D-dimer and platelet aggregability are related to thrombotic events in patients with peripheral arterial occlusive disease


1Department of Atherothrombosis, and 2Department of Angiology, Cardiology Research Center, Moscow, Russia; 3Laboratory of Biostatistics, National Research Center for Preventive Medicine, Moscow, Russia

Aims To evaluate the frequency of arterial thrombotic events in patients with peripheral arterial occlusive disease during 3–5 years of follow-up and to determine whether baseline levels of haemostatic factors were related to the risk of future thrombotic events.

Methods and Results One hundred and twenty-three patients, mean age 56 years, with peripheral arterial occlusive disease and intermittent claudication were followed prospectively for an average of 4·2 years. Fibrinogen, prothrombin fragment 1+2, D-dimer, tissue plasminogen activator, plasminogen activator inhibitor type I antigen and activity, plasmin-α2-antiplasmin complex, β-thromboglobulin and ADP-induced platelet aggregation were measured at the recruitment. Thirty-eight new vascular events (15 fatal) were identified. Age- (and other clinical and laboratory variables) -adjusted relative risks (RR) of thrombotic events were significantly elevated (P<0·05) per higher value of D-dimer (RR: 14·1, 95% CI 1·7;115·8) and platelet aggregation was low (RR: 4·6, 95% CI 1·3;16·3).


Key Words: D-dimer, platelet aggregation, thrombotic event, atherosclerosis.

Introduction

Considerable evidence indicates that the haemostatic system plays an important role in the pathogenesis of atherosclerotic vascular disease. Recent pathological studies of postmortem arteries and samples obtained during reconstructive vascular surgery relate the progression of atherosclerosis to the extent of fibrin deposition and its degradation products in the arterial wall[1–3]. In prospective epidemiological studies of atherosclerotic patients as well as healthy subjects, baseline abnormalities in several coagulation and fibrinolytic variables, including plasma fibrinogen, fibrin degradation products, coagulation factor VII, and tissue-type plasminogen activator have been associated with increased risk of acute thrombotic events[4–13]. The blood coagulation cascade was reported to be activated in patients with peripheral arterial occlusive disease and intermittent claudication[14,15]. Previous longitudinal studies demonstrated that these patients have an increased risk of arterial thrombotic events (especially in coronary and cerebral circulation)[16,17]. The aim of our study was to evaluate the frequency of thrombotic events in patients with peripheral arterial occlusive disease during 3–5 years of follow-up and to determine whether the baseline levels of haemostatic factors were related to the risk of future thrombotic events.
Methods

Patients

One hundred and twenty-three patients (121 men) with a mean (± m) age 56 ± 0.7 years (range from 34 to 72) with peripheral arterial occlusive disease and stable intermittent claudication Fontaine stage II–III were enrolled in the study.

Exclusion criteria were myocardial infarction, stroke or acute peripheral arterial thrombosis within 6 months before inclusion. Patients with severe arterial hypertension (diastolic BP >120 mmHg), cancer, serious liver or kidney failure, as well as other conditions resulting in a life expectancy of less than 2 years were not included in the study. Patients did not receive anticoagulants or antiplatelet drugs within 3 weeks before enrolment into the study.

Peripheral atherosclerosis was confirmed by either angiography (n=37) or ultrasound Doppler signal and duplex scanning (n=86) of lower limb arteries. Duplex sonography and/or angiography of the extracranial cerebral arteries were carried out in all patients. It was assumed that patients had atherosclerosis of extracranial cerebral arteries if the examination revealed a stenosis >50%. Prevalence of coronary artery disease was evaluated in all participants. The criteria for coronary artery disease were ischaemic ECG changes during stress testing (treadmill exercise test, atrial pacing) and/or documented myocardial infarction.

Treadmill exercise test (speed 1·7 mph, slope 14%) was used to assess the pain-free and maximum walking distances.

All patients were evaluated every 6 months for 3–5 years. All patients were recommended to take acetylsalicylic acid 125 mg daily and pentoxifylline 800–1200 mg daily on a regular basis. Calcium channel antagonists, ACE-inhibitors, beta-blockers and nitrates were prescribed if needed.

End-points

End-points were fatal or non-fatal thrombotic events in any main arterial area and deaths from non-vascular causes. Thrombotic events included sudden cardiac death, definite myocardial infarction, ischaemic stroke, acute thrombosis in any other arterial areas documented by angiography or ultrasound duplex scanning (including acute peripheral ischaemia requiring limb salvage or amputation). End-points were documented by reviewing hospital records, necropsy reports and interviewing physicians and family members and were classified by WHO criteria.

