Bleeding Increases the Risk of Ischemic Events in Patients With Peripheral Arterial Disease

Eline S. van Hattum, MD; Ale Algra, MD, PhD; James A. Lawson, MD, PhD; Bert C. Eikelboom, MD, PhD; Frans L. Moll, MD, PhD; Marco J.D. Tangelder, MD, PhD

Background—Patients with peripheral arterial disease are at high risk of ischemic events and therefore are treated with antithrombotics. In patients with coronary artery disease or cerebrovascular disease, bleeding is related to the subsequent occurrence of ischemic events. Our objective was to assess whether this is also the case in patients with peripheral arterial disease.

Methods and Results—All patients from the Dutch Bypass and Oral Anticoagulants or Aspirin (BOA) Study, a multicenter randomized trial comparing oral anticoagulants with aspirin after infrainguinal bypass surgery, were included. The primary outcome event was the composite of nonfatal myocardial infarction, nonfatal ischemic stroke, major amputation, and cardiovascular death. To identify major bleeding as an independent predictor for ischemic events, crude and adjusted hazard ratios with 95% confidence intervals were calculated with multivariable Cox regression models. From 1995 until 1998, 2650 patients were included with 101 nonfatal major bleedings. During a mean follow-up of 14 months, the primary outcome event occurred in 218 patients; 22 events were preceded by a major bleeding. The mean time between major bleeding and the primary outcome event was 4 months. Major bleeding was associated with a 3-fold increased risk of subsequent ischemic events (crude hazard ratio, 3.0; 95% confidence interval, 1.9 to 4.6; adjusted hazard ratio, 3.0; 95% confidence interval, 1.9 to 4.7).

Conclusions—In patients with peripheral arterial disease, as in patients with coronary artery disease or cerebrovascular disease, major bleeding was independently associated with major ischemic complications. Without compromising the benefits of antithrombotics, these findings call for caution relative to the risks of major bleeding. (Circulation. 2009;120:1569-1576.)

Key Words: atherosclerosis ■ epidemiology ■ hemorrhage ■ peripheral vascular disease ■ risk factors

Peripheral arterial disease (PAD) resulting from atherosclerosis is a major public health burden, with a prevalence of ~27 million people in Europe and North America. Because atherosclerosis is a progressive and systemic disease, patients with PAD are at a high risk of cardiovascular and cerebrovascular ischemic events, including fatal events. The risk of death from a cardiovascular cause in 10 years is 3 to 6 times greater in patients with PAD compared with patients without PAD. Thus, patients with PAD should be treated with antithrombotics to prevent these ischemic events.

Clinical Perspective on p 1576

The main adverse effect of antithrombotic therapy is the risk of bleeding. Nonfatal bleeding leads not only to great discomfort at the time of bleeding but also to more harmful and even life-threatening ischemic events in the long term. In patients with coronary artery disease (CAD), bleeding was found to be independently associated with the occurrence of ischemic events within 30 days to 1 year after bleeding. Recent studies in patients admitted with an acute coronary syndrome have shown that bleeding led to a 4- to 10-fold increased risk of death, myocardial infarction, or stroke during hospital admission with a graded response related to the severity of bleeding. In addition, patients who were admitted with an acute ischemic stroke had a 3- to 4-fold increased risk of in-hospital recurrent stroke, myocardial infarction, and death or severe dependence at discharge.

To the best of our knowledge, the ischemic consequences of bleeding, possibly promoted by antithrombotic treatment, have been described only in patients with CAD or cerebrovascular disease and have not yet been studied in patients with PAD. Patients with PAD have a vascular morbidity and mortality at least as high as patients with CAD or cerebrovascular disease. Additionally, patients with PAD show a trend toward a higher incidence of bleeding. Hence, our aim was to study the influence of major bleeding on the risk...
of subsequent ischemic events in patients with PAD receiving antithrombotic therapy in a large randomized controlled trial.

