Randomized trial

Randomized clinical trial of the antiplatelet effects of aspirin–clopidogrel combination *versus* aspirin alone after lower limb angioplasty

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Background: **There is a high risk of reocclusion after successful lower limb angioplasty. Platelets play a central role in this process. The aim of this study was to investigate the antiplatelet effect of a combination of aspirin and clopidogrel compared with aspirin alone in patients with claudication undergoing endovascular revascularization.**

Methods: **This was a double-blind randomized placebo-controlled trial. Some 132 patients were randomized to clopidogrel and aspirin or placebo and aspirin, with a loading dose 12 h before endovascular intervention. Flow cytometric measurements of platelet fibrinogen binding and P-selectin expression were taken as measures of platelet function at baseline, 12 h after the loading dose, and 1 h, 24 h and 30 days after intervention.**

Results: **Within 12 h of the loading dose, platelet activation in the clopidogrel group had decreased (P-selectin by 27·3 per cent, $P = 0{\cdot}017$; fibrinogen binding by 34·7 per cent, $P = 0{\cdot}024$; stimulated fibrinogen binding by 49·2 per cent, $P < 0{\cdot}001$). No change was observed in the placebo group. Platelet function in the clopidogrel group was significantly suppressed compared with baseline at 1 h, 24 h and 30 days after endovascular intervention (stimulated fibrinogen binding by 53·9, 51·7 and 57·2 per cent respectively; all $P < 0{\cdot}001$).**

Conclusion: **A combination of clopidogrel and aspirin inhibited platelet function more than aspirin alone in patients with claudication before and after angioplasty.**

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Introduction

Intermittent claudication is a common problem affecting up to 10 per cent of the population over the age of 50 years[1–4], with a higher prevalence in men. Endovascular recanalization by angioplasty with or without stenting is now widely used to provide symptomatic relief from intermittent claudication, with low associated morbidity and mortality rates[3,4]. Restenosis and reocclusion remain limitations of the long-term effectiveness of endovascular recanalization. At 5 years after angioplasty for occlusion of the femoropopliteal vessels, only 35 per cent of vessels remain patent[5]. Patency rates are better after angioplasty for iliac occlusions, although rates of less than 60 per cent are recorded after 3 years[6,7]. Angioplasty of stenoses rather than occlusions is associated with slightly better patency rates[8].

Platelet activation, adhesion and aggregation at the site of angioplasty play a pivotal role in the subsequent development of restenosis and reocclusion[9]. This is thought to be primarily through thrombus formation, but in addition by release of activated platelets. Platelet-derived growth factor induces migration and proliferation of smooth muscle cells in the intima[10], eventually leading to myointimal hyperplasia[11].

The Antiplatelet Trialists' Collaboration concluded in a meta-analysis that antiplatelet treatment is of value in maintaining patency in patients with peripheral arterial disease undergoing peripheral angioplasty[12]. Furthermore, combining antiplatelet drugs such as dipyridamole and aspirin reduced the risk of restenosis and reocclusion after endovascular intervention even further[13,14]. This suggests that the more effective the antiplatelet treatment used, the better the long-term patency.

The aim of this experimental study was to compare the effect of a combination of aspirin and clopidogrel on platelet function with that of aspirin only in patients with lifestyle-limiting intermittent claudication. The combination of aspirin and clopidogrel is often recommended in patients with coronary heart disease undergoing angioplasty; in contrast, patients in most UK centres are advised to stop clopidogrel before planned angioplasty for peripheral arterial disease.

Patients and methods

Eligibility criteria

All patients between the ages of 18 and 80 years referred to the Vascular Unit, Aberdeen Royal Infirmary with lifestyle-limiting claudication of the legs, and duplex imaging that showed arterial stenosis or occlusion in either the aortoiliac or femoropopliteal segments suitable for angioplasty, were considered for participation in the study. Eligible participants were included if they were able to provide informed consent and satisfied inclusion and exclusion criteria (*Table 1*). Patients were recruited by the first author between March 2002 and January 2003. Approval for the study was granted by the local ethics committee. Permission for Sanofi-Synthelabo, Guildford, UK, to supply clopidogrel for this study was obtained from the Medicines Control Agency.

