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Low Molecular Weight Heparin Significantly Reduces Embolisation After Carotid Endarterectomy — A Randomised Controlled Trial

G.S. McMahon*, S.E. Webster, P.D. Hayes, C.I. Jones, A.H. Goodall, A.R. Naylor

Department of Cardiovascular Sciences, University of Leicester, Clinical Sciences Building, Leicester Royal Infirmary, Leicester LE1 7LX, UK

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Abstract *Objectives:* The administration of unfractionated heparin (UFH) prior to carotid clamping during carotid endarterectomy (CEA) transiently increases the platelet aggregation response to arachidonic acid (AA) despite the use of aspirin. We hypothesized that this phenomenon might be reduced by using low molecular weight heparin (LMWH) resulting in fewer emboli in the early post-operative period.
Methods: 183 aspirinated patients undergoing CEA were randomised to 5000 IU UFH ($n = 91$) or 2500 IU LMWH (dalteparin, $n = 92$) prior to carotid clamping. End-points were: transcranial Doppler (TCD) measurement of embolisation, effect on bleeding and platelet aggregation to AA and adenosine 5′-diphosphate (ADP).
Results: Patients randomised to UFH had twice the odds of experiencing a higher number of emboli in the first 3 h after CEA, than those randomised to LMWH ($p = 0.04$). This was not associated with increased bleeding (mean time from flow restoration to operation end: 23 min (UFH) vs. 24 min (LMWH), $p = 0.18$). Platelet aggregation to AA increased significantly following heparinisation, but was unaffected by heparin type ($p = 0.90$). The platelets of patients randomised to LMWH exhibited significantly lower aggregation to ADP compared to UFH ($p < 0.0001$).
Conclusions: Intravenous LMWH is associated with a significant reduction in post-operative embolisation without increased bleeding. The higher rate of embolisation seen with UFH may be mediated by increased platelet aggregation to ADP, rather than to AA.

* Corresponding author. Tel.: +44 116 252 3252; fax: +44 116 252 3179.
E-mail address: gregmcmahon@hotmail.com (G.S. McMahon).

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Introduction

The causes of stroke after carotid endarterectomy (CEA) are multifactorial.[1,2] Intra-operative stroke (i.e. apparent upon recovery from anaesthesia) tends to follow inadvertent technical error (haemodynamic failure, intra-operative embolisation).[3] Post-operative stroke can follow either hyperperfusion or haemorrhage, but the most common cause is early post-operative carotid thrombosis (POCT).[2,3]

POCT was previously thought to be unpredictable and unpreventable. However, it is now generally accepted that stroke due to POCT is preceded by 1–2 h of increasing embolisation.[4,5] This reliable forecaster of cerebral ischaemia can be diagnosed using transcranial Doppler (TCD) and progression onto stroke can be prevented by the use of an incremental dose of Dextran.[6]

Notwithstanding this ability to recognise and then intervene in high risk patients for POCT, it would clearly be preferable to determine whether any 'patient factor' mediated the susceptibility to early thrombosis. Previous work from this unit has shown that the platelets of patients with higher rates of post-operative embolisation were more sensitive to stimulation by adenosine 5'-diphosphate (ADP).[7] A subsequent randomised trial showed that the magnitude of post-operative embolisation after CEA was significantly reduced in patients randomised to 75 mg clopidogrel the night before surgery (in addition to their normal aspirin).[8] However, an unexpected finding from that study was that immediately following administration of unfractionated heparin (UFH), and prior to carotid clamping, platelet aggregation to arachidonic acid (AA) *increased* tenfold despite all of the patients being on aspirin.[9,10] This was not related to the known enhancing effects of UFH on the platelet response to ADP and collagen[10] and is clearly counter-intuitive to classical teaching regarding the irreversible effect of aspirin on the cyclo-oxygenase pathway.[11]

Low molecular weight heparin (LMWH) has a number of pharmacological advantages over UFH, some of which are directly influenced by its shorter chain length.[12–14] The rationale underlying the current study was that, since it is recognised that a number of platelet responses was affected less with LMWH than with UFH,[12,13] the use of LMWH might be associated with less platelet activation by AA (following heparin administration) and, consequently, fewer emboli in the early post-operative period.

