Reduction of Requirement for Leg Vascular Surgery During Long-term Treatment of Claudicant Patients with Ticlopidine: Results from the Swedish Ticlopidine Multicentre Study (STIMS)

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Objective: To study the effect of long-term treatment of the platelet inhibitor ticlopidine as secondary prevention against the need of vascular surgery in patients with intermittent claudication.

Design: The Swedish Ticlopidine Multicentre Study (STIMS), was conducted in six medical and surgical clinics of university hospitals in Sweden.

Methods: 687 claudicants were randomised to ticlopidine 250mg bd or placebo and vascular surgery events were recorded prospectively over a 7-year period. Cox proportional hazards models of risk for leg vascular surgery were constructed using drug treatment and 11 putative risk factors for vascular disease as covariates. Surgical event-free survivals were compared by Kaplan-Meier analysis.

Results: The overall rate of first operations was 2.4% per annum. More than half of these operations were in the aortoiliac region. One-quarter of patients operated during the period required further operations but amputation was rare. Ticlopidine treatment reduced the need for vascular reconstructive surgery by about half, both in intention-to-treat and on-treatment analyses (unadjusted relative risks 0.486, 95% CI 0.317–0.745: $p < 0.001$; 0.493, 95% CI 0.290–0.841: $p < 0.01$, respectively). In Cox model analysis only male sex was confirmed as a risk factor for surgery. Previous peripheral arterial surgery was the strongest predictor of the need for surgery. None of the risk factors examined interacted statistically with the effect of treatment with ticlopidine.

Conclusion: In patients with intermittent claudication it seems possible to prevent the need for future vascular surgery by the use of platelet inhibition with ticlopidine.

Key Words: Claudication; Platelets; Risk; Vascular surgery; Ticlopidine; Randomised controlled trial.

In the Swedish Ticlopidine Multicentre Study (STIMS)[1,2] a large group of patients with atherosclerosis characterised by intermittent claudication and reduced ankle/arm blood pressure index was treated with multiple interventions, including randomised allocation of the platelet aggregation inhibitory drug ticlopidine hydrochloride (Ticlid[R]),[3] 250 mg bd, or placebo. The primary events of the study were cardiac or cerebral vascular events and total mortality: ticlopidine was found to reduce the incidence of such events, chiefly through an effect on cardiac mortality.

It is now clear that antiplatelet treatment reduces

the risk of acute thrombotic events in a variety of circumstances.[4-7] Whether or not antiplatelet treatment can reduce the need for peripheral vascular surgery in a risk population is not known for certain. In a recent publication from the U.S. Physicians' Health Study there is clear evidence that aspirin does reduce the need for arterial surgery,[8] which is consistent with earlier evidence that aspirin reduces the rate of progression of atherosclerotic vessel occlusion in leg arteries.[9] The aim of this report is two-fold. First, the secondary effect of ticlopidine treatment of claudicants on the requirement for vascular surgery is described. Second, information concerning the risks for vascular surgery and amputation during long-term management of patients with claudication is presented.

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Table 1a,b. Study outcomes – Vascular surgical events(a) Intention-to-treat

Class of vascular surgery	First event in study period		All events in study period	
	Placebo	Ticlopidine	Placebo	Ticlopidine
	Number of Patients			
Total treatment group	341	346	341	346
No surgery	284	303	284	303
Missing surgery code	0	1*	0	1*
	Number of events			
1 Aortoiliac region	33	18	56	28
2 Femorodistal region	13	7	31	17
Total reconstructive events	46^a	25^a	87	45
3 Thrombectomy	4	3	15	17
4 Other surgery related to 1, 2 or 3	3	8	8	17
6 Amputation of lower limb at any level	0	2	8	7
Total leg surgical events	53^b	38^b	118	86
5 Non-leg peripheral vascular surgery	4†	3	4	3
7 Coronary artery surgery	0	1	0	1
Total vascular surgical events	57^c	42^c	122	90

^{a} χ^2 = 7.27; p < 0.01; ^{b} χ^2 = 3.11; p < 0.10; ^{c} χ^2 = 2.92; p < 0.10.* Missing data counted as an event for statistical analyses.†Two of these patients has subsequent type 1 or type 6 operations.