Interventions

Patients were randomized to receive either 75 mg clopidogrel and 75 mg aspirin daily for 30 days with a loading dose of 300 mg clopidogrel administered 12 h before planned intervention, or 75 mg aspirin and placebo daily, with a 'loading dose' of placebo administered 12 h before intervention. The drugs were supplied in identical packs by the Trial Drugs Pharmacy Department. The placebo was independently sourced by the Trial Drugs Pharmacy and not supplied by the producing company. Pharmacists dispensed placebo or active drug packs according to a computer-generated randomization process that matched the control and treatment groups with respect to sex, diabetes and smoking status using a minimization method. The decision to accept or reject participants was made and informed consent obtained from participants before randomization ensuring allocation concealment. The code was held by the Trial Drugs Pharmacy Department and was only revealed to the researchers once recruitment, data collection and laboratory analyses were complete.

Table 1 Inclusion and exclusion criteria

Inclusion criteria
Haemoglobin > 10 g/l
Platelet count > 150 × 10^9/l
Aspartate aminotransferase, alkaline phosphatase, γ-glutamyltransferase < 3 times upper normal limit
Creatinine < 2 times upper normal limit
Body mass index < 33
Age 18–80 years
No contraindication to either aspirin or clopidogrel
Exclusion criteria
History of haematological malignancy
Acute illness within 14 days of randomization
Transfusion of whole blood or red cells within 14 days or randomization
Known or suspected drug or alcohol abuse
On steroids
On warfarin or heparin
History of bleeding diathesis or coagulopathy
History of severe neutropenia (neutrophil count < 1·8 × 10^9/l)
History of thrombocytopenia (platelet count < 150 × 10^9/l)

Patients underwent digital subtraction angiography followed by endovascular intervention as indicated. Endovascular procedures were performed by one of two experienced consultant interventional radiologists.

Blood samples were taken at baseline before clopidogrel or placebo, 12 h after administration of the loading dose and just before intervention, then at 1 h, 24 h and 30 days after endovascular intervention. Platelet function was assessed by whole-blood flow cytometry. The primary endpoint was the level of platelet responsiveness to stimulation measured as the percentage of adenosine 5′-diphosphate (ADP)-stimulated platelets binding fibrinogen at each time point. Secondary outcomes included level of platelet activation measured in terms of percentage of resting platelets expressing P-selectin and percentage binding fibrinogen.

Blood samples were collected using a 21-G needle inserted into an antecubital vein with the cuff applied to the upper arm. The cuff was removed once the first trickle of blood appeared into the first of two 1 : 10 3·2 per cent sodium citrate Vacutainers® (Becton Dickinson, Oxford, UK). For measurement of platelet activation, 50 μl blood was transferred immediately from the second sodium citrate container using a micropipette and diluted in 450 μl buffer containing 10 mmol/l HEPES, 145 mmol/l sodium chloride, 5 mmol/l potassium chloride and 1mmol/l magnesium sulphate, pH 7·4.

Whole-blood flow cytometry

Platelet fibrinogen binding and P-selectin expression were measured by flow cytometry of diluted whole blood as described previously[15,16]. The test was performed in a 'resting' sample of diluted whole blood, and also after *ex vivo*

stimulation with 10 μM ADP. Whole-blood flow cytometric measurement of resting platelet activation reflected the situation *in vivo*. The results were reported as percentage of platelets expressing P-selectin or binding fibrinogen.

Statistical analysis

For calculation of sample size, platelet responsiveness to stimulation was chosen as the primary outcome variable. In a study by Moshfegh *et al.*[17], a combination of clopidogrel and aspirin reduced ADP-stimulated platelet activation by approximately 50 per cent compared to baseline, in contrast to aspirin alone which had no significant effect ($P < 0{\cdot}001$). Based on published normograms and prediction of the proportion of patients expected to respond to aspirin alone *versus* aspirin and clopidogrel, a sample size of 100 was required to obtain a power of 0·8 with a 0·05 level of significance.

Data analysis was carried out according to a pre-established plan. Between-subjects ANOVA was used to compare the clopidogrel and placebo groups. $P < 0{\cdot}050$ was accepted as statistically significant. Within-subjects ANOVA was used to estimate the treatment effect; 95 per cent confidence intervals for the treatment effect were calculated. The χ^2 test or Fisher's exact test was used to compare the incidence of minor adverse events in the two groups.

