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Risk of Major Haemorrhage in Patients after Infrainguinal Venous Bypass Surgery: Therapeutic Consequences? The Dutch BOA (Bypass Oral Anticoagulants or Aspirin) Study

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on behalf of the Dutch Bypass Oral Anticoagulants or Aspirin (BOA) Study Group

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Objectives. *The beneficial effect of oral anticoagulants after infrainguinal venous bypass surgery is compromised by bleeding complications. We developed a model to identify patients, treated with anticoagulation, at risk of major haemorrhage and estimated whether this complication could have been prevented if patients had received aspirin.*
Design. *Randomised clinical trial.*
Methods. *Data of patients who participated in the Dutch Bypass Oral Anticoagulation or Aspirin Study were reanalysed using Cox regression. After infrainguinal bypass surgery these patients were randomised to oral anticoagulants* (n=*1326) or aspirin* (n=*1324).*
Results. *Predictors of major haemorrhage for patients on oral anticoagulants were increased systolic blood pressure (≥140 mmHg, hazard ratio [HR] 1.62), age ≥75 years (HR 2.77) and diabetes mellitus (HR 1.60). If the 345 patients in the highest risk quartile had received aspirin, major haemorrhages would have been reduced from 46 to 22, with no major changes in ischemic events and graft occlusions. In the subgroup with venous bypasses major haemorrhages would have been reduced from 27 to 13, at the cost of seven more ischemic events (mostly fatal) and 17 more graft occlusions.*
Conclusions. *Treating patients at highest risk of major haemorrhage with aspirin instead of oral anticoagulants would have resulted in a reduction of non-fatal haemorrhages, but for venous bypasses this reduction was outweighed by an increase in ischemic events and graft occlusions. We still recommend treatment with oral anticoagulants after peripheral venous bypass surgery.*

Keywords: Infrainguinal bypass; Prognosis; Haemorrhage; Anticoagulants; Antiplatelets.

Introduction

The Dutch Bypass Oral anticoagulants or Aspirin (BOA) Study has demonstrated that oral anticoagulants are more effective than aspirin for the prevention of occlusion of venous bypass grafts in patients with atherosclerosis of the femorodistal arteries, hazard ratio (HR) 0.69 (95% confidence interval (CI) 0.54–0.88).[1] Oral anticoagulant treatment tended to decrease the total number of vascular ischemic deaths, myocardial infarctions, cerebrovascular accidents and amputations compared with aspirin: HR 0.89 (95% CI 0.75–1.06). Fatal bleeding complications and haemorrhagic strokes were included in this composite endpoint. On the other hand, there was a two-fold increased risk of all bleeding complications in the patients treated with oral anticoagulants: HR 1.96 (95% CI 1.42–2.71). Health care costs, event-free survival, and quality-adjusted life years in patients after infrainguinal bypass surgery were not different in patients treated with aspirin and patients treated with oral anticoagulants. The extra costs of monitoring patients treated with oral anticoagulants were limited and play no role in the decision for treatment.[2]

This fragile balance of beneficial antithrombotic effects and adverse bleeding events emphasises the

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need for monitoring the optimal intensity of anticoagulant treatment, to offer the best risk–benefit ratio, i.e. the optimal balance of ischemic and haemorrhagic events. The optimal target range of international normalized ratio (INR) for these patients after infrainguinal bypass surgery appeared to be an INR between 3 and 4.[3]

To further minimize the risk of oral anticoagulant treatment it is important to identify risk factors and quantify their predictive values for bleeding complications. Previous studies have searched for risk factors for major haemorrhage in patients on oral anticoagulation.[4–9] In two of these studies, the authors developed a model to predict bleeding complications.[5–7] Predictors of bleeding complications were increasing age, male sex, malignancy and history of gastrointestinal tract bleeding, history of stroke and one of the following co-morbidities: recent myocardial infarction, renal insufficiency, severe anaemia at discharge or diabetes mellitus. Both risk scores were developed in outpatients treated with oral anticoagulation. Hence, the authors could not study whether the bleeding complications could have been prevented if these patients had received other antithrombotic drugs.

The aim of the first part of the present study was to develop a model to predict major haemorrhage in patients who received anticoagulant therapy after infrainguinal bypass surgery to identify the group at highest risk. In the second part of this study, it was estimated whether in patients at highest risk of major haemorrhage these haemorrhages could have been prevented if patients would have received aspirin. Furthermore, the number of ischemic events and graft occlusions on oral anticoagulation and on aspirin are estimated in the group at highest risk of major haemorrhage.

Methods

Study population

All patients from the Dutch BOA Study were subjects of the current study. The Dutch BOA Study was a multicentre randomised trial in which the effectiveness of oral anticoagulants (phenprocoumon or acenocoumarol INR 3.0–4.5) was compared with that of aspirin (80 mg daily) in the prevention of graft occlusions and other thrombotic events after infrainguinal bypass grafting. Background, design, and results of the trial have been reported elsewhere.[10] Between April 1995 and March 1998, 1326 patients were randomised to oral anticoagulant treatment and 1324 to aspirin treatment. Patients were assessed 3 and 6 months after surgery and every 6 months thereafter.

Study outcome

The outcome of interest of the first part of the study was major haemorrhage. It was defined as fatal bleeding, intracranial haemorrhage, or any bleeding requiring hospital attendance, irrespective of interventions. Postoperative bleeding episodes were not included in the analyses because of frequent modifications in antithrombotic therapy perioperatively and because these episodes may be related to surgery rather than allocated antithrombotic treatment.

The outcome of the interest of the second part of the study was major haemorrhage classified as described above, ischemic events classified as non-fatal myocardial infarction, non-fatal ischemic stroke or vascular ischemic death, and infrainguinal graft occlusions.[10]

Data Analysis

First part

For approximately 20% of the patients data for systolic blood pressure was missing. Linear regression analysis with the variables age, history of hypertension, history of myocardial infarction, history of transient ischemic attack or ischemic stroke, smoking and hyperlipidemia was used to impute the missing data on systolic blood pressure.

Univariable associations between potential predictors and the occurrence of major haemorrhage were assessed with Cox regression analyses and expressed as HRs with corresponding 95% CIs.

Candidate predictor variables associated with major haemorrhage in the univariate analyses (p value ≤ 0.20) were selected. The selected variables were entered into multivariable Cox regression analyses with forward stepwise selection to develop a multivariable prognostic model. The variables systolic blood pressure and age were categorized in the multivariable analyses to develop a prediction model that could be applied easily in clinical practice.

To adjust for overfitting we performed bootstrapping.[11] Bootstrapping replicates the process of sample generation from an underlying population by drawing samples with replacement from the original data set, of the sample size of the original data-set.[12] With bootstrapping the internal validity can be estimated.[11] Finally, a risk score was constructed and categorized