Laboratory analysis

Blood samples were taken at the recruitment between 0900h and 1100h after overnight fasting and non-smoking. Blood was collected without stasis from supine subjects after a 20-min rest.

Routine measurements of total cholesterol, triglycerides, glucose, creatinine and enzymes were done in all participants.

For platelet aggregation assay, blood was added to 3·2% sodium citrate (nine volumes of blood to one volume of sodium citrate) and centrifuged (5 min, 1000 × g, 22 °C). The platelet-rich plasma was separated. Platelet aggregation was performed in a dual-channel aggregometer (Biola, Russia) within 45–90 min after blood collection. Aggregation was initiated by the addition of ADP to a final concentration of 10⁻⁶ M. The maximal decrease in light transmission (%) was evaluated.

For other haemostatic tests, blood was collected into STAD anticoagulant (nine volumes of blood to one volume of STAD) and centrifuged (15 min, 3000 × g, 4 °C), and the plasma was separated into polypropylene tubes. Samples were stored at −70 °C until analysis. Fibrinogen and activity of plasminogen activator inhibitor type I (PAI-1) were assayed by functional photometric assays according to Becker et al.[18] and Chandler et al.[19], respectively. D-dimer, β-thromboglobulin, tissue plasminogen activator (t-PA) antigen and PAI-1 antigen were measured by ELISA using the reagent kits from Boehringer Mannheim. Prothrombin fragment 1+2 and plasmin-α₂-antiplasmin complex were measured by ELISA using the reagent kits from Behring.

Statistical analysis

Data were analysed using the SAS statistical package. The results are given at the mean ± m. The Duncan’s multiple range test was used to examine differences of each haemostatic factor across the categories of patients. Levels of haemostatic factors were logarithmically transformed because the distribution was skewed. Pearson correlation coefficients between plasma D-dimer level and total cholesterol, triglycerides, prothrombin fragment 1+2, PAI-1 antigen and activity, t-PA antigen, plasmin-α₂-antiplasmin complex and fibrinogen was calculated. Odds ratios for D-dimer and platelet aggregation were calculated by dividing the range of values into quintiles or tertiles, respectively. The relative risks of thrombotic events were estimated using Cox proportional hazards model.

Results

The baseline characteristics of the patients included in the study are listed in Table 1.

Assessment of risk factors for vascular disease revealed 100% smokers/exsmokers according to self-reported cigarette use, 45 (47%) hypertensives and 12 (9%) patients with diabetes mellitus or impaired glucose tolerance. Coronary artery disease was found in 52 (42%) patients. Twenty (16%) patients had clinical signs
Diabetes mellitus type II or impaired glucose tolerance
Total cholesterol (mmol l\(^{-1}\))
Triglycerides (mmol l\(^{-1}\))
Maximum walking distance on a treadmill (m) 125
Pain free walking distance on a treadmill (m) 68

Patients with Fontaine stage III 9 (7·5%)
IIIA 9 (7·5%)
IIIB 105 (85%)

Table 1 Study population

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Number (Percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (male/female; n)</td>
<td>123 (121/2)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>56 ± 0·7</td>
</tr>
<tr>
<td>Smokers - Current</td>
<td>95 (77%)</td>
</tr>
<tr>
<td>Smokers - Past</td>
<td>28 (33%)</td>
</tr>
<tr>
<td>Total</td>
<td>123 (100%)</td>
</tr>
<tr>
<td>Arterial hypertension</td>
<td>45 (37%)</td>
</tr>
<tr>
<td>Body mass index (kg m(^{-2}))</td>
<td>25·6 ± 0·3</td>
</tr>
<tr>
<td>Diabetes mellitus type II or impaired glucose tolerance</td>
<td>12 (9%)</td>
</tr>
<tr>
<td>Total cholesterol (mmol l(^{-1}))</td>
<td>6·4 ± 0·11</td>
</tr>
<tr>
<td>Triglycerides (mmol l(^{-1}))</td>
<td>2·1 ± 0·11</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>52 (42%)</td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>29 (24%)</td>
</tr>
<tr>
<td>Carotid arterial stenosis &gt;50%</td>
<td>31 (25%)</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>20 (16%)</td>
</tr>
<tr>
<td>Previous ischaemic stroke</td>
<td>7 (6%)</td>
</tr>
<tr>
<td>Patients with Fontaine stage</td>
<td></td>
</tr>
<tr>
<td>IIA</td>
<td>9 (7·5%)</td>
</tr>
<tr>
<td>IIIB</td>
<td>105 (85%)</td>
</tr>
<tr>
<td>III</td>
<td>9 (7·5%)</td>
</tr>
<tr>
<td>Continuing worsening of intermittent claudication</td>
<td>36 (19%)</td>
</tr>
<tr>
<td>Pain free walking distance on a treadmill (m)</td>
<td>68 ± 3·6</td>
</tr>
<tr>
<td>Maximum walking distance on a treadmill (m)</td>
<td>125 ± 6·5</td>
</tr>
</tbody>
</table>