Results

One hundred and thirty-two patients with claudication were recruited and randomized, 65 to aspirin with placebo (placebo group) and 67 to aspirin plus clopidogrel (clopidogrel group) (*Fig. 1*). Seven patients were excluded after randomization because of failure to attend for angiography or the diagnosis of malignancy after randomization but before administration of treatment. A total of 125 proceeded to angiography, 103 of whom underwent vascular intervention; in 22 patients endovascular intervention was deemed not feasible or too risky mainly owing to run-off being a single patent calf vessel. Duplex examination failed to detect significant proximal calf vessel disease in these patients which substantially increased the risk of intervention. Forty-nine patients in the placebo group and 54

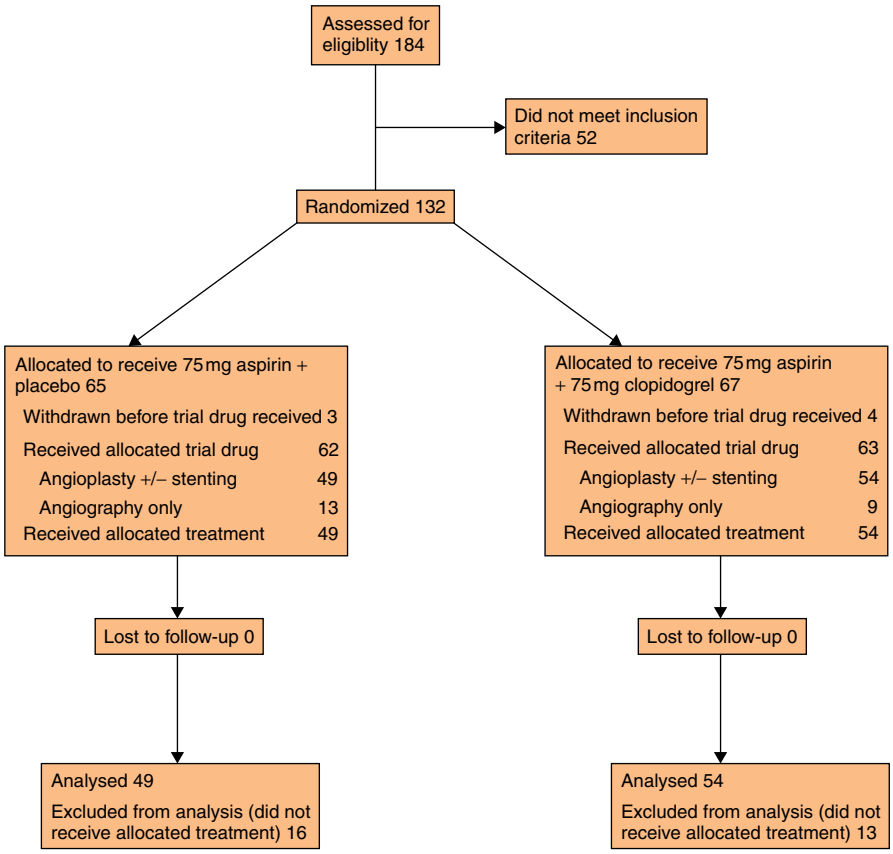

Fig. 1 Flow diagram of trial participants

Table 2 Baseline clinical characteristics of 132 patients with claudication

	Placebo Group ($n = 65$)	Clopidogrel group ($n = 67$)
Sex ratio (M : F)	50 : 15	52 : 15
Mean (range) age (years)	65·4 (46–80)	66·1 (43–80)
Smoking		
Never smoked	3 (5)	5 (7)
Ex-smoker > 1 year	27 (42)	28 (42)
Ex-smoker < 1 year	13 (20)	11 (16)
Smoker	22 (34)	23 (34)
Diabetes*	11 (17)	12 (18)
Mean(s.d.) serum cholesterol (mmol/l)	3·7(2·2)	4·2(2·0)
Mean(s.d.) body mass index	26·1(3·9)	25·5(4·1)
Median (range) ABPI	0·63 (0·36–1·14)	0·65 (0·36–0·91)
Intervention		
None	3	4
Angiography only	13	9
Transluminal PTA	29	33
Subintimal PTA	10	6
Stenting	10	15
Site of disease treated		
None	16	13
Aortoiliac segment	15	16
Femoropopliteal segment	34	37
Aortoiliac and femoropopliteal segments	0	1

*Values in parentheses are percentages. ABPI, ankle : brachial pressure index. PTA, percutaneous transluminal angioplasty.

in the clopidogrel group underwent angioplasty. *Table 2* shows the baseline demographics and clinical details of the patients in both groups, the type of intervention performed and the site of disease treated. None of these patients was lost to follow-up. All follow-up visits were completed by March 2003.