(b) On-treatment

Class of vascular surgery	First event in study period		All events in study period	
	Placebo	Ticlopidine	Placebo	Ticlopidine
	Number of Patients			
Total treatment group	339	341	339	341
No surgery	293	309	293	309
Missing surgery code	0	1*	0	1*
	Number of events			
1 Aortoiliac region	29	12	49	20
2 Femorodistal region	10	4	27	11
Total reconstructive events	39^a	16^a	76	31
3 Thrombectomy	1	3	8	13
4 Other surgery related to 1, 2 or 3	2	6	4	14
6 Amputation of lower limb at any level	0	2	6	4
Total leg surgical events	42^b	27^b	94	62
5 Non-leg peripheral vascular surgery	4†	3	4	3
7 Coronary artery surgery	0	1	0	1
Total vascular surgical events	46^c	31^c	98	66

^{a} χ^2 = 10.61; p = 0.001; ^{b} χ^2 = 3.73; 0.10 > p > 0.05; ^{c} χ^2 = 3.40; 0.10 > p > 0.05.*
Missing data counted as an event for statistical analyses.
†Two of these patients has subsequent type 1 or type 6 operations.

Methods

Patient population and database

The patient population has been described in detail elsewhere,[1] particularly as regards the comparability of leg disease between the treatment groups.[2] Briefly, 687 patients with intermittent claudication as a result of peripheral arterial disease were randomised to receive ticlopidine hydrochloride (Ticlid^R-250 mg tablets, bd) or placebo tablets according to a stratified minimisation procedure: treatment extended for up to 7 years (median observation period from entry to the common trial termination date 5.6 years). Many of the patients entered were already participating in management programmes for control by diet or drugs of hypertension, hyperglycaemia (insulin-dependent diabetics were excluded from the study) and hyperlipidaemia and for advice on smoking cessation and exercise. Patients newly identified for the study were entered into these programmes and all were regularly reviewed during up to 7 years follow-up, including quarterly clinic visits. Causes of death, non-fatal myocardial infarctions and strokes, transient

ischaemic attack, vascular surgery, amputations and adverse events were recorded together with the results of regular laboratory investigations.

Stratification variables included presence or absence of previous leg vascular surgery: these data were verified before the randomisation code was broken only for those patients recorded as having had surgery. The surgical records of all patients were reviewed again without reference to the drug allocation some time after the code had been broken and the principal analyses completed. In this process, aimed at verifying and classifying the surgical interventions, several events (c. 5% of the total) not recorded prospectively were acquired. This process also led to a small number of changes of stratification category for risk factor analysis,[10] for example because surgery had taken place between screening and randomisation. Those events that occurred after premature cessation of study medication (approximately one-third of patients) were also acquired, so that both "on-treatment" (OT) and "intention-to-treat" (ITT) analyses were possible. Patients were regarded as taking study medication and events were counted as being "on treatment" unless the patient had been formally withdrawn because of death, a vascular thrombotic event, adverse event or non-compliance; patients interrupting medication temporarily for any reason, e.g. to undergo elective surgery, were counted as continuously on treatment. Median treatment periods were 4.8 years for placebo and 4.0 years for ticlopidine. In the OT analysis, events and patients at risk were censored from the date of formal withdrawal.

Classification of the surgical and endovascular procedures was made without knowledge of the allocated treatment according to the following scheme:

Type 1: reconstruction in the aortoiliacofemoral region (bifurcation graft; femorofemoral cross-over bypass; unilateral reconstructive graft or thromboendarterectomy of the iliac system);

Type 2: femorodistal bypass, either leg;

Type 3: thrombectomy in relation to previous interventions of Types 1 or 2, either leg;

Type 4: other peripheral vascular surgery, including angioplasty, related to previous interventions of Types 1, 2 or 3, either leg;

Type 5: other peripheral vascular surgery not related to the legs, such as renovascular or carotid surgery;

Type 6: amputation, either leg, at any level;

Type 7: coronary artery surgery.