Table 2 Details of events

<table>
<thead>
<tr>
<th>Enrolled/followed up (n)</th>
<th>123/121</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observation period (years)</td>
<td>4·2 ± 0·2</td>
</tr>
<tr>
<td>Fatal thrombotic events (n)</td>
<td>15</td>
</tr>
<tr>
<td>Sudden cardiac death</td>
<td>3</td>
</tr>
<tr>
<td>Fatal MI</td>
<td>8</td>
</tr>
<tr>
<td>Fatal stroke</td>
<td>2</td>
</tr>
<tr>
<td>Other vascular deaths</td>
<td>2</td>
</tr>
<tr>
<td>Non-fatal thrombotic events (n)</td>
<td>23</td>
</tr>
<tr>
<td>Non-fatal myocardial infarction</td>
<td>8</td>
</tr>
<tr>
<td>Non-fatal ischaemic stroke</td>
<td>9</td>
</tr>
<tr>
<td>Other non-fatal vascular events</td>
<td>6</td>
</tr>
<tr>
<td>Total number of thrombotic events (n)</td>
<td>38</td>
</tr>
<tr>
<td>Non-vascular deaths (n)</td>
<td>16</td>
</tr>
<tr>
<td>Total number of events (n)</td>
<td>54</td>
</tr>
</tbody>
</table>

Mean levels of haemostatic factors across the categories of events are shown in Table 3. The baseline concentrations of fibrinogen, prothrombin fragment 1+2, D-dimer and \(\beta\)-thromboglobulin exceeded the upper limit of normal levels in all groups of patients.

The age-adjusted relative risk of fatal and non-fatal thrombotic events for the lower vs the middle tertile of platelet aggregation distribution was 2·67 (95% CI 0·84–7·46; \(P=0·02\)) and for the higher vs the middle tertile of platelet aggregation distribution was 2·23 (95% CI 1·29–13·86; \(P=0·02\)).

The age-adjusted relative risk of fatal and non-fatal events for the lower vs the middle tertile of platelet aggregation distribution was 2·67 (95% CI 0·84–7·46; \(P=0·02\)).

The age-adjusted relative risk of fatal and non-fatal events for the higher vs the middle tertile of platelet aggregation distribution was 2·23 (95% CI 1·29–13·86; \(P=0·02\)).

