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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

Table 1. Univariable associations of potential predictors with major haemorrhage in patients on oral anticoagulation after infrainguinal bypass surgery

Variables	Major haemorrhage		HR	95% CI	*p* value
	Yes ($n=108$)	No ($n=1218$)			
Sex (men)	62 (57%)	797 (65%)	0.76	0.52–1.11	.15*
Mean age (SD) (HR per SD (10 years))	72 (10)	68 (10)	1.49	1.21–1.84	.00*
Mean systolic blood pressure (SD) (HR per SD (26 mmHg))	165 (24)	160 (27)	1.18	0.99–1.40	.07*
Systolic blood pressure ≥140 mmHg	96 (89%)	983 (81%)	1.84	1.01–3.35	.05*
History of					
Hypertension	47 (44%)	485 (40%)	1.11	0.76–1.63	.58
Diabetes mellitus	40 (37%)	312 (26%)	1.73	1.17–2.56	.01*
Hyperlipidemia	16 (15%)	195 (16%)	0.91	0.53–1.54	.71
Transient ischemic attack or stroke	14 (13%)	146 (12%)	1.19	0.68–2.08	.55
Angina pectoris	18 (17%)	196 (16%)	1.00	0.61–1.67	.99
Myocardial infarction	20 (19%)	201 (17%)	1.20	0.74–1.95	.46
Smoking	47 (44%)	668 (55%)	0.63	0.43–0.92	.02*
Type of bypass (femorocrural graft vs. femoropopliteal graft)	46 (43%)	496 (41%)	1.47	0.95–2.27	.08*
Bypass material (non-venous vs. venous)	27 (25%)	229 (19%)	1.09	0.74–1.60	.66

SD, standard deviation.
* Variables with a *p* value ≤0.20 were introduced in the multivariable Cox regression analyses with stepwise forward selection.

into quartiles of risk of major haemorrhage. Kaplan–Meier methods were used to estimate the cumulative proportion of patients with major haemorrhage.

Second part

To evaluate the distribution of events, if patients at highest risk of major haemorrhage on oral anticoagulants had received aspirin, the observed numbers of major haemorrhages, ischemic events and graft occlusions in the patients in the highest risk group were compared with the observed numbers in patients with the same characteristics who received aspirin. The numbers were reported separately according to graft material, since the main report of the Dutch BOA Study demonstrated that oral anticoagulation was more effective for the prevention of graft occlusion in patients with a venous bypass and aspirin more effective in patients with a non-venous bypass.[10]

Results

First part

The risk of major haemorrhage was 4.9% per year (95% CI 4.0–5.8%) for patients on oral anticoagulation; 108 major haemorrhages occurred in 2192 person years. The mean follow-up time was 1.7 years. Factors that were associated with major haemorrhage in patients on oral anticoagulation in the univariate analyses were male sex, increasing age, increasing systolic blood pressure, diabetes mellitus, smoking and a femorocrural bypass (Table 1).

In the multivariable Cox regression analyses, age (≥75 years, HR 2.77), hypertension (systolic blood pressure ≥140 mmHg, HR 1.62) and diabetes mellitus (HR 1.60) were predictors of major haemorrhage (Table 2). After bootstrapping the regression coefficients were shrunk by 7% to adjust for overfitting.

Table 2. Independent predictors of risk of major haemorrhage in patients on oral anticoagulation after infrainguinal bypass surgery

Variable	Hazard ratio	95% CI	*p* value	Coefficients after shrinkage*	Score
Age					
≤60 years	1 (ref.)		.001	0	0
61–74 years	1.56	0.83–2.94		0.41	4
≥75 years	2.77	1.46–5.25		0.94	9
Systolic blood pressure					
<140 mmHg	1 (ref.)		.12	0	0
≥140 mmHg	1.62	0.89–2.97		0.44	4
History of diabetes mellitus					
No	1 (ref.)		.02	0	0
Yes	1.60	1.08–2.37		0.44	4

CI, confidence interval.
* Regression coefficients of the multivariable model were shrunken with bootstrapping to adjust for overfitting.