Data analysed

The outcome data used for these present analyses are given in Table 1a (for intention-to-treat analyses — ITT, all patients included) and Table 1b (for on-treatment analysis — OT, patients who never received medication and end-points which occurred more than 15 days after treatment was first discontinued were excluded). The patients' complicance to the therapy was controlled by regular tablet counting. The variables (covariates) examined for predictive power were glycaemia, cholesterolaemia, blood pressure, smoking status, duration of local disease (each three levels), gender, evidence of coronary artery disease, previous leg vascular surgery, triglyceridaemia (each two levels), white cell count and age (continuous variables). Slightly different strata cut-offs were used in this analysis than were used for randomisation: the actual values used appear in the footnotes to Table 3. White cell counts were not recorded at entry for approximately 20% of the patients and so (in order not to lose a large amount of data from the final Cox model) the median of all available entry data has been assigned to each patient with a missing value. A few blood glucose values were missing but the remaining variables were recorded for stratification in the randomisation and were verified before the study was unblinded: these data sets are complete.

Methods of analysis

All statistical methods used are contained within the Statistical Analysis System (SAS)[11] or Biomedical Data Package (BMDP)[12] statistical packages. The predictive power of each covariate (relative risk for each level) for time to outcome was examined by Cox proportional hazards model methods. Study treatment was included as one covariate in order to obtain adjusted estimates of treatment effect and (using log-rank χ^2 testing of times to outcome within each level of the risk variable) a view of the extent of interaction on estimates of treatment effect by other risk variables. Probability values derived from the models are unadjusted and should be interpreted in the context of the multiple comparisons made. Surgery-free survival (Kaplan-Meier) plots were also constructed.

Results

Overall and on an ITT basis, 2.4% of patients per annum, required vascular surgical interventions on

the legs. The rate was higher in patients who had had leg arterial vascular surgery before entry into the study (4.2% pa) than for those who had not (1.5% pa: χ^2 = 33.97; d.f. 2; $p < 0.001$). Kaplan–Meier plots for first operations illustrate that the drug effect is sustained and uniform over the whole treatment period of up to 7 years (Figs. 1a, b). The operations analysed are summarised in Table 1a, b (ITT and OT populations respectively) and include both first and subsequent operations carried out during the relevant periods. In Table 2a, the requirements for further surgical intervention on each leg are set out. Ninety-three patients (13.2%) underwent leg vascular surgery at some time during the study period. For comparison, 33% of patients had had leg vascular surgery or amputation before entry into the study. One hundred legs were operated on with 33 requiring further interventions. This is to be compared with the 32% of legs operated before the start of the study period which required further interventions. Fourteen of 468 patients who had not had surgery before entry and 19 of the 219 patients who had been operated before entry underwent sequences of operations on the same
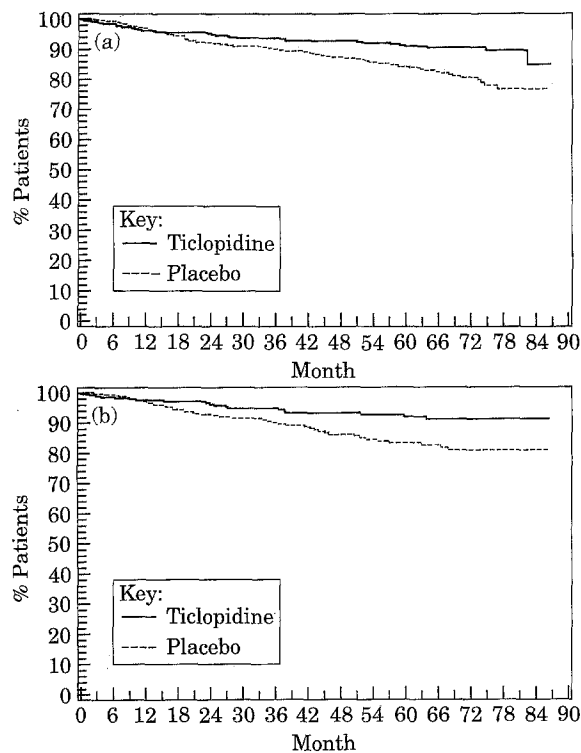