Methods

Patients and Treatment
All patients in the Dutch Bypass and Oral Anticoagulants or Aspirin (BOA) Study were included in the present study. Full details of the Dutch BOA Study have been published elsewhere, and are briefly summarized here. Between 1995 and 1998, this multicenter randomized trial included a total of 2650 patients with PAD after infragenual bypass surgery. The effectiveness of oral anticoagulation with phenprocoumon or acenocoumarol with a target international normalized ratio range of 3.0 to 4.5 was compared with that of aspirin (100 mg carbasulate calcium daily) for the prevention of infrainguinal bypass occlusion, amputation, and other vascular events. Follow-up visits took place at 3 and 6 months after surgery and every 6 months thereafter to record graft patency, the occurrence of ischemic or bleeding complications, and adherence to trial medication.

Outcome Events
Major bleeding was defined as nonfatal bleeding requiring hospital attendance regardless of the interventions applied, including bleeding in a critical area or organ, ie, intracranial, retroperitoneal, gastrointestinal, and intraocular bleeding, which largely corresponded with the criteria of the International Society on Thrombosis and Hemostasis. Hospital attendance for epistaxis, hematuria, and menorrhagia was defined as minor bleedings. Bleeding episodes that occurred within 30 days after surgery were excluded from the present study because they were considered surgery related. The primary outcome event was the composite of death resulting from cardiovascular causes, nonfatal myocardial infarction, nonfatal ischemic stroke, or major amputation above the ankle (whichever occurred first during follow-up). Secondary outcome events were death resulting from all causes, death resulting from cardiovascular causes, fatal or nonfatal myocardial infarction, fatal or nonfatal ischemic stroke, major amputation, and the composite of death resulting from cardiovascular causes, nonfatal myocardial infarction, and nonfatal ischemic stroke. Death resulting from cardiovascular causes did not include fatal bleedings; however, a sensitivity analysis was done in which we included fatal bleedings. Fatal bleeding was defined as a bleeding event that resulted in death within 30 days after bleeding. In addition, sensitivity analyses were conducted with intracranial and intraocular bleedings excluded.

Statistical Analyses
Baseline variables with a continuous outcome were summarized as means and discrete variables as frequencies and percentages. Any missing data were imputed with simple linear regression analysis incorporating variables associated with the missing data. In patients with multiple bleedings, the bleeding that occurred first was the index bleeding. Baseline characteristics associated with major bleeding were estimated with univariable Cox regression models and reported as hazard ratios (HRs) with corresponding 95% confidence intervals (CIs). Those with a value of \( P \leq 0.25 \) were introduced in a multivariable Cox regression model to identify independent predictors for major bleeding. All models incorporated major bleeding as a dependent variable and baseline characteristics as independent variables with time from study entry to index bleeding or last follow-up.

In analyses of the association between bleeding and vascular events, the time of major bleeding was considered the start date. To equalize the start date between bleeders and nonbleeders, the start date of nonbleeders was pushed up with the mean time between study entry and the index bleeding. Patients without any follow-up time left after the mean time to index bleeding was subtracted from their total follow-up time were excluded from further analyses.

Only outcome events that occurred after the start date were included. Nonfatal ischemic events that occurred before the index bleeding or within the censored follow-up time were considered medical history and added to the baseline variables for further analyses.

Risks of vascular events in patients with and without bleeding were compared with HRs and corresponding 95% CIs. Crude HRs were derived from univariable Cox regression models, with the primary outcome event incorporated as the dependent variable and bleeding as the independent variable with time from start date to the first outcome event or last follow-up. Adjusted HRs were calculated by including independent predictors for bleeding in the multivariable Cox regression model. Additional analyses were done for the first 30 days of follow-up and from that time up to 40 months. The assumption of proportionality of the hazards for events over time was tested with the Schoenfeld test. To assess whether HRs differed between patients treated with aspirin and those treated with oral anticoagulation, we calculated the interaction term of bleeding and trial medication.