It should be mentioned that there was a tendency to higher levels of proteins released from activated platelets in patients with low platelet aggregation compared to
<table>
<thead>
<tr>
<th>Factor</th>
<th>Normal range</th>
<th>All patients (n=121)</th>
<th>Total thrombotic events (n=38)</th>
<th>Fatal thrombotic events (n=15)</th>
<th>Non-fatal thrombotic events (n=23)</th>
<th>Non-vascular deaths (n=16)</th>
<th>No events (n=74)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrinogen (g . l⁻¹)</td>
<td>&lt;3·5</td>
<td>4·38 ± 0·1</td>
<td>4·13 ± 0·3</td>
<td>3·93 ± 0·3</td>
<td>4·32 ± 0·5</td>
<td>4·36 ± 0·3</td>
<td>4·48 ± 0·2</td>
</tr>
<tr>
<td>F₁+₂ (nm)</td>
<td>0·4–1·1</td>
<td>3·54 ± 0·3</td>
<td>3·87 ± 0·7</td>
<td>3·13 ± 0·5</td>
<td>4·46 ± 1·2</td>
<td>5·27 ± 1·7</td>
<td>3·13 ± 0·3</td>
</tr>
<tr>
<td>D-dimer (ng . ml⁻¹)</td>
<td>&lt;400</td>
<td>811·7 ± 100·0</td>
<td>1194·6* ± 241·7</td>
<td>1278·43* ± 348·1</td>
<td>1121·19 ± 345·1</td>
<td>588·7 ± 127·3</td>
<td>701·84 ± 121·9</td>
</tr>
<tr>
<td>PAI-1 (IU . ml⁻¹)</td>
<td>5–15</td>
<td>14·62 ± 0·9</td>
<td>13·67 ± 1·7</td>
<td>14·82 ± 2·3</td>
<td>12·42 ± 2·6</td>
<td>13·54 ± 3·7</td>
<td>15·35 ± 1·2</td>
</tr>
<tr>
<td>PAI-1 (ng . ml⁻¹)</td>
<td>11–69</td>
<td>55·5 ± 5·0</td>
<td>44·2 ± 8·5</td>
<td>40·7 ± 11·9</td>
<td>51·1 ± 12·4</td>
<td>64·4 ± 8·9</td>
<td>57·9 ± 7·3</td>
</tr>
<tr>
<td>TPA (ng . ml⁻¹)</td>
<td>1–12</td>
<td>9·9 ± 0·7</td>
<td>11·4 ± 1·9</td>
<td>9·9 ± 0·7</td>
<td>11·5 ± 2·1</td>
<td>10·3 ± 3·2</td>
<td>9·5 ± 0·8</td>
</tr>
<tr>
<td>PAP complex (μg . l⁻¹)</td>
<td>99–368</td>
<td>332 ± 35·4</td>
<td>369 ± 59·7</td>
<td>166 ± 25·7</td>
<td>384 ± 62·2</td>
<td>337 ± 69·6</td>
<td>323 ± 43·5</td>
</tr>
<tr>
<td>β-TG (IU . ml⁻¹)</td>
<td>10–40</td>
<td>312·2 ± 21·6</td>
<td>285·9 ± 59·7</td>
<td>309·6 ± 44·4</td>
<td>268·7 ± 67·9</td>
<td>251·3 ± 20·4</td>
<td>329·5 ± 28·2</td>
</tr>
</tbody>
</table>

F₁+₂ = prothrombin fragment 1+2; PAI-1 = plasminogen activator inhibitor type I; PAP = plasmin-α₂-antiplasmin; *P<0·05 vs no event group.
those with high platelet aggregation (β-thromboglobulin: 332·5/±45·5 vs 256·6/±23·3 IU . ml/·1, P=0·2; and PAI-1 antigen: 71·7/±14·0 vs 46·7/±5·5 ng . ml/·1, P=0·08, respectively).

To consider the significance of D-dimer and platelet aggregation as predictors of thrombotic events, a multiple logistic regression analysis was performed. All clinical and laboratory variables listed in Tables 1 and 3 were included in the Cox regression model. As shown in Table 5, high D-dimer level and low platelet aggregation remained significant predictors of thrombotic events. Multiple regression analyses also indicated independent associations between diabetes mellitus, cerebrovascular disease, worsening of intermittent claudication at the recruitment and incidence of events.

Discussion

Intermittent claudication has been considered to be a 'surgical' disease, possibly because the most effective and rapid treatment is vascular reconstruction. However, atherosclerotic lesions in lower limb arteries have a benign course. Our findings, consistent with other prospective studies/16,20,21/ found that relatively few patients with intermittent claudication experience significantly deteriorating leg symptoms without surgical treatment. Most patients in our study improved their walking distance, and only three of them had to undergo amputation.

On the other hand, intermittent claudication is not only a symptom of peripheral occlusive disease, but is also an indicator of generalized atherosclerotic disease, associated with a greatly increased cardio- and cerebrovascular morbidity and mortality rate/16,17,22–24/. In the present study, at least 42% of patients have coexisting coronary artery disease, and 16% have evidence of cerebrovascular disease. Despite improvement of leg symptoms during the observation period, the prevalence of coronary and cerebrovascular diseases had risen significantly and the proportion of patients with coronary and cerebrovascular diseases increased one-, six- and two-fold respectively.

Patients with peripheral arterial occlusive disease are at increased risk of developing thrombotic events, in particular, myocardial infarctions, ischaemic strokes and vascular deaths. The overall mortality in our study was 26%, one half of deaths were due to thrombotic events, and the total rate of vascular events during the observation period was as high as 31%, and agrees with results obtained in large prospective studies/16,17,24/.

Now it is generally accepted that thrombosis superimposed on a disrupted atherosclerotic plaque causes acute coronary syndromes, ischaemic stroke, and peripheral vascular occlusion/1–3/. The possibility that organization of relatively common asymptomatic non-occlusive thrombi contributes to plaque growth also seems likely/2,3/. Thus, thrombosis accompanying atherosclerosis (atherothrombosis) is the most important mechanism by which arteries become occluded.