Fig. 1. Kaplan–Meier plots of the proportions of patients (ordinate) who had not undergone leg vascular surgery (types 1, 2, 3, 4 or 6) at each time after randomisation (abscissa). (a) All events occurring up to the determined end of study medication (31.12.1978 or prior death — intention-to-treat analysis). (b) Events occurring and patients at risk only while taking study medication (on-treatment analysis).

leg during the study period: 16% of sequences ended with amputation compared with the 5.3% of operation sequences which had ended with amputation before entry into the study.

By univariate analysis, ticlopidine treatment reduced the requirement for reconstructive surgery of leg arteries by over 50% (relative risks 0.486, 95% confidence interval 0.317–0.745, $p = 0.0009$ ITT; 0.493, 0.290–0.841, $p = 0.0093$, OT.

Risk factors

Each of the baseline characteristics considered as putative risk factors for atherothrombotic events was entered into a Cox model regression analysis to assess possible influence on outcomes. All of the 11 factors chosen gave interpretably narrow confidence intervals for the relative risk estimate. Analysis of outcomes with these 11 factors and treatment gave the estimates of risk shown in Table 3. Interactions between the 11 covariates and study treatment effect were examined within the ITT and OT sets of data: none even approached conventional significance. Alternatively expressed, the variations in ticlopidine effect between covariate strata are not, within the limitations of size of the study, statistically significant and are probably clinically insignificant. It is also therefore unlikely that any conjunction of major risk factors could explain the treatment effect. Adjustment of the estimate of treatment effect (by the Cox model methods) for baseline risk factors suggests more significant action with a reduction of requirement for surgery of more than 55% (Table 3). The adjusted survival curves diverge smoothly (Fig. 2a, b).

Surgical intervention

The indication for surgery was not given in the collected data, but the dominance of aortoiliac reconstruction suggests that most operations were performed because of intermittent claudication. The patients operated on for a femorodistal reconstruction would have had either disabling claudication or critical ischaemia. The predominant interventions, both as first events (68%) and in total (60%), were for reconstructive surgery. Only three of the 46 diagnosed (non-insulin dependent) diabetic patients required surgery. Patients with mild or moderate hyperglycaemia at entry appeared no more likely to require surgery than normoglycaemics (Table 4). Only one of

Table 2a,b. Repetitive surgery* on the same leg(a) Intention-to-treat population

	Patients surgery-free before study period		Patients surgery-free before study period	
	Placebo	Ticlopidine	Placebo	Ticlopidine
Total Patients	232	236	109	110
Patients having no (further) surgery	209	220	77	88
		Number of Operations		
1 operation	26	15	37	22
2 operations	4	5	9	4
3 operations	1	1	1	1
4 operations	0	0	1	1
5 operations	1	0	0	0
> 5 operations	1	1	1	1
Total legs operated	33	22	49	29
Total operations carried out	49	43	69	43

	Patients surgery-free before study period		Patients surgery-free before study period	
	Placebo	Ticlopidine	Placebo	Ticlopidine
Total patients	230	231	109	110
Patients having no (further) surgery	209	220	86	94
		Number of Operations		
1 operation	25	11	28	18
2 operations	2	2	7	2
3 operations	1	1	0	1
4 operations	1	0	1	1
5 operations	1	0	0	0
> 5 operations	0	1	1	0
Total legs operated	30	15	37	22
Total operations carried out	41	33	53	29

* Surgery types 1,2,3,4 and 6 only.