Four patients in the placebo group stopped the trial medication early because of a rash (two), loss of medication (one) or voluntarily (one). Seven patients in the clopidogrel group stopped taking the trial medication early because of a rash (two), upper gastrointestinal bleeding (one), epigastric pain (one), ischaemic stroke (one), loss of medication (one) and for no apparent reason (one). Two patients failed to take their loading dose on time and one 30-day postintervention visit took place on day 38. Analysis was by intention to treat and results from all patients who underwent endovascular intervention were analysed, irrespective of compliance with trial medication.

Platelet responsiveness to stimulation and platelet activation

ADP-stimulated platelet fibrinogen binding, a surrogate measure of platelet responsiveness to stimulation, decreased by 49·2 per cent within 12 h of administration of clopidogrel ($P < 0·001$) (*Table 3*). No significant change in ADP-stimulated fibrinogen binding was observed in the placebo group. Resting platelet activation was also significantly diminished from baseline within 12 h of the loading dose of clopidogrel as measured by P-selectin expression (27·3 per cent reduction; $P = 0·017$) and fibrinogen binding (34·7 per cent reduction; $P = 0·024$). No significant

Table 3 Platelet function in placebo and clopidogrel groups

	Placebo group ($n = 49$)	*P versus* baseline (Within-subjects ANOVA)	Clopidogrel group ($n = 54$)	*P versus* baseline (Within-subjects ANOVA)	*P* (Between-subjects ANOVA)
Resting P-selectin expression (%)					0·03
Baseline	0·89 (0·72, 1·07)		0·94 (0·69, 1·19)		
12 h after loading dose	0·88 (0·68, 1·08)	0·872	0·68 (0·49, 0·87)	0·017	
1 h after intervention	0·96 (0·73, 1·19)	0·526	0·59 (0·46, 0·72)	0·001	
24 h after intervention	0·99 (0·80, 1·19)	0·314	0·75 (0·57, 0·93)	0·205	
30 days after intervention	0·98 (0·75, 1·21)	0·491	0·65 (0·49, 0·79)	0·009	
Resting fibrinogen binding (%)					0·026
Baseline	2·53 (1·6, 3·46)		2·84 (2·12, 3·55)		
12 h after loading dose	2·57 (1·81, 3·33)	0·952	1·85 (1·23, 2·47)	0·024	
1 h after intervention	2·93 (1·95, 3·92)	0·595	1·95 (1·37, 2·53)	0·026	
24 h after intervention	2·73 (1·73, 3·72)	0·788	1·94 (1·26, 2·62)	0·065	
30 days after intervention	2·59 (1·73, 3·47)	0·915	1·68 (1·27, 2·09)	0·005	
ADP-stimulated fibrinogen binding (%)					< 0·001
Baseline	74·29 (68·87, 79·32)		70·04 (64·77, 75·31)		
12 h after loading dose	70·66 (64·59, 76·63)	0·197	35·89 (29·61, 42·18)	< 0·001	
1 h after intervention	68·08 (61·97, 74·18)	0·052	32·39 (26·47, 38·31)	< 0·001	
24 h after intervention	61·81 (54·01, 69·61)	0·006	29·85 (23·77, 35·93)	< 0·001	
30 days after intervention	70·14 (64·18, 76·09)	0·311	33·97 (26·44, 41·05)	< 0·001	

Values in parentheses are 95 per cent confidence intervals. ADP, adenosine 5′-diphosphate.

difference in either resting platelet P-selectin expression or fibrinogen binding was observed in the placebo group.

A reduction in platelet responsiveness to stimulation, as measured by ADP-stimulated fibrinogen binding, was observed in the clopidogrel group at 1 h after endovascular intervention (reduction 53·9 per cent; $P < 0·001$), at 24 h (reduction 57·2 per cent; $P < 0·001$) and at 30 days (reduction 51·7 per cent; $P < 0·001$) compared with baseline. In the placebo group no significant change in platelet responsiveness to stimulation was observed after 1 h or 30 days after intervention, but at 24 h after angioplasty a drop of 17·8 per cent ($P = 0·006$) was observed in the placebo group. Comparison of the clopidogrel and placebo groups by between-subjects ANOVA revealed a highly significant difference ($P < 0·001$) in ADP-stimulated fibrinogen binding (*Table 3*).