Materials and Methods

Study design

Approval was granted from the Local Research Ethics Committee for a double-blinded randomised controlled trial in consecutive patients scheduled for CEA at the Leicester Royal Infirmary, UK. Patients gave their written informed consent, and all received 75 mg daily aspirin for at least 2 weeks prior to surgery. At commencement of the trial, computer-generated randomisation of treatment method (LMWH vs. UFH) were consecutively numbered and sealed in opaque envelopes. Starting with envelope number one, these were allocated on a consecutive basis immediately following induction of anaesthesia. Prior to carotid clamping patients were anticoagulated either in our standard fashion, with 5000 IU UFH (Multiparin, CP Pharmaceuticals, Wrexham, UK) or with 2500 IU dalteparin sodium (Fragmin, Pfizer, New York, USA) intravenously. Because our usual practice is to anticoagulate with a standard, patient-independent dose of UFH, we aimed to use an equally effective, universal dose of LMWH, as suggested by the drug's manufacturers.

Exclusion criteria included: refusal to give consent; aspirin intolerance; absence of a transcranial window for TCD monitoring; patients on other anticoagulants or antiplatelet agents within 14 days pre-operatively (heparin, warfarin, dipyridamole or clopidogrel). Consequently, all individuals undergoing ''urgent'' carotid endarterectomy were excluded, since our practice is to manage these patients with a continuous intravenous infusion of unfractionated heparin until surgery. Power calculations were performed based on previous studies, which suggested that randomizing 180 patients would enable an 80% chance of detecting a 20% difference in embolisation between the two groups and that a 20% difference in platelet response would be seen in 48 patients (24 in each group).

Blood collection

Blood samples were taken at four time-points: at induction of general anaesthesia; then at 3, 120 and 330 min following systemic heparinisation. All blood samples were taken from an indwelling arterial line into vacutainer tubes (Becton Dickinson, Oxford, UK), with the first 3 ml of blood taken into EDTA (0.184 M) and used to obtain a full blood count (A^CT Diff™ Analyser, Coulter Electronics Ltd, Luton, UK), and subsequent samples were taken into 0.105 M buffered sodium citrate solution for immediate processing for platelet aggregometry.

Platelet aggregometry

Based on a power calculation, ex vivo platelet aggregometry was performed in the last 65 patients recruited (32 patients in the LMWH group; 33 patients in the UFH group). Platelet-rich plasma was prepared by centrifugation of the citrated samples at 150×g for 20 min. Born-type aggregometry[10] was used to assess platelet aggregation in response to a high concentration of AA (4×10^{-3} mol/L; Sigma, Poole, Dorset, UK) and an intermediate concentration of ADP (3×10^{-6} mol/L; Sigma, Poole, Dorset, UK) using a PAP4 aggregometer (BioData Corp, Horsham, USA). The concentrations of agonists were chosen from previous titrations, and were designed to test the efficacy of the patients' aspirinisation (with maximal AA) and the variation in the patients' platelets' response to ADP. Aggregation was performed over a 10-min period and recorded as the percentage of maximal aggregation compared to autologous, platelet poor plasma. Where technical failure of platelet aggregometry occurred (8 instances across the four AA-mediated aggregometry time-points; 12 in the ADP-mediated aggregometry) the results were not plotted.