Table 3. Risk ratios[a] derived from full cox model risk for proximal leg artery surgery[b] during period

Covariate	Intention-to-treat	On-treatment
Gender Female/Male	0.68 (0.38–1.20)	0.67 (0.34–1.30)
Age (year on year)	1.03 (0.99–1.06)	1.02 (0.98–1.06)
Blood pressure H/M/L	0.89 (0.67–1.17)	0.89 (0.63–1.26)
Cholesterol H/M/L	1.11 (0.87–1.41)	1.21 (0.91–1.63)
Triglycerides H/L	1.28 (0.79–2.06)	1.74 (0.99–3.07)†
Glycaemia H/M/L	0.96 (0.66–1.40)	0.76 (0.42–1.35)
White cells	1.01 (0.88–1.14)	0.97 (0.83–1.14)
Smoking C/F/N	1.52 (0.95–2.44)‡	1.46 (0.84–2.55)
Duration PAD L/M/S	1.08 (0.78–1.49)	1.01 (0.68–1.50)
Vascular surgery Y/N	2.60 (1.66–4.08)***	2.66 (1.53–4.62)**
IHD Y/N	0.74 (0.44–1.23)	0.69 (0.35–1.35)
Treatment T/P	0.41 (0.26–0.64)***	0.43 (0.24–0.76)*

[a] Ratios given are the relative risks between contiguous strata (rate for nth stratum/rate for $n + 1$th stratum).[b] Types 1 and 2 operations, only.* $p = 0.0035$; ** $p = 0.0005$; *** $p = 0.0001$; † $p = 0.055$; ‡ $p = 0.082$Intesnsity of covariates: blood pressure: L systolic $\leq$ 140 and diastolic $\leq$ 90, M systolic $>$ 140 or diastolic $>$ 90, H systolic $>$ 165 or diastolic $>$ 105 mmHg; Cholesterol: L $<$ 6.2, M 6.2 - $\leq$ 6.5, H $>$ 6.5 mmol/l; triglycerides: L $<$ 2.2, H $\geq$ 2.2 mmol/l; glycaemia: L $<$ 5.8, M 5.8 - $<$ 6.7 H $\geq$ 6.7 mmol/l; white cell count: risk increment for increase of $1.0 \times 10^9/l$ in count; smoking: current/former/never; duration of peripheral arterial diseases: l $>$ 3 years, M 1–3 years, S $<$ 1 year; Y, covariate factor present (previous lower limb *vascular surgery*, evidence of ischaemic heart disease: IHD), N, covariate factor absent, T, ticlopidine; P, placebo.

the diabetic patients underwent amputation compared to 13 of the non-diabetics (2.0%). For one patient an amputation during the study was the only vascular surgical event, while another had had a sequence of operations before entry which culminated in amputation as the first and only study event: both patients survived beyond the end of the study. Seven patients had thrombectomy as a first event in the study period but this always followed pre-study reconstructive surgery on the same leg. The interval between reconstruction and thrombectomy could be as great as 10 years. On one occasion thrombus had spread into the contralateral leg vessels. On all except one occasion, type 4 operations followed prior reconstructive surgery to the same leg (or a bilateral graft): the exception was a thromboendarterectomy. Type 4 operations had either no particular relation to the patency of the other operations (pseudoaneurysm resections, with or without patching — 7) or were attempts to deal with inadequate blood flow in earlier reconstructive surgery (eight thromboendarterectomies, two percutaneous transluminal angioplasties, six instances of re-grafting (with PTFE) and two of repair or patching of faulty anastomoses). In one case

an infected and fibrosed graft segment was removed. Only seven patients underwent non-leg peripheral vascular surgery: four carotid endarterectomies, one with Dacron patch, and three operations for occlusive renovascular disease. Five of these patients had no other vascular surgery, one had prior aortobiiliac graft and the seventh a subsequent single amputation. Only one patient underwent coronary artery surgery: the patient also underwent both prior and subsequent leg artery surgery.