The occurrence of the primary outcome event for patients with and without major bleeding is presented graphically as Kaplan-Meier curves stratified for trial medication. Separate analyses were done for minor bleedings.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Patients and Follow-Up
A total of 2650 patients were included in our study. The baseline characteristics of the patients (64% male; mean age, 69 years; median age, 70 years) are listed in Table 1.

The mean time between randomization and major bleeding was 9.2 months (range, 0 to 37.5 months). Patients without major bleeding and a total follow-up of \( \leq 9.2 \) months \((n = 420)\) were excluded from further analyses. The remaining 2230 patients had a mean follow-up of 14 months (range, 0 to 39 months). When minor bleedings were included, the mean time between randomization and occurrence of major or minor bleeding was 9.9 months (range, 0 to 37.5 months). Patients without any bleeding and a total follow-up of \( \leq 9.9 \) months \((n = 464)\) were excluded from further analyses. The remaining 2186 patients had a mean follow-up of 14 months (range, 0 to 39 months).

Incidence and Predictors of Bleeding
A total of 120 initial major bleeding events (4.5%) occurred, 19 of which were fatal (Table 2). Nine of the initial major bleeding events were followed by a second fatal bleeding, resulting in a total of 28 fatal bleedings. Of the 101 initial nonfatal major bleedings, almost half were gastrointestinal bleedings (48%), followed by intracranial bleedings (9%). Blood transfusions were given in 20 patients, and 20 patients stopped their allocated trial medication after index bleeding.

Patients who experienced a major bleeding were older; had critical limb ischemia with ulcers or gangrene, diabetes mellitus, and hypertension; and were more frequently allocated to oral anticoagulants compared with patients without major bleeding (Table 1). Patients without major bleeding more often had intermittent claudication without signs of critical limb ischemia and more frequently received a femoropopliteal bypass with the distal anastomosis above the knee compared with patients who did experience a major bleeding. Independent predictors for major bleeding were age (HR, 1.032 per year; 95% CI, 1.010 to 1.055), use of oral
anticoagulants (HR, 2.5; 95% CI, 1.6 to 3.8), and critical limb ischemia (HR, 1.7; 95% CI, 1.1 to 2.5).

In total, 45 initial minor bleedings occurred. The majority of these minor bleedings were hematuria (69%), followed by epistaxis (27%) and menorrhagia (4%; Table 2).

**Outcome Events**

The primary outcome event occurred in 218 patients: 98 (45%) in the anticoagulant group and 120 (55%) in the aspirin group (Table 3). A first myocardial infarction occurred in 36 patients, a first ischemic stroke in 37 patients, a first major amputation in 67 patients, cardiovascular death in 127 patients, and all-cause death in 240 patients.

The mean time between major bleeding and the primary outcome event was 3.9 months (range, 0 to 19.6 months). Of the 101 patients with a nonfatal major bleeding, 22 patients (22%) had a primary outcome event compared with 196 events (9%) in 2230 patients without a major bleeding (crude HR, 3.0; 95% CI, 1.9 to 4.6; Table 3 and Figure 1A). After multivariable adjustment, the risk of the primary outcome event remained 3 times higher in patients with a previous major bleeding compared with those without major bleeding (adjusted HR, 3.0; 95% CI, 1.9 to 4.7). Although no violation of proportional hazards was found for the first 30 days after the start date \( (P=0.375) \) and from 1 to 40 months of follow-up \( (P=0.162) \), the increased risk of the primary outcome event was present mainly in the first 30 days after bleeding (adjusted HR, 3.3; 95% CI, 1.5 to 7.2; Figure 1B) compared with the risk from 1 to 40 months after bleeding (adjusted HR, 1.5; 95% CI, 0.8 to 2.9; Figure 1C).