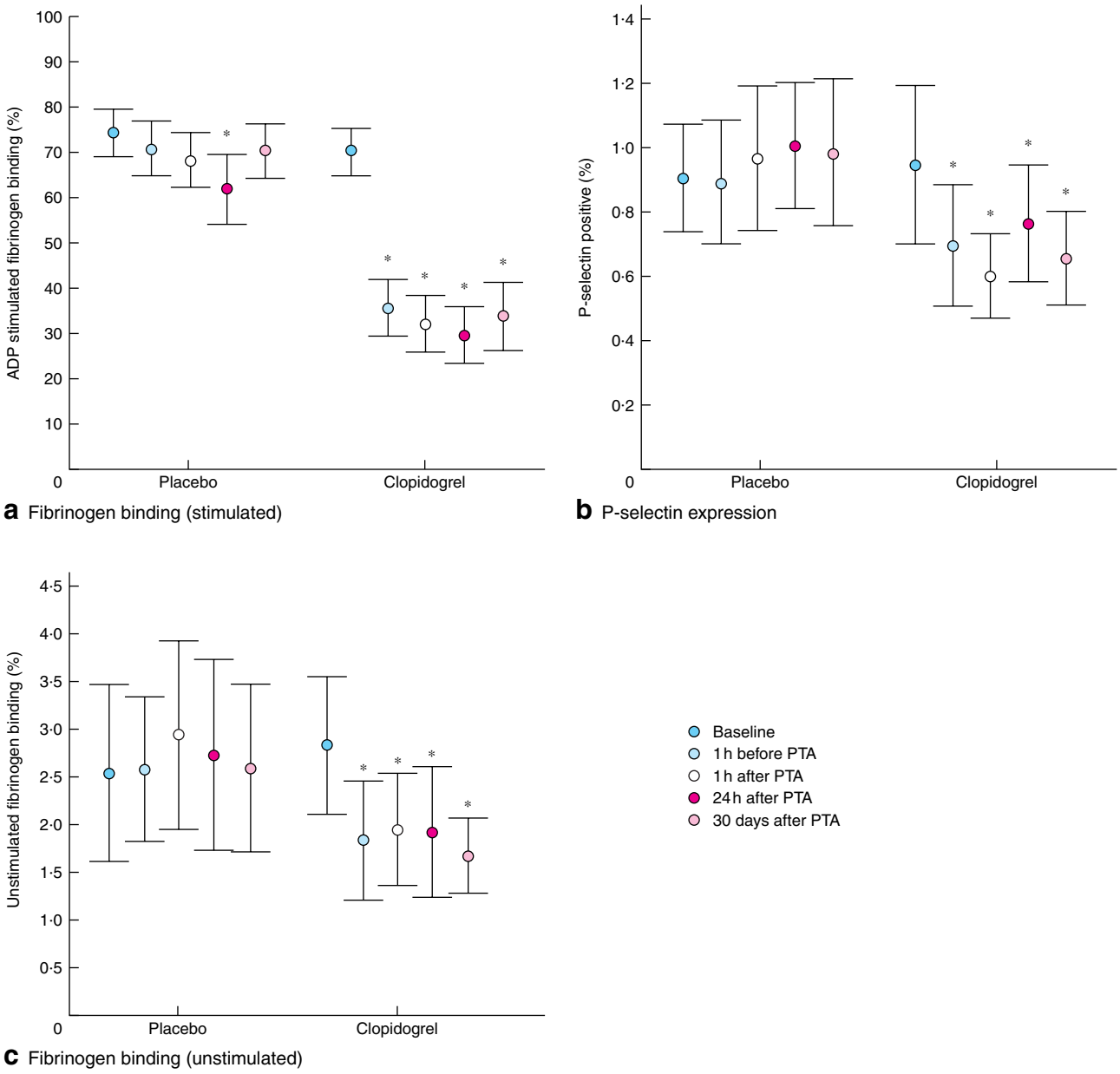

Fig. 2 Platelet responsiveness. **a** Percentage of platelets binding fibrinogen in response to stimulation with 10 μM adenosine 5′-diphosphate (ADP), **b** percentage of unstimulated platelets expressing P selectin and **c** percentage of unstimulated platelets binding fibrinogen. Values are means with 95 per cent confidence intervals. *$P < 0·050$ *versus* baseline (within-subjects ANOVA)

The results of resting platelet P-selectin expression and fibrinogen binding in the placebo and clopidogrel groups are shown in *Fig. 2b* and *c*. ANOVA revealed a significant difference between the clopidogrel and placebo groups in both P-selectin expression ($P = 0{\cdot}03$) and fibrinogen binding ($P = 0{\cdot}026$). There was a consistent inhibition of P-selectin expression and fibrinogen binding in the clopidogrel group at all time points after treatment, whereas there was a slight rise in the placebo group after angioplasty.