Operation and intra-operative monitoring

All patients underwent a standardized CEA with the use of normotensive, normocarbic general anaesthesia, and the

routine placement of a Pruitt-Inahara intra-luminal shunt. There were six consultant surgeons either performing the CEA or supervising a trainee. Independent pharmacists dispensed either 5000 IU UFH or 2500 IU LMWH, and systemic heparinisation was administered intravenously by the anaesthetist 4 min prior to carotid clamping and insertion of the shunt. The surgeon was blinded to the type of heparin used. Continuous TCD monitoring of the blood flow velocity in the ipsilateral middle cerebral artery was performed for the duration of the operation. All TCD waveform data were stored on digital audiotape for blinded offline analysis by the same vascular technician. Post-operative embolisation was quantified with the use of standardized consensus criteria.[15] The carotid arteriotomy was closed with a Dacron patch (W. L. Gore, Flagstaff, Arizona, USA) in all cases, and completion angioscopy was performed in patients prior to restoration of flow.[1]

Post-operative monitoring

All patients were monitored for 3 h post-operatively with TCD. Using pre-existing Unit criteria, any patient with more than 25 emboli in a 10 min period was given a 30 ml intravenous bolus of Dextran-40 (Pharmacia Ltd, Milton Keynes, United Kingdom), followed by an infusion starting at 20 ml/h and then systematically increased until the rate of embolisation diminished. Thereafter Dextran was continued for 12 h.

Bleeding tendency

The time from restoration of blood flow to removal of the surgical drapes was used to estimate the time required to secure haemostasis, and acted as a surrogate measure of excess bleeding.

Statistical analysis

Discrete data were analyzed using SPSS version 14.0.0 for Windows (SPSS Inc., Chicago, Illinois, USA) with the use of contingency tables (Fisher's exact test), and continuous data were analyzed with the use of a 2-tailed Mann–Whitney *U* test. Data are presented as mean ± SD. Probability values <0.05 were considered statistically significant.

Whilst 50% of patients will have one or more emboli detected in the early post-operative period, only 5% will develop sustained embolisation,[16] making meaningful statistical analysis difficult. In order to be able to demonstrate a difference between the two groups, as in previous work,[8] an arbitrary distinction between ''low embolisation'' and ''high embolisation'' was used, in this case the upper quartile (11 emboli).

Results

Epidemiology

Of the 229 patients undergoing CEA during the study period 46 (21%) were excluded (Fig. 1). The 183 (79%) remaining patients were randomised to either LMWH ($n = 92$) or UFH ($n = 91$). The two groups were demographically matched (Table 1).

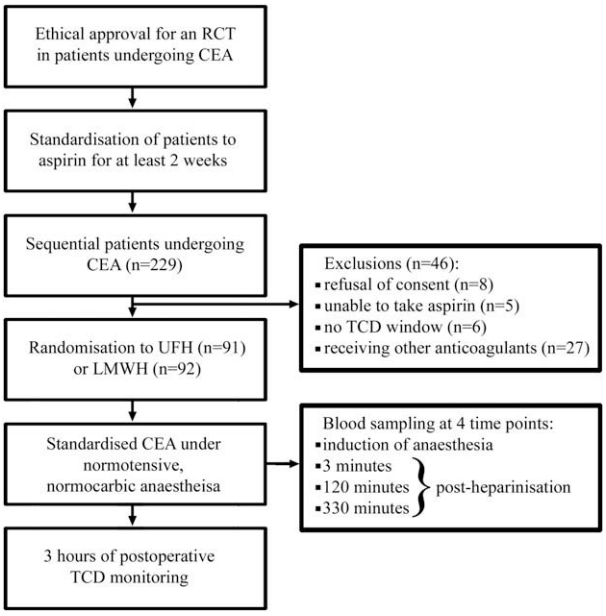

Figure 1 Study design and recruitment and breakdown of patients.

Post-operative embolisation

The mean number of post-operative emboli was 12 in the LMWH group, vs. 18 in the UFH group ($p = 0.247$), but patients randomised to UFH were found to be twice as likely to be ''higher'' embolisers (29 of 91; 31.9%) than those randomised to LMWH (17 of 92; 18.5%) (Fig. 2b). This equates to an odds ratio of 2.06; 95% CI, 1.04–4.10; $p = 0.0418$, Fisher's exact test. Fig. 2 illustrates the total number of patients in each group, showing the proportion experiencing ''high embolisation'' (shaded bars).