Discussion

This study was the first secondary prevention trial of any intervention in the field of atherosclerotic disease to show a convincing reduction of overall mortality (29% lower in the ticlopidine group), a reduction which is precisely accounted for by the reduction of vascular deaths. These results are consistent with the now well known effect of antiplatelet agents in reducing the risk of acute thrombotic events in the
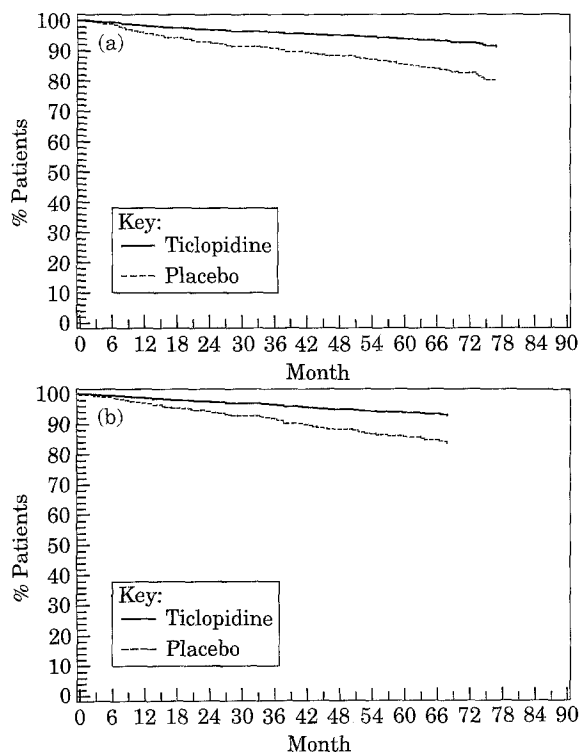

Fig. 2. Survival plots from the Cox models showing the estimated proportions of patients (ordinate) who had not undergone leg vascular surgery (Types 1, 2, 3, 4 or 6) at each time after randomisation (abscissa), adjusted for risk factors. (a) All events occurring up to the determined end of study medication (31.12.1987) or prior death — intention-to-treat analysis). (b) Events occurring and patients at risk only while taking study medication (on-treatment analysis).

cardiac and cerebral circulations when there is already clear evidence of atheromatous arterial disease.[4-7] The present paper confirms that treatment with ticlopidine also results in a 50% decrease in the requirement for surgical reconstruction of diseased arteries in the legs from the aortic bifurcation downwards. As with the reduction in vascular mortality (and vascular events), the effect is immediate, sustained and uniform over the whole treatment period of up to 7 years.

The study population had an increased prevalence of acknowledged risk factors for peripheral arterial disease compared to their peers in the general population.[10] These factors — hyperglycaemia, hypertension, hyperlipidaemia, evidence of ischaemic heart disease, male sex and tobacco use — are also generally accepted as risk factors for development of coronary and/or cerebral arterial disease. However, in an analysis of this study population for risk factors for vascular thrombotic events only age, sex, identified ischaemic heart disease, hyperglycaemia, smoking and white cell count appeared to be important predictors of an event. This was interpreted as suggesting that, since the risk factors are different, the mechanisms for development of atherosclerotic disease and for the subsequent occurrence of acute thrombotic events are different, an obvious but rarely articulated point.

These risk factors have not been studied in the same population and study period in relation to the risk of requiring leg vascular surgery. Only previous leg vascular surgery was strongly and significantly predictive of the need for further surgery, a reversal of its (non-significant) protective influence on acute thrombotic events. This mirrors the pattern for ischaemic heart disease, which in this population showed a strong predictive effect for (the predominantly cardiac) acute thrombotic events[10] but which now appears mildly protective for surgery, though not significantly so. It is possible that this is because ischaemic heart disease imposes limitations in daily physical activities such that the limitations from leg ischaemia are not obvious to the point of triggering a requirement for surgery. The duration of peripheral vascular disease has no predictive power for either type of outcome event.