For all secondary outcome events, the risks were higher among bleeders than nonbleeders and reached statistical significance for ischemic stroke and fatal events. The adjusted risks of ischemic stroke, cardiovascular death, all-cause death, and the composite of cardiovascular death, nonfatal myocardial infarction, and nonfatal ischemic stroke were \( \approx 3 \) to 4 times higher in bleeders than in nonbleeders.

### Table 1. Baseline Characteristics of Patients With and Without Major Bleeding

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>Major Bleeding Present ( (n=101), n (%) )</th>
<th>Major Bleeding Absent ( (n=2549), n (%) )</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic characteristics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>61 (60)</td>
<td>1637 (64)</td>
<td>0.9 (0.6–1.3)</td>
</tr>
<tr>
<td>Median age &gt;70 y</td>
<td>62 (61)</td>
<td>1264 (50)</td>
<td>1.7 (1.1–2.5)</td>
</tr>
<tr>
<td>Age, mean ± SD, y</td>
<td>72±9.5</td>
<td>69±10.0</td>
<td>1.041 (1.019–1.064)*</td>
</tr>
<tr>
<td>Medical history</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angina pectoris</td>
<td>22 (22)</td>
<td>414 (16)</td>
<td>1.4 (0.9–2.3)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>22 (22)</td>
<td>442 (17)</td>
<td>1.4 (0.9–2.2)</td>
</tr>
<tr>
<td>TIA and/or stroke</td>
<td>16 (16)</td>
<td>290 (11)</td>
<td>1.6 (0.9–2.7)</td>
</tr>
<tr>
<td>ABI =0.9</td>
<td>95 (94)</td>
<td>2396 (94)</td>
<td>1.0 (0.5–2.3)</td>
</tr>
<tr>
<td>ABI ≤0.6</td>
<td>71 (70)</td>
<td>1689 (66)</td>
<td>1.2 (0.8–1.9)</td>
</tr>
<tr>
<td>Critical limb ischemia</td>
<td>65 (64)</td>
<td>1230 (48)</td>
<td>2.0 (1.3–3.0)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>34 (34)</td>
<td>666 (26)</td>
<td>1.5 (1.0–2.2)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>48 (48)</td>
<td>983 (39)</td>
<td>1.4 (1.0–2.1)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>18 (18)</td>
<td>418 (16)</td>
<td>1.1 (0.7–1.9)</td>
</tr>
<tr>
<td>Smoking</td>
<td>48 (48)</td>
<td>1390 (55)</td>
<td>0.7 (0.5–1.1)</td>
</tr>
<tr>
<td>Vascular intervention</td>
<td>48 (48)</td>
<td>1154 (45)</td>
<td>1.1 (0.7–1.6)</td>
</tr>
<tr>
<td>Trial bypass</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Femorocrural/pedal bypass</td>
<td>28 (28)</td>
<td>503 (20)</td>
<td>1.6 (1.0–2.5)</td>
</tr>
<tr>
<td>Venous bypass</td>
<td>60 (59)</td>
<td>1486 (58)</td>
<td>1.0 (0.7–1.5)</td>
</tr>
<tr>
<td>Trial medication</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral anticoagulants</td>
<td>72 (71)</td>
<td>1254 (49)</td>
<td>2.5 (1.6–3.9)</td>
</tr>
</tbody>
</table>

\*HR based on age as a continuous variable.