In the aspirin–clopidogrel combination group, the inhibition of platelet activation persisted throughout the treatment interval, and the percentage of circulating activated platelets remained significantly different from that in the placebo group at each time point.

Adverse events

Two patients in each group developed a skin rash and two in each group developed a haematoma at the site of radiological access that did not require intervention. The number of patients who developed bruising at and around the site of access was slightly higher in the clopidogrel group (25 *versus* 16) but the difference between the two groups was not statistically significant. Two patients in the clopidogrel group had an ischaemic stroke at day 7 and day 12 after angioplasty. One of these patients, however, had stopped taking all medication immediately after intervention. Another patient developed melaena secondary to bleeding from multiple small gastric ulcers. Further investigation revealed that the patient had metastatic colonic cancer. One patient in the clopidogrel group became hypotensive immediately after intervention and was found to have a retroperitoneal haematoma. This resulted in a delay in discharge from hospital of 7 days but no surgical intervention was necessary.

Discussion

This randomized study has shown that combination antiplatelet therapy results in a powerful antiplatelet effect both before and after endovascular intervention in patients with lifestyle-limiting claudication. Platelet function, as measured by both platelet responsiveness to stimulation and the levels of resting platelet activation, was dramatically reduced within 12 h of a loading dose of 300 mg clopidogrel. Furthermore, combination antiplatelet treatment led to significant suppression of platelet activity during the first 24 h after endovascular intervention, whereas platelet activation was increased in patients receiving aspirin alone. This suppression of platelet function extended to 30 days after intervention. This suggests that patency rates after angioplasty could be improved by combination antiplatelet treatment.

The potent antiplatelet action observed with the combination regimen is believed to reflect the different and complementary mechanisms of action of clopidogrel and aspirin. ADP is an important physiological platelet agonist, the effects of which are mediated by the purinergic receptor types P2Y(1) and P2Y(12). Clopidogrel exerts its antiplatelet actions through irreversible blockade of the P2Y(12) receptor, whereas aspirin inactivates cyclo-oxygenase activity, thereby inhibiting platelet activation mediated by formation of thromboxane A2.

The effect of combined treatment with aspirin and clopidogrel on platelet responsiveness to stimulation has been investigated in two previous studies[17,18]. Moshfegh *et al.*[17] demonstrated a significant reduction in ADP-stimulated P-selectin expression in patients taking clopidogrel–aspirin who had sustained a myocardial infarction, whereas Helft *et al.*[18] observed a reduction in ADP-stimulated fibrinogen binding in 20 patients with either peripheral arterial or coronary heart disease.

In an earlier study the authors showed that platelet activation levels at rest, measured in terms of P-selectin expression and fibrinogen binding, were increased in patients with peripheral arterial disease compared with levels in healthy controls of a similar age, and that the more severe the arterial disease the greater the degree of platelet activation[16]. There is little doubt that platelet activity plays an important part in the development of cerebrovascular and cardiovascular acute events, and that antiplatelet medication reduces these events as well as the risk of death[19]. Patients with intermittent claudication are at high risk of thrombo-occlusive events.

Combination treatment with aspirin and clopidogrel has previously raised concerns over increased morbidity related to bleeding complications. Data from the Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) study showed that, compared with aspirin alone, the combination of aspirin and clopidogrel resulted in a significant increase in minor bleeding (5·1 *versus* 2·4 per cent; $P < 0{\cdot}001$), major bleeding (3·7 *versus* 2·7 per cent; $P = 0{\cdot}001$) and in the need for blood transfusion (2·8 *versus* 2·2 per cent; $P = 0{\cdot}02$)[20]. In the present study, there was no increase in the rate of fatal bleeding, bleeding requiring surgical intervention or haemorrhagic stroke in the combination aspirin–clopidogrel group compared with that in patients receiving aspirin alone. Further information regarding the safety of combination antiplatelet treatment comes from the Clopidogrel for the Reduction of Events During Observation (CREDO) trial[21], which showed that

the risk of major bleeding was significantly higher with aspirin and clopidogrel than with aspirin alone.