Two patients (2.2%) in the LMWH group received Dextran therapy to control high-grade embolisation, whereas four

Table 1 Demographic breakdown of trial patients.

Variable *N*	UFH 91	LMWH 92	*p* value
Age/years	67 ± 10.3	70 ± 8.3	0.13
Sex			
Male	70 (77%)	69 (75%)	0.76
Female	21 (23%)	23 (25%)	
Weight/kg	76 ± 12.7	80 ± 14.2	0.64
Hypertension	69 (76%)	75 (82%)	0.35
Diabetes	14 (15%)	22 (24%)	0.15
Current smoker	20 (22%)	25 (27%)	0.41
Presentation			
Asymptomatic	17 (19%)	13 (14%)	0.41
Stroke	24 (28%)	24 (26%)	0.97
TIA	34 (37%)	43 (47%)	0.20
Amaurosis fugax	16 (18%)	12 (13%)	0.40
Mean carotid stenosis/%	77 ± 8	80 ± 8	0.29

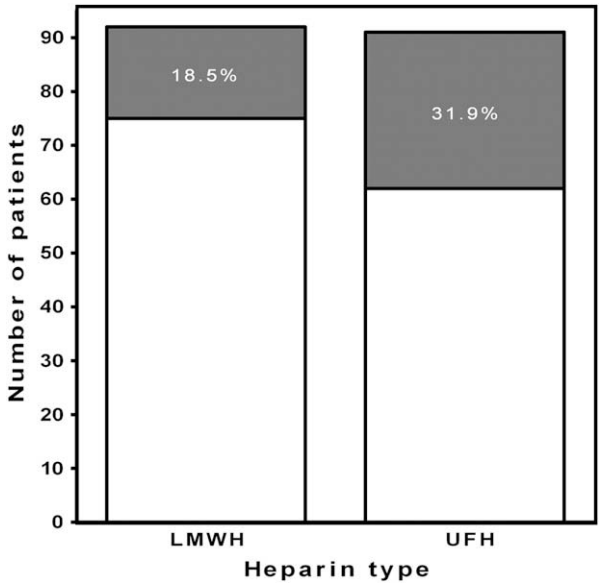

Figure 2 Proportion of patients randomized to 5000 IU UFH or 2500 IU LMWH intravenously prior to carotid clamping experiencing post-operative high-rate embolisation (shaded bars), compared to those who did not (open bars) ($p = 0.04$).

patients (4.4%) in the UFH group received Dextran ($p > 0.05$).

Perioperative haemostatic function

One (1.1%) patient in each group required re-exploration for post-operative bleeding. The length of time taken from flow restoration to skin closure was used as an indirect marker of haemostasis, and was not significantly different between the two groups: the median time from restoration of flow to removal of the drapes was 23 ± 8.5 min in the LMWH group and 24 ± 7.5 min in the UFH group ($p = 0.18$).

Perioperative morbidity and mortality

The 30-day disabling stroke or death rate was 2.2% (2 patients) in both the LMWH and UFH groups. One patient in the UFH group suffered an acute, intra-operative carotid artery dissection and a second patient died following a post-operative intra-cerebral haemorrhage, likely related to post-operative hyperperfusion on post-operative day 11. In the LMWH group, one patient suffered an intra-operative stroke due to embolic occlusion of the ipsilateral middle cerebral artery following shunt insertion. The second patient died following a myocardial infarction on post-operative day 5. None of these patients experienced high embolisation post-operatively. Complications were evenly distributed amongst the six consultant surgeons.