The overall risk for surgery appears unrelated to both glycaemia and white cell count in contrast to the strong predictive power of each of these factors for acute thrombotic events. There is no evidence in this study that mild or moderate hyperglycaemia give any differential risk for surgery affecting blood supply below the groin (type 2 operation) compared to above the groin (type 1 — Table 4). Insulin-dependent diabetics (who are prone to microvascular disease leading

Table 4. Surgery and glycaemia

	Normoglycaemic patients[a]		Hyperglycaemic patients[a]	
	Placebo	Ticlopidine	Placebo	Ticlopidine
Total patients	273	280	49	49
Type 1 surgery — aortofemoral region: number of operations	29	13	4	2
Type 2 surgery — femorodistal region: number of operations	10	5	2	1

[a] Fasting blood glucose as measured at study entry: normoglycaemic - fasting blood glucose < 5.8 mmol/l; hyperglycaemic - fasting blood glucose ≥ 5.8 mmol/l. Five events of types 1 or 2 were recorded for the 36 patients for whom a pre-study fasting glucose value was not recorded.

to ulceration, gangrene and amputation) were excluded from the study: non-insulin-dependent diabetics did not appear to be more susceptible than non-diabetics to conditions leading to amputation. The finding that tobacco use increases the risk for surgery, while not reaching significance, is consistent with previous studies. In the U.S. Physicians' Health Study[8] both past and current smoking were very strong risk factors for the need of leg peripheral vascular surgery, as they were in an earlier study of claudicants.[13]

The estimates of effect of female gender on surgery risk, while less than the effect on thrombosis risk, are of consistent magnitude, suggesting that significance might be revealed in a larger study which included more women. Similarly, age might be revealed as a significant predictor in a larger study with more outcome events. In contrast, the influences of blood pressure, lipidaemia and duration of peripheral arterial disease on the risks for surgery and thrombosis appear about the same and minimal, with the exception of a near significant risk in OTT analysis from raised triglyceride. The present findings are almost entirely consistent with those of Hess and co-workers[9] that diabetes and lipidaemia are not predictive of the progression of occlusion of the leg arteries whilst smoking is:[13] there is disagreement over the role of hypertension.

The effect of ticlopidine on reducing the need for first-time surgery at first sight appears not to be clearly reflected in an equivalent reduction in the need for further vascular surgery. However, the numbers of legs undergoing multiple operations was small (seven legs each in the placebo and active groups for patients who had not had prior leg vascular surgery and 12 and 7 legs in the placebo and active groups who had, respectively. On the other hand, all those patients who had had leg vascular surgery before starting treatment could be regarded as eligible for re-operation: here 49 and 29 legs were re-operated in the placebo and active groups, respectively. The benefit of ticlopidine treatment, started even after previous surgery, seems clear

although because of the confounding of legs and patients, it was not possible to make a formal statistical evaluation.

The clear and important benefit from ticlopidine treatment found in this study is consistent with that found for other antiplatelet treatments.[8,9] The fact that the benefit effectively begins on starting treatment might suggest that the effect is a purely antithrombotic one since other interventions to slow or reverse atheroma progression (e.g. on cholesterol or smoking) appear to require many months before an effect on risk becomes evident. However, it is generally acknowledged that platelets are intimately involved in plaque enlargement even in the absence of occlusive thrombosis. The platelet activities involved may be only a part of those which lead to catastrophic occlusive thrombosis, e.g. adhesion to subendothelium and the release reaction. The present findings point to the general conclusions that modification of platelet reactivity may be clinically very significant in slowing the progression of atherosclerotic disease and that, by implication, platelets are indeed involved in the progression of atheromatous plaque.

Acknowledgements

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