Optimal oral anticoagulant intensity to prevent secondary ischemic and hemorrhagic events in patients after infrainguinal bypass graft surgery

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Objectives: **The purpose of this study was to determine the optimal intensity of oral anticoagulation in patients who participated in a randomized trial of oral anticoagulants or aspirin after infrainguinal bypass graft surgery.**
Methods: **The distribution of patient-time spent in international normalized ratio (INR) classes of 0.5 INR unit was calculated assuming a linear change between successive measurements. INR-specific incidence rates of ischemic and hemorrhagic events were calculated as the ratio of the number of events at a certain INR category and the