### Table 2. Bleeding Characteristics per Trial Medication

<table>
<thead>
<tr>
<th>Bleeding Characteristics</th>
<th>Aspirin, n (%)</th>
<th>Oral Anticoagulants, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonfatal major bleeding</td>
<td>29</td>
<td>72</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>23 (79)</td>
<td>44 (61)</td>
</tr>
<tr>
<td>Intracranial</td>
<td>1 (3)</td>
<td>8 (11)</td>
</tr>
<tr>
<td>Intraocular</td>
<td>0 (0)</td>
<td>7 (10)</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>2 (7)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Other</td>
<td>3 (10)</td>
<td>11 (15)</td>
</tr>
<tr>
<td>Nonfatal minor bleeding</td>
<td>19</td>
<td>26</td>
</tr>
<tr>
<td>Hematuria</td>
<td>15 (79)</td>
<td>16 (62)</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>4 (21)</td>
<td>8 (31)</td>
</tr>
<tr>
<td>Menorrhagia</td>
<td>0 (0)</td>
<td>2 (8)</td>
</tr>
<tr>
<td>Fatal bleeding</td>
<td>11</td>
<td>17</td>
</tr>
<tr>
<td>Blood transfusion</td>
<td>6</td>
<td>14</td>
</tr>
</tbody>
</table>
The HRs for the primary and secondary outcomes did not differ significantly between patients treated with aspirin and those treated with oral anticoagulants according to the probability values of the interaction terms for bleeding and trial medication (range, 0.16 to 0.95). Figure 2 shows the occurrence of the primary outcome event in bleeders and nonbleeders stratified for trial medication over time.

If fatal bleedings were included in the primary outcome event, the HRs increased (crude HR, 4.0; 95% CI, 2.8 to 5.9; adjusted HR, 4.0; 95% CI, 2.7 to 5.9). If intracranial bleedings were excluded from the definition of major bleeding, the HRs decreased slightly (crude HR, 2.7; 95% CI, 1.7 to 4.3; adjusted HR, 2.7; 95% CI, 1.7 to 4.4). If intraocular bleedings were excluded from the definition of major bleeding, the results remained essentially the same (crude HR, 3.0; 95% CI, 1.9 to 4.7; adjusted HR, 2.9; 95% CI, 1.8 to 4.6). Minor bleeding showed a trend toward an increased risk of subsequent ischemic events without reaching statistical significance after adjustment for independent predictors of minor bleeding (crude HR, 2.2; 95% CI, 1.1 to 4.5; adjusted HR, 1.6; 95% CI, 0.8 to 3.4; Figure 3).

Discussion

Our study in patients with PAD treated with infringuinal bypass surgery and antithrombotics showed that, like in patients with CAD or cerebrovascular disease, nonfatal major bleeding was a strong and independent predictor for subsequent major ischemic events, resulting in a 3-fold increased risk for the occurrence of nonfatal myocardial infarction, nonfatal ischemic stroke, major amputation, or cardiovascular death. Importantly, this adverse outcome was driven mainly by fatal cardiovascular events.

International guidelines advocate antiplatelets, mainly aspirin, to reduce the risk of secondary vascular ischemic events in patients with PAD.4,5 The Dutch BOA Study proved that oral anticoagulants are more effective for the prevention of autologous vein graft occlusion compared with aspirin and tended to be more effective in the prevention of cardiovas-
cicular death, myocardial infarction, stroke, and amputation. However, the annual risk of bleeding with aspirin was 2.3% and with oral anticoagulants almost twice as high at 4.1%. The relatively high value of avoiding hemorrhagic complications and the low value of long-term graft patency, in addition to the practical complexity of anticoagulation therapy with vitamin K antagonists, have diminished the widespread recommendation and use of oral anticoagulants in patients with severe PAD treated with vein grafts.