Many studies indicated that blood coagulation cascade is activated in patients with peripheral atherosclerosis/14,15,25,26/. Plasma levels of F 1+2 that reflect the enzymatic activity of Factor Xa on prothrombin was found to be elevated, indicating that thrombin is formed

### Table 4 Age-adjusted correlation coefficients between plasma D-dimer level and prothrombin fragment 1+2, β-thromboglobulin, PAI-1, t-PA, plasmin-α-antiplasmin complex, fibrinogen, cholesterol and triglycerides

<table>
<thead>
<tr>
<th>Parameter</th>
<th>r</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prothrombin fragment 1+2</td>
<td>0·35</td>
<td>&lt;0·01</td>
</tr>
<tr>
<td>PAI-1 activity</td>
<td>−0·30</td>
<td>&lt;0·05</td>
</tr>
<tr>
<td>PAI-1 antigen</td>
<td>0·05</td>
<td>ns</td>
</tr>
<tr>
<td>t-PA antigen</td>
<td>0·02</td>
<td>ns</td>
</tr>
<tr>
<td>Plasmin-α-antiplasmin complex</td>
<td>0·32</td>
<td>&lt;0·05</td>
</tr>
<tr>
<td>β-thromboglobulin</td>
<td>0·03</td>
<td>ns</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>0·08</td>
<td>ns</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>−0·06</td>
<td>ns</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>−0·03</td>
<td>ns</td>
</tr>
</tbody>
</table>

ns=not significant; PAI-1=plasminogen activator inhibitor type I; t-PA=tissue plasminogen activator.

### Table 5 Results of multiple logistic regression for prediction of thrombotic events in patients with peripheral arterial occlusive disease

<table>
<thead>
<tr>
<th>Variable</th>
<th>RR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>D-dimer (quintiles of distribution)*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quintiles II–IV, 280–861 ng . ml/·1</td>
<td>7·49</td>
<td>0·96–58·60</td>
<td>0·06</td>
</tr>
<tr>
<td>Quintile V, &gt;861 ng . ml/·1</td>
<td>14·07</td>
<td>1·72–115·18</td>
<td>0·01</td>
</tr>
<tr>
<td>Platelet aggregation (tertile of distribution)#</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lower tertile (&lt;7%)</td>
<td>4·63</td>
<td>1·31–16·33</td>
<td>0·02</td>
</tr>
<tr>
<td>Higher tertile (&gt;17·8%)</td>
<td>2·61</td>
<td>0·85–8·02</td>
<td>0·09</td>
</tr>
<tr>
<td>Glucose intolerance and/or diabetes mellitus</td>
<td>5·18</td>
<td>1·53–17·51</td>
<td>0·008</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>8·63</td>
<td>2·72–27·57</td>
<td>0·0003</td>
</tr>
<tr>
<td>Continuing worsening of intermittent claudication</td>
<td>2·58</td>
<td>1·17–5·69</td>
<td>0·02</td>
</tr>
</tbody>
</table>

RR=relative risk; CI=confidence interval.

*Relative risk was computed vs the lower quintile of D-dimer distribution.

#Relative risk was computed vs the middle third of platelet aggregation distribution.
in these patients\cite{14}. The platelets are also in an increased state of activation. As has clearly been demonstrated, products released from activated platelets, such as /afii9826-thromboglobulin (measured in our study) and platelet factor 4 and thromboxane A\textsubscript{2} are raised in patients with peripheral arterial occlusive disease\cite{27}. Whether the hypercoagulability state is a cause or a consequence of occlusive vascular disease, however, remains uncertain. It is likely that much of the observed activation of blood coagulation is secondary to vascular disease, then predisposing an individual to further development of atherosclerosis and thrombosis.

Our results demonstrate that the plasma concentration of D-dimer — a breakdown product of cross-linked fibrin — exceeded the upper limit of normal level in patients with peripheral arterial occlusive disease. This implies that the intensity of the blood coagulation is sufficient for formation of stabilized fibrin which overlies atherosclerotic plaques. It has been demonstrated in our previous study\cite{25} that intravascular fibrin thrombus formation significantly correlated with the extent of atherosclerotic lesions, and was in accordance with the results reported by Lassila et al.\cite{15} and Fowkes et al.\cite{8}.