The present study provided evidence that combination antiplatelet treatment significantly suppressed platelet function both before and after endovascular intervention, without jeopardizing safety. A further randomized study is now required to investigate whether the observed platelet suppression might translate into improved vessel patency after angioplasty.

Acknowledgements

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References

1 Leng GC, Lee AJ, Fowkes FGR, Whiteman M, Dunbar J, Housley E *et al*. Incidence, natural history and cardiovascular events in symptomatic and asymptomatic peripheral arterial disease in the general population. *Int J Epidemiol* 1996; **25**: 1172–1181.
2 Schmieder FA, Comerota AJ. Intermittent claudication: magnitude of the problem, patient evaluation, and therapeutic strategies. *Am J Cardiol* 2001; **87**: 3D–13D.
3 Gutteridge B, Torrie P, Galland B. Trends in arterial reconstruction, angioplasty and amputation. *Health Trends* 1994; **26**: 88–91.
4 Pell JP, Whyman MR, Fowkes FGR, Gillespie I, Ruckley CV. Trends in vascular surgery since the introduction of percutaneous transluminal angioplasty. *Br J Surg* 1994; **81**: 832–835.
5 Hunink MGM, Wong JB, Donaldson MC, Meyerovitz MF, de Vries J, Harrington DP. Revascularization for femoropopliteal disease: a decision and cost–effectiveness analysis. *JAMA* 1995; **274**: 165–171.
6 Johnston KW. Iliac arteries: reanalysis of results of balloon angioplasty. *Radiology* 1993; **186**: 207–212.
7 Gupta AK, Ravimandalam K, Rao VR, Joseph S, Unni M, Rao AS *et al*. Total occlusion of iliac arteries: results of balloon angioplasty. *Cardiovasc Intervent Radiol* 1993; **16**: 165–177.
8 Transatlantic Intersociety Consensus Document. Treatment of intermittent claudication. *J Vasc Surg* 2000; **31**: S1–S296.
9 Cassar K, Bachoo P, Brittenden J. The role of platelets in peripheral vascular disease. *Eur J Vasc Endovasc Surg* 2003; **25**: 6–15.
10 Jawien A, Bowen-Pope DF, Lindner V, Schwartz SM, Clowes AW. Platelet-derived growth factor promotes smooth muscle migration and intimal thickening in a rat model of balloon angioplasty. *J Clin Invest* 1992; **89**: 507–511.
11 Nakamura H, Ohtsubo K. Ultrastructural appearance of atherosclerosis in human and experimentally-induced animal models. *Electron Microsc Rev* 1992; **5**: 129–170.
12 Antiplatelet Trialists' Collaboration. Collaborative overview of randomised trials of antiplatelet therapy. II. Maintenance of vascular graft or arterial patency by antiplatelet therapy. *BMJ* 1994; **308**: 159–168.
13 Hess H, Muller-Fassbender H, Ingrisch H, Mietaschk A. Prevention of re-occlusion after recanalisation of occluded arteries by the catheter method. *Dtsch Med Wochenschr* 1978; **103**: 1994–1997.
14 Heiss HW, Just H, Middleton D, Deichsel G. Reocclusion prophylaxis with dipyridamole combined with acetylsalicylic acid following PTA. *Angiology* 1990; **41**: 263–269.
15 Warkentin TE, Powling MJ, Hardisty RM. Measurement of fibrinogen binding to platelets in whole blood by flow cytometry: a micromethod for the detection of platelet activation. *Br J Haematol* 1990; **76**: 387–394.
16 Cassar K, Bachoo P, Ford I, Greaves M, Brittenden J. Platelet activation is increased in peripheral arterial disease. *J Vasc Surg* 2003; **38**: 99–103.
17 Moshfegh K, Redondo M, Julmy F, Wuillemin WA, Gebauer MU, Haeberli A. Antiplatelet effects of clopidogrel compared with aspirin after myocardial infarction: enhanced inhibitory effects of combination therapy. *J Am Coll Cardiol* 2000; **36**: 699–705.
18 Helft G, Osende JI, Worthley SG, Zaman AG, Rodriguez OJ, Lev EI *et al*. Acute antithrombotic effect of a front-loaded regimen of clopidogrel in patients with atherosclerosis on aspirin. *Arterioscler Thromb Vasc Biol* 2000; **20**: 2316–2321.
19 Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ* 2002; **324**: 71–86.
20 The Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial Investigators. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med* 2001; **345**: 494–502.
21 Steinhubl SR, Berger PB, Mann JT III, Fry ET, DeLago A, Wilmer C *et al* for the CREDO investigators. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomised controlled trial. *JAMA* 2002; **288**: 2411–2420.