The net clinical benefit of antithrombotic treatment depends on the subtle balance between a reduction in the risk of ischemic events and the inherent bleeding risk. However, this balance is more complicated than previously considered because bleeding seems to be associated with ischemic consequences. In 40,087 patients from the Global Registry of Acute Coronary Events (GRACE) trial admitted for an acute myocardial infarction, a 2-fold risk of in-hospital death was found in patients with a major bleeding compared with those without a major bleeding. Pooled data of the Organisation to Assess Strategies for Ischaemic Syndromes (OASIS) registry, the OASIS-2 study, and the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial showed an increased adjusted risk of death (HR, 5.4; 95% CI, 4.0 to 7.3), second myocardial infarction (HR, 4.4; 95% CI, 3.2 to 6.2), and stroke (HR, 6.5; 95% CI, 3.5 to 11.8) within 30 days after bleeding in patients admitted for myocardial infarction. Six months later, patients with bleeding still had a
significantly increased risk of in-hospital death (HR, 1.5; 95% CI, 1.0 to 2.4) compared with patients without bleeding. These observations have led to a statement in the latest European Society of Cardiology guidelines for non-ST-segment elevation acute coronary syndromes. The prevention of bleeding is stated to be equally as important as the prevention of ischemic events because prevention of bleeding is also associated with a significant reduction in the risk for death, myocardial infarction, and stroke. In addition, in patients admitted for ischemic stroke, gastrointestinal bleeding during hospitalization was independently associated with recurrent stroke, myocardial infarction, venous thromboembolism, and death at 6 months.

Our findings on the predictors, risk, and consequences of bleeding are in accordance with the results in patients with CAD or cerebrovascular disease. Increasing age, hypertension, renal disease, history of stroke, and a history of CAD were repeatedly reported to be independent predictors for bleeding. In line with previous studies, we found increasing age to be independently related to the risk of major bleeding and identified trends for hypertension, a history of angina pectoris, and myocardial infarction. We also found critical limb ischemia and the use of oral anticoagulants to be independently associated with the occurrence of major bleeding.

No statistical significant differences were seen for the occurrence of ischemic events after major bleeding between oral anticoagulant– and aspirin-treated groups on the basis of the probability values of the interaction terms for bleeding and trial medication included in multivariable models. Patients allocated to oral anticoagulants had twice as many bleedings compared with patients who used aspirin but had fewer major ischemic events. With bleeding independently associated with the occurrence of ischemic events, one would expect patients in the oral anticoagulant group to have more ischemic events. The observed discrepancy of more bleeding events followed by fewer ischemic events might be explained by the concurrent effect of oral anticoagulants in preventing ischemic events. Moreover, the majority of ischemic events were prevented in patients treated with oral anticoagulants who did not experience a major bleeding. This balance between beneficial and adverse effects of oral anticoagulants has been described in greater detail in our report on the main results of the Dutch BOA Trial.

Several hypotheses are suggested to explain the association between bleeding and new ischemic events. First, bleeding often leads to cessation of antithrombotic therapy. After bleeding, fewer patients admitted with an acute coronary syndrome used antithrombotics at discharge compared with patients without bleeding. The mortality risks were significantly increased among patients who discontinued their aspirin (odds ratio [OR], 7.6; 95% CI, 4.4 to 12.0), thienopyridines (OR, 8.9; 95% CI, 4.4 to 18.1), or unfractionated heparin (OR, 1.9; 95% CI, 1.1 to 3.4) after bleeding compared with those who continued antithrombotic therapy despite bleeding. This would suggest that antithrombotic therapy should be continued after bleeding. In our study, only 20 patients (1%) stopped their antithrombotic treatment as a result of index bleeding. These numbers are too small to draw any conclusions. More research is warranted to study the consequences of discontinued antithrombotic therapy. For now, the main concern is to minimize the patient’s increased bleeding risk when given oral anticoagulants by means of intensive international normalized ratio monitoring, avoidance of dual antithrombotic therapy, and thorough screening for vascular risk factors to intensify secondary prevention.

Second, bleeding might indicate that the patient has a more advanced stage of atherosclerosis with fragile blood vessels and is more vulnerable to adverse outcomes. This is supported by the observed dose-related association between the severity of bleeding and ischemic events (Figure 3).

Other proposed mechanisms include the effects of hypotension, anemia, and blood transfusion. In our study, 20 patients (1%) received blood transfusion after bleeding, which was too few to assess whether blood transfusion was independently associated with adverse outcomes.