From the shrunken regression coefficients a risk score was computed (range 0–17) and categorized into quartiles (Q1–Q4) of the total population: Q1: 0–4; Q2: 8; Q3: 9–12 and Q4: 13–17 (Table 3).

Second part

In the patients on oral anticoagulants the annual risk of major haemorrhage was 9.0% for the group with a score in the fourth quartile ($n=345$) and 43% of all major haemorrhages occurred in this group (Table 3 and Fig. 1).

The number of major haemorrhages that would have occurred in these 345 patients, in the highest risk quartile of major haemorrhage, if they had received aspirin would have reduced from 46 to 22 (Table 4). The number of fatal bleeds would not have altered. The number of ischemic events that would have occurred with aspirin was estimated to be 76 instead of the observed 75 ischemic events. The number of graft occlusions would have been similar.

For patients with a venous graft only ($n=202$ (59%)), non-fatal major haemorrhage would have been reduced from 27 to 13 cases. However, in patients with a venous bypass the number of fatal haemorrhages would have increased from 1 to 2, non-fatal ischemic events from 8 to 9 events and graft occlusions from 25 to 42 events. The number of vascular ischemic deaths would have increased from 35 to 41.

Discussion

In the Dutch BOA Study, oral anticoagulants improved venous bypass patency at cost of more major bleeding episodes. If patients at highest risk of major haemorrhage on oral anticoagulation with a venous bypass had received aspirin, less major non-fatal haemorrhages would have occurred. However, this benefit would have been at the cost of more vascular ischemic deaths, non-fatal ischemic events and graft occlusions. Therefore, we conclude that even patients with a venous bypass, at highest risk of major haemorrhage, should be treated with oral anticoagulation.

Age, systolic blood pressure and diabetes mellitus are predictors of risk of major haemorrhage in patients treated with oral anticoagulants after infrainguinal bypass surgery. The results of this study are supported by results from previous studies in various patients with vascular disease treated with oral anticoagulation, that have shown that older age is associated with increased occurrence of major haemorrhage.[4,6,9,13]

Table 3. Score quartiles and risk of major haemorrhage in patients on oral anticoagulation after infra-inguinal bypass surgery

Score quartiles	Combination of predictors			Annual risk	Patient years	Major haemorrhages	Type of major haemorrhage				Hazard ratio (95% CI)
	Age	Hypertension	History of diabetes			Total	GI	Urinary	ICH	Other	
Q1: 0–4	*	*	*	2.5%	530	13	4	2	2	5	1 (ref.)
	61–74 years	*	*								
	*	≥140 mmHg	*								
	*	*	Yes								
Q2: 8	61–74 years	≥140 mmHg	*	4.0%	886	35	16	4	5	10	1.62 (0.86–3.06)
	61–74 years	*	Yes								
	*	≥140 mmHg	Yes								
Q3: 9–12	≥75 years	*	*	5.2%	267	14	4	2	1	7	2.09 (0.98–4.45)
	61–74 years	≥140 mmHg	Yes								
Q4: 13–17	≥75 years	≥140 mmHg	*	9.0%	509	46	22	8	5	11	3.58 (1.94–6.63)
	≥75 years	*	Yes								
	≥75 years	≥140 mmHg	Yes								
Total				4.9%	2192	108	46	16	13	33	

GI, gastrointestinal; ICH, intracranial haemorrhage; CI, confidence interval.
* Value of the predictor smaller than the used cut-off value.