European Colorectal Congress

28 November – 1 December 2022, St.Gallen, Switzerland

Monday, 28 November 2022

09.50
Opening and welcome
Jochen Lange, St.Gallen, CH

10.00
It is leaking! Approaches to salvaging an anastomosis
Willem Bemelman, Amsterdam, NL

10.30
Predictive and diagnostic markers of anastomotic leak
Andre D'Hoore, Leuven, BE

11.00
SATELLITE SYMPOSIUM
ETHICON
PART OF THE Johnson&Johnson FAMILY OF COMPANIES

11.45
Of microbes and men – the unspoken story of anastomotic leakage
James Kinross, London, UK

12.15
LUNCH

13.45
Operative techniques to reduce anastomotic recurrence in Crohn's disease
Laura Hancock, Manchester, UK

14.15
Innovative approaches in the treatment of complex Crohn Diseases perianal fistula
Christianne Buskens, Amsterdam, NL

14.45
To divert or not to divert in Crohn surgery – technical aspects and patient factors
Pär Myrelid, Linköping, SE

15.15
COFFEE BREAK

15.45
Appendiceal neoplasia – when to opt for a minimal approach, when and how to go for a maximal treatment
Tom Cecil, Basingstoke, Hampshire, UK

16.15
SATELLITE SYMPOSIUM
Medtronic
Further,Together

17.00
Outcomes of modern induction therapies and Wait and Watch strategies, Hope or Hype
Antonino Spinelli, Milano, IT

17.30
EAES Presidential Lecture - Use of ICG in colorectal surgery: beyond bowel perfusion
Salvador Morales-Conde, Sevilla, ES

18.00
Get-Together with your colleagues
Industrial Exhibition

Tuesday, 29 November 2022

9.00
CONSULTANT'S CORNER
Michel Adamina, Winterthur, CH

10.30
COFFEE BREAK

11.00
SATELLITE SYMPOSIUM
INTUITIVE

11.45
Trends in colorectal oncology and clinical insights for the near future
Rob Glynne-Jones, London, UK

12.15
LUNCH

13.45
VIDEO SESSION

14.15
SATELLITE SYMPOSIUM
BD

15.00
COFFEE BREAK

15.30
The unsolved issue of TME: open, robotic, transanal, or laparoscopic – shining light on evidence and practice
Des Winter, Dublin, IE
Jim Khan, London, UK
Brendan Moran, Basingstoke, UK

16.30
SATELLITE SYMPOSIUM
Takeda

17.15
Lars Pahlman lecture
Søren Laurberg, Aarhus, DK

Thursday, 1 December 2022
Masterclass in Colorectal Surgery
Proctology Day

Wednesday, 30 November 2022

9.00
Advanced risk stratification in colorectal cancer – choosing wisely surgery and adjuvant therapy
Philip Quirke, Leeds, UK

09.30
Predictors for Postoperative Complications and Mortality
Ronan O'Connell, Dublin, IE

10.00
Segmental colectomy versus extended colectomy for complex cancer
Quentin Denost, Bordeaux, FR

10.30
COFFEE BREAK

11.00
Incidental cancer in polyp - completion surgery or endoscopy treatment alone?
Laura Beyer-Berjot, Marseille, FR

11.30
SATELLITE SYMPOSIUM

12.00
Less is more – pushing the boundaries of full-thickness rectal resection
Xavier Serra-Aracil, Barcelona, ES

12.30
LUNCH

14.00
Management of intestinal neuroendocrine neoplasia
Frédéric Ris, Geneva, CH

14.30
Poster Presentation & Best Poster Award
Michel Adamina, Winterthur, CH

15.00
SATELLITE SYMPOSIUM
OLYMPUS

15.45
COFFEE BREAK

16.15
Reoperative pelvic floor surgery – dealing with perineal hernia, reoperations, and complex reconstructions
Guillaume Meurette, Nantes, FR

16.45
Salvage strategies for rectal neoplasia
Roel Hompes, Amsterdam, NL

17.15
Beyond TME – technique and results of pelvic exenteration and sacrectomy
Paris Tekkis, London, UK

19.30
FESTIVE EVENING

Information & Registration **www.colorectalsurgery.eu**