Ex vivo platelet aggregation

At induction of anaesthesia, prior to heparin, platelet aggregation to AA (4×10^{-3} mol/L) was less than 20% of maximum in 50/65 (77%) patients, indicating adequate aspirinisation. Seven patients in the LMWH group and 8 (24%) patients in the UFH group were still responsive to AA (range 22.1%—90.3%), suggestive of ''aspirin failure''[17] and were subsequently excluded from the analysis of the platelet response to AA. The level of aggregation in response to AA prior to heparin in the remaining 50 patients was similar in both groups ($8.3 \pm 4.2\%$ for LMWH vs. $8.7 \pm 4.4\%$ for UFH; $p = 0.66$) (Fig. 3).

Three minutes after the administration of heparin, the platelet response to AA increased dramatically (six to seven-fold) to $56.9 \pm 28.2\%$ in the LMWH group ($p < 0.0001$) and to $57.6 \pm 26.8\%$ in the UFH group ($p < 0.0001$). However, this increase was not significantly different between the two heparin groups ($p = 0.75$). The platelet response to AA subsequently fell so that by 120 min it was $38.3 \pm 32.4\%$ in the LMWH group and $27.3 \pm 26.1\%$ in the UFH group ($p = 0.46$), and at 330 min was $29.4 \pm 31.6\%$ and $21.4 \pm 20.7\%$ in the LMWH and UFH groups respectively ($p = 0.81$). This fall in the AA response occurred without further aspirin therapy.[9,10]

Fig. 4 shows platelet aggregation in response to ADP at a concentration of 3×10^{-6} mol/L for all 65 subjects. At induction of anaesthesia, the mean platelet response was similar in both groups ($27.8 \pm 13.1\%$ in the LMWH group and $31.7 \pm 12.2\%$ in the UFH group ($p = 0.10$)). Three minutes after the administration of heparin, aggregation in response to ADP increased to $44.1 \pm 16.4\%$ in the LMWH group ($p < 0.0001$). The increase observed in the UFH group was even greater, rising to $63.3 \pm 11.6\%$ ($p < 0.0001$). By 120 min the platelet response to ADP had fallen slightly in both groups but remained significantly greater in patients randomised to UFH ($48.6 \pm 15.0\%$) compared to the LMWH group ($40.0 \pm 14.4\%$; $p = 0.02$). At 330 min the UFH group still showed greater aggregation to ADP ($45.1 \pm 15.3\%$) compared to the LMWH group ($37.4 \pm 15.2\%$), which remained statistically significant ($p = 0.04$).

Discussion

These findings confirm our previous observations, that systemic heparinisation causes a transient increase in *ex vivo* platelet aggregation in response to AA, despite adequate aspirinisation.[9,10] We have extended these laboratory observations to a randomised clinical study and shown a potential clinical benefit of LMWH compared to UFH in terms of reduced POCT.

Post-operative embolisation has a well-proven relationship to post-operative cerebral ischaemic events, and has been shown to be an effective surrogate outcome measure for stroke risk.[4,5] By using this surrogate end-point we were able to show a significant effect of the different heparins on a smaller cohort than would be required using the clinical end-point of stroke.

The thromboembolic material that leads to POCT is invariably platelet-rich.[1,2] However, while antiplatelet therapy has been shown to reduce the risk of post-operative stroke,[18] embolisation does still occur despite adequate aspirin therapy.[7] In this study we have shown that LMWH produced a lower level of POCT than UFH, which raises the question of why LMWH appears to have a beneficial effect.

