces biomarkers of atherothrombosis without increasing life-threatening bleeds. A large-scale randomised controlled trial would establish whether dual antiplatelet therapy improves clinical outcomes in high-risk patients undergoing vascular surgery.

A novel nanocomposite polymer for the development of a new aortic stent graft

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Objective: We have developed an innovative self-expanding, sutureless stent graft for coronary, peripheral and EVAR use that incorporates a NiTi alloy scaffold with a nanocomposite polymer (UCL-Nano^{TM}) with improved haemocompatibility. Because of novel physicochemical and biological properties this new polymer has superior properties to Dacron and PTFE and favours spontaneous endothelialisation. This study assessed the bond strength between the polymer and metal stent over the lifespan of the device.

Method: An atomization spraying method was used to deposit polymer coatings on the NiTi using trialkoxysilane to improve bonding strength without suturing. A tensometer equipped with a 500N load cell measured peel strength of the polymer-coated NiTi alloy. Polymer- coating stability and durability were investigated by a battery of FDA non-clinical tests including accelerated cardiac cycle studies.

Results: A three-times increase in the bond strength of the polymer to the scaffold was achieved using this surface treatment. The nanocomposite coating remained stable after exposure to accelerated biological degradative solutions. The sutureless design of the stent graft demonstrated durability in extensive in vitro testing.

Conclusion: A new stent based on a biocompatible, biostable nanocomposite polymer bonded to an origami-designed folding nitinol alloy has been shown to have durable bonding without the need for sutures. This stent has demonstrated durability in extensive in vitro testing and is ready for in vivo study.

Decellularised porcine ureter (DURE) is a strong, biocompatible and compliance-matched scaffold for tissue engineering of a novel small calibre cardiovascular graft

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Objective: Current synthetic grafts perform poorly in small calibre anastomosis. Autologous conduits are often unavailable due to previous surgery or disease. We aimed to investigate the utility of decellularised porcine ureter as a tissue engineering scaffold for a small calibre cardiovascular graft.

Method: Porcine ureter was decellularised using a Tris buffer, 0·1% SDS and nucleases. Contact and extract cytotoxicity of the acellular scaffold was determined with L929 mouse fibroblast and A549 human cell lines. Decellularised ureter was then assessed biomechanically using uniaxial tensile testing, and compliance, burst pressure and suture retention testing. Controls included porcine femoral artery (FA) and human saphenous vein (HSV) (n = 6 each group).

Results: Decellularisation was confirmed histologically. DURE did not demonstrate contact or extract cytotoxicity. Tensile strength for DURE (6·02 ± 0·82 MPa) was higher than FA (2·53 ± 0·13 MPa; p < 0·0001). At high pressures (80–260 mm Hg), DURE compliance (3·77 ± 1·24% mm Hg-1) matched native artery (2·31 ± 0·44% mm Hg-1) and was more compliant than HSV (1·4 ± 0·34% mm Hg-1; p = 0·037). Burst pressure and suture retention strength for DURE (3071 ± 351mm Hg; 1·94 ± 0·2N) were not significantly different (p > 0·05) from FA (2509 ± 320mm Hg; 2·17 ± 0·87 N) and HSV (3004 ± 444 mm Hg; 2·22 ± 0·75 N).

Conclusion: DURE was biocompatible, of comparable strength with matching or higher compliance than FA and HSV. It may offer an exciting alternative to current prostheses.

The 6-minute walk test provides an accurate measure of exercise capacity for risk assessment before major non-cardiac surgery

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Objective: To assess the validity of the 6-minute walk test (6MWT), undertaken at pre-operative assessment for scheduled major non-cardiac surgery, against a criterion measure, anaerobic threshold (AT), derived from cardiopulmonary exercise testing (CPET). Functional assessment of exercise capacity forms a cornerstone of pre-operative assessment and risk prediction before major surgery. We have previously demonstrated that reporting exercise capacity using maximum exercise tolerance (METs), as recommended by the ACC/AHA, provides a poor test that does not correlate with measured exercise capacity. We propose that the 6MWT may represent a more robust test and, importantly, provide an accurate surrogate for expensive CPET.

Method: Following ethics and research committee approval 15 participants awaiting major non-cardiac surgery entered this study. Oxygen consumption (VO$_2$) at AT was measured by CPET and maximum distance walked during two 6MWTs was recorded. Statistical analysis employed an ordinary least-squares linear regression method, using Pearson's correlation coefficient, to derive the validity co-efficient (r) and the standard error of the estimate (SEE), providing the typical prediction error associated with the prediction of AT from the results of a 6MWT in an individual patient.

Results: We found a validity coefficient of r = 0·76, with a standard error of prediction of AT from distance walked during 6MWT of ±2·4 ml O$_2$ kg^{-1} min^{-1}.

Conclusion: The 6MWT correlates strongly with AT in this study. Based on this encouraging exploratory phase correlation we will now undertake a definitive concurrent validity study. We hope to provide an appropriate surrogate for CPET allowing improved risk assessment and outcome prediction for scheduled major non-cardiac surgery.