Anemia was found to be associated with an increased risk of death, repeat revascularization, or myocardial infarction within 30 days after percutaneous coronary intervention (OR, 1.9; 95% CI, 1.2 to 6.0). At 1 year after percutaneous coronary intervention, anemia was still significantly associated with higher mortality rates (OR, 1.9; 95% CI, 1.5 to 2.4); HR, 1.8; 95% CI, 1.3 to 2.3). The risk of ischemic events and death within 30 days after admission for an acute coronary syndrome appeared to be related to the hemoglobin plasma level.

Blood transfusion was reported to be significantly associated with increased in-hospital (OR, 2.0; 95% CI, 1.1 to 3.2) and 1-year (OR, 1.9; 95% CI, 1.4 to 2.5) mortality risk after percutaneous coronary intervention independently of prior bleeding severity but was significantly related to the number of transfusion units (OR, 1.5 per unit transfused; 95% CI, 1.4 to 1). Certain biochemical and immunological effects of stored blood that negatively influence systemic oxygen delivery might partially explain this association.

Some limitations apply to our study. Our analyses were posthoc but were applied to a large prospective trial data set. This trial was pragmatic in nature, reflecting normal daily practice, and thus applicable to a wide PAD population. The number of clinical variables collected in the Dutch BOA Study was limited. Therefore, we do not have information on the influence of other potentially relevant variables such as hemoglobin. Major bleeding was defined in the Dutch BOA Study as any nonfatal bleeding requiring hospital attendance regardless of applied treatment. To define major bleeding for the present study in line with the more widely accepted International Society on Thrombosis and Hemostasis criteria, we excluded hospital attendance for epistaxis, hematuria, and menorrhagia and defined them as minor bleedings. Still, the definition of major bleeding by the International Society on Thrombosis and Hemostasis is less stringent and possibly will detect more bleeding episodes than the 2 most frequently applied classifications for major bleeding in cardiology trials defined by the Thrombolysis in Myocardial Infarction (TIMI) and Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) study groups. Thus, comparing our results with other studies requires appropriate caution. Finally, studying the consequences of bleeding is limited to an
observational study design with methodological challenges because patients with and without bleeding differ in vascular risk factors, resulting in bias caused by confounding, and differ in follow-up time, resulting in survival bias (Table 1). To reduce confounding as much as possible, we adjusted for known differences in risk factors for bleeding in multivariable models. To adjust for survival bias, we equalized the time at risk for ischemic events in bleeders and nonbleeders in a practical and interpretable manner by starting the follow-up period in nonbleeders 9.2 months after study entry (the mean time between study entry and time of the index major bleeding). Nevertheless, the time scales will never be identical between study groups; therefore, the estimated HRs for determining the impact of bleeding on clinical events should be interpreted with appropriate caution. These first data in PAD patients are in line with growing evidence that bleeding is independently associated with subsequent death, myocardial infarction, and stroke in patients across the spectrum of atherosclerotic disease. Therefore, optimal antithrombotic treatment should go hand in hand with optimal prevention of bleeding complications. Measures to achieve this include the use of low-dose aspirin and gastrointestional protection if needed, optimization of treatment compliance, and maintenance of optimal anticoagulant intensity.

Conclusions
We provide the first insight into the independent adverse effect of bleeding on subsequent ischemic events in a large trial reflecting the general population of patients with PAD treated with oral anticoagulants or aspirin after peripheral bypass surgery. These new findings are in line with evidence in patients with CAD or cerebrovascular disease and call for bleeding in clinical investigations of antithrombotic medicinal products in peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): executive summary: a collaborative report from the American Association for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines (Writing Committee to Develop Management of Patients with Peripheral Arterial Disease) endorsed by the American Association for Cardiovascular and Pulmonary Rehabilitation; National Heart, Lung, and Blood Institute; Society for Vascular Nursing; TransAtlantic Inter-Society Consensus; and Vascular Disease Foundation. J Am Coll Cardiol. 2006;21:1239–1312.

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Disclosures
None.

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