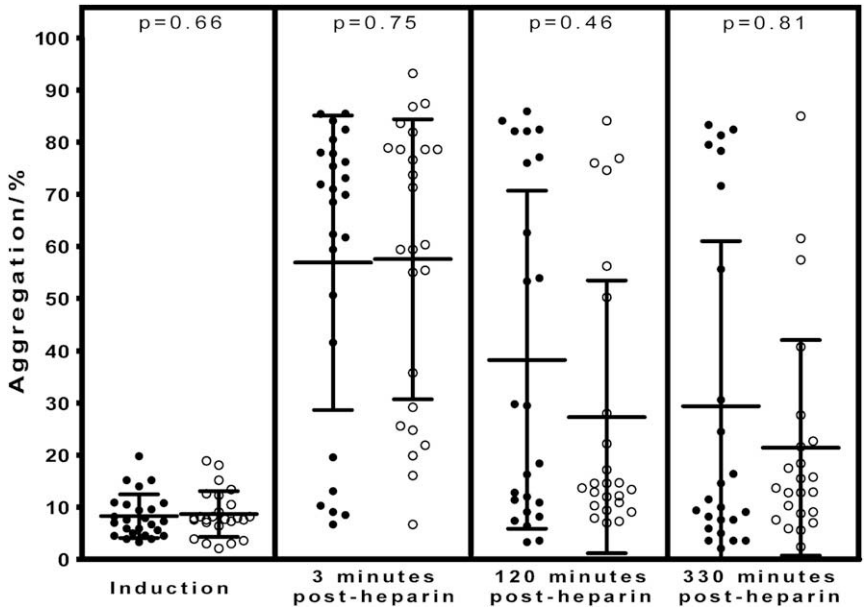

Figure 3 Platelet aggregation in response to 4×10^{-3} mol/L arachidonic acid in 50 patients undergoing CEA. Closed circles; LMWH group ($n = 25$); open circles; UFH group ($n = 25$), horizontal bar represents mean ($\pm$ SD). 15 patients who exhibited greater than 20% platelet aggregation to AA at induction have been excluded.

The success of vascular reconstruction has relied upon the anticoagulant properties of heparin since the inception of these techniques,[19] and intravenous UFH has traditionally been the drug of choice for the prevention of arterial thromboembolic events. Compared with UFH, LMWH is considered to induce a more stable and predictable anticoagulant dose response, and to have a greater ratio of anti-factor Xa activity to anti-factor IIa activity, which reduces the generation and activation of thrombin.[20] In addition to reducing the incidence of venous thromboembolism,[21] LMWH has previously been shown to be effective in preventing arterial thrombosis,[22] and the findings of this study support this in a group of patients with carotid artery disease.

However, it is known that while heparin inhibits the enzymic effects of thrombin, including thrombin-induced platelet aggregation, it paradoxically potentiates platelet aggregation induced by a range of platelet agonists, including ADP, TRAP, PAF and epinephrine.[12,23–25] The binding of heparin to platelets is known to increase with increasing molecular weight,[26] and LMWH is less effective

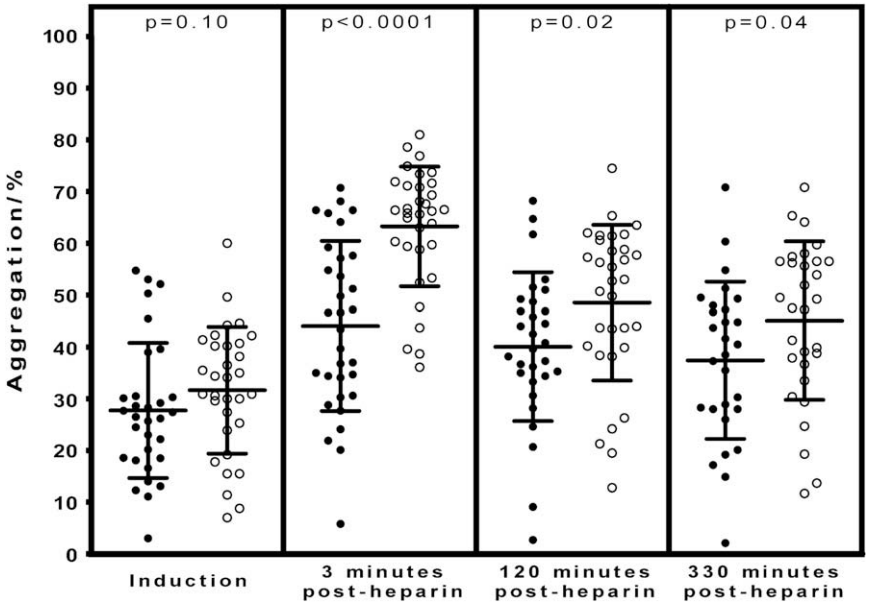

Figure 4 Platelet aggregation in response to 3×10^{-6} mol/L adenosine diphosphate in 65 patients undergoing CEA. Closed circles; LMWH group ($n = 32$); open circles; UFH group ($n = 33$), horizontal bar represents mean ($\pm$ SD).