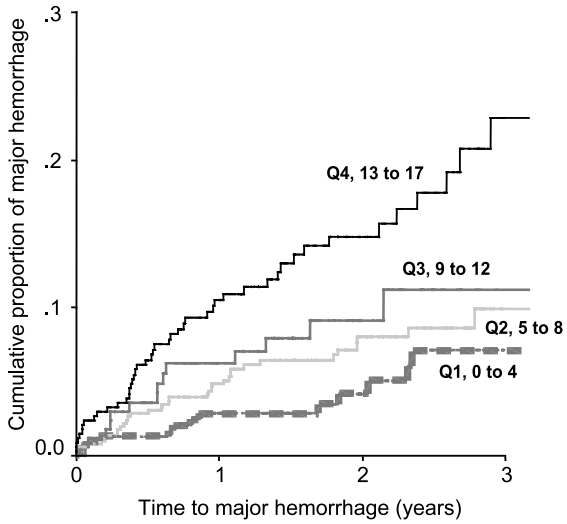

Fig. 1. Cumulative proportion of major haemorrhage per score category in patients on oral anticoagulation after infrainguinal bypass surgery.

Furthermore, hypertension was found to be associated with major haemorrhage.[13] One study in outpatients on oral anticoagulation showed that older age and diabetes mellitus were predictive of risk of major haemorrhage.[5] Furthermore, diabetes mellitus also was shown to be associated with intracerebral haemorrhage.[14]

A limitation of our study is that data from a trial were used to develop a model. For prognostic studies one prefers observational cohort data and not trial data, since in a trial predictors might have been more carefully measured than in normal clinical practice. Moreover, a trial population may not be reflective of the normal population. However, in this study, the predictors of major haemorrhage were age, systolic blood pressure and diabetes mellitus. These characteristics were extracted from the patients' medical record and therefore it is unlikely that these would have been different from those measured in routine clinical practice. Moreover, the trial protocol was pragmatic with patient inclusion and data registration conforming to routine practice. Another limitation of this study was that systolic blood pressure was not reported for all patients. Therefore, we imputed the missing systolic blood pressure with linear regression. To verify the imputation procedure, the mean systolic blood pressure before and after imputation were compared and appeared to be the same. Furthermore, the association with major haemorrhage appeared the same before and after imputation and the point estimates of the co-variables in the model appeared almost similar. Therefore, the imputation was considered to be adequate and we chose to include systolic blood pressure in the multivariable model. Although systolic blood pressure was not associated significantly with major haemorrhage, at a *p*-value cut-off of 0.05, inclusion of systolic blood pressure increased the discriminative power of the model.

We performed bootstrapping to internally validate our model. Optimal estimates of internal validity of regression models are obtained with bootstrapping.[11] Internal validation refers to the performance of a model in patients from a similar population from which the sample originated. In this study after bootstrapping the regression coefficients were shrunk minimally, by approximately 7%, indicating acceptable internal validity.

In conclusion, our model identified a subgroup of patients on oral anticoagulation at highest risk of major haemorrhage. It does not appear to be beneficial

Table 4. Number of major haemorrhagic events and major ischemic events in patients at highest risk (Q4) of major haemorrhage on oral anticoagulation and number if these 345 patients would have received aspirin and numbers for patients at high risk with a venous bypass

	All patients in Q4 ($N=345$)			Patients in Q4 with venous bypass ($N=202$ of 345 patients (59%))		
	Oral anticoagulation	Aspirin	Difference	Oral anticoagulant	Aspirin	Difference
Major haemorrhages	46	22	−24	27	13	−14
Fatal haemorrhage	4	4	=	1	2	+1
Non-fatal haemorrhage						
Intracranial haemorrhage	3	0	−3	2	0	−2
Gastrointestinal	21	9	−12	15	5	−10
Urinary	8	5	−3	4	3	−1
Other	10	4	−6	5	3	−2
Major ischemic events	75	76	+1	43	50	+7
Vascular ischemic death	58	57	−1	34	39	+5
Non-fatal ischemic events						
Ischemic stroke	7	10	+3	4	6	+2
Myocardial infarction	6	5	−1	4	3	−1
Infrainguinal bypass occlusions	73	73	=	25	42	+17

to treat the high risk venous bypass patients with aspirin instead of oral anticoagulants as any reduction of major non-fatal haemorrhage would be outweighed by an increase in ischemic events and graft occlusions. Therefore, the optimal treatment should still be determined according to bypass graft material: oral anticoagulants for venous graft and aspirin for prosthetic grafts.

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