It should be emphasized that D-dimer levels in circulating blood depends not only on fibrin formation, but also on fibrinolytic activity. Thus, an increased D-dimer level indicates the presence of active fibrinolysis, which may limit thrombus formation in patients with peripheral atherosclerosis. Our finding of a positive correlation between D-dimer and plasmin-\alpha\textsubscript{2}-antiplasmin complex and an inverse correlation between D-dimer and PAI-1 activity support this concept. We have previously shown\cite{25} that D-dimer level was directly associated with the activity of t-PA, a primary mediator of intravascular fibrinolysis.

The main finding in this study was that the high level of D-dimer was associated with thrombotic events, independent of conventional cardiovascular risk factors and baseline clinical manifestations of cardiac, cerebral and peripheral atherosclerosis. In several prospective studies, D-dimer was also predictive of stroke and myocardial infarction in samples of the general population as well as in patients with peripheral arterial disease\cite{7–9,28,29}.

We also found a relationship between platelet aggregation and thrombotic events. Relative risk was significantly elevated for the lowest vs the middle tertile of the ADP-induced platelet aggregation value. As far as we know, this is the first study which demonstrates that low platelet aggregation is associated with the subsequent development of vascular events. It is tempting to speculate that this paradoxical association between low platelet aggregation and thrombosis may be a consequence of platelet activation in the circulation leading to a decrease of their sensitivity to agonists in vitro. This suggestion is confirmed by our finding of an inverse association between in vitro platelet aggregation and plasma concentrations of platelet alpha granule proteins (\beta-thromboglobulin and PAI-1 antigen). However, these findings have yet to be confirmed in other studies.

Diabetes mellitus was also strongly predictive of thrombotic events in our study. Diabetes mellitus is thought to contribute to acceleration of atherosclerosis...
through smooth-muscle-cell hypertrophy and hyperplasia, increased synthesis of extracellular matrix proteins, endothelial dysfunction and subsequent hypercoagulation[30].

Impaired glucose metabolism as well as high D-dimer level and ‘low’ platelet aggregation may indicate endothelial damage and an increase in thrombosis. It is important to notice that none of our patients had clinical signs or symptoms of acute thrombosis at the recruitment.

Active treatment aimed at reducing cardiovascular complications is particularly important in patients with peripheral arterial occlusive disease. Platelet inhibitors play a key role in the secondary prevention of arteriothrombosis. The Antiplatelet Trialists’ Collaboration provides strong evidence that long-term use of antiplatelet drugs provides a reduction of approximately 10–25% of incidence of acute ischaemic events[31]. Aspirin is by far the most widely used antiplatelet agent, and all patients included in our study were recommended to take it. However, acetylsalicylic acid is a relatively weak platelet inhibitor, that only moderately affects platelet adhesion and/or aggregation triggered by thrombin, ADP and collagen. Novel agents, such as clopidogrel, that selectively inhibit platelet activation by ADP, have been shown to be more potent antiplatelet drugs than aspirin[32]. There is also evidence that, when combined with aspirin, ADP-receptor antagonists may further reduce the incidence of ischaemic events[33,34]. We also may hypothesize that patients with peripheral occlusive disease, who have increased platelet activation, could benefit from platelet glycoprotein IIb/IIIa inhibitors. However, the efficacy of oral agents for chronic IIb/IIIa receptor antagonism needs further evaluation[35].

Enhanced thrombin formation in patients with chronic leg ischaemia makes it reasonable to use heparin in the management of intermittent claudication. It has been reported that long-term treatment with low-molecular weight heparin can improve the claudication time and is well tolerated[36,37].

Evidence suggests that oral anticoagulants may be effective in both primary and secondary prevention of arterial thrombotic events[38,39]. We also suppose that people with elevated D-dimer levels, who are at increased risk of myocardial infarction and stroke, could benefit from oral anticoagulants. Finally, results obtained by Meade et al.[38] allow us to assume that combined treatment with both aspirin and low-dose warfarin may be more effective in patients with peripheral vascular disease that either approach alone.

In conclusion, our results indicate that haemostatic factors may have important aetiological roles in the development of cardiovascular and cerebrovascular events. In particular, measurement of D-dimer level may help to identify patients with peripheral arterial occlusive disease at high risk of future thrombotic complications. An active treatment aimed at modifying the progression and complications of atherosclerosis is extremely important in these patients.

References

[22] Hertzer NR, Beven EG, Young JR et al. Coronary artery disease in peripheral vascular patients — a classification of