than UFH in inducing several pathways of platelet activation.[12,13,27] Here we reproduced our earlier observations of a transient failure of aspirin therapy immediately following systemic heparinisation. As before,[9,10] this was seen in patients who had been adequately aspirinated and was therefore unrelated to ''aspirin resistance''. As previously described, the inhibitory effect of aspirin was subsequently regained by the patients' platelets over a few hours, without any further therapy. Since the major antithrombotic effect of aspirin is irreversible, via the acetylation of platelet cyclo-oxygenase-1 which inhibits thromboxane A_2 synthesis,[11] and since platelets do not possess a nucleus from which to synthesize new COX-1, this recovery is not attributable to restoration of COX-1 activity in the platelets. However, although systemic heparinisation resulted in a significant increase in the *ex vivo* platelet aggregation response to AA, there was no significant difference in this increased response between heparin types, despite the observed benefit in embolic signals in the patients. The mechanism and clinical significance underlying this heparin-induced increase in platelet aggregation to AA remain to be resolved.

In contrast, although we observed no significant difference between the effects of UFH and LMWH on AA-induced platelet aggregation, we found that the platelets of patients receiving UFH were significantly more responsive to ADP-induced aggregation than the patients who received LMWH. Importantly, this difference persisted into the immediate post-operative period, with the platelets of the patients in the UFH group remaining significantly more responsive to ADP-induced aggregation 330 min following heparinisation. This difference may, in part, explain the difference observed in post-operative embolisation, and is compatible with our previous observation that the response to ADP is a significant predictor of embolisation risk.[7]

The implementation of effective monitoring and quality-control techniques[4] has corresponded with a decline in intra-operative stroke rates,[28] and a re-evaluation of the pre-eminence of ''technical error'' as the cause of CEA-related stroke.[2] The importance of patient-specific factors in POCT is increasingly recognised.[7,29,30] Studies from this unit have shown that patients undergoing CEA have a ''thromboembolic potential'', which remains stable over time and is predictable pre-operatively by the *ex vivo* platelet response to ADP stimulation.[7,29] Furthermore, we have demonstrated that preoperative platelet ADP-inhibition with clopidogrel significantly reduces post-operative embolisation.[8] Following completion of the current trial, all patients undergoing CEA in our unit now are given a single 75 mg dose of clopidogrel the night before surgery.

It could be argued that a weight-adjusted dosing of the heparins may have provided a more reliably standardized anticoagulation, and that the patients' response could have been formally assessed. Nonetheless, although a relatively small sample size, both heparin regimes provided adequate anticoagulation at the time of carotid clamping, evidenced by the absence of proximal carotid thromboses. However, it is accepted that our findings may have been partly influenced by differences in the pharmacological effects of the two heparins, aside from their impact on platelet responsiveness.

In conclusion, this study has shown that intra-operative anticoagulation with LMWH (2500 IU dalteparin) rather than UFH (5000 IU heparin) was associated with a significant (twofold) reduction in higher rate embolisation following CEA, without an increase in bleeding. Somewhat surprisingly heparin type did not influence the immediate and transient *ex vivo* increase in platelet aggregation to AA. While further studies are required to establish the mechanism and clinical significance of heparin's effect on the platelet aggregation to AA, this study has further underlined the potential value of targeted ADP-inhibition in patients undergoing CEA. Whilst LMWH is not currently licensed for intravenous use in this setting, the results of this study would support its further evaluation as an alternative, and perhaps superior, anticoagulant for invasive vascular procedures.

Conflict of Interest Statement

There were no conflicts of interest involving any of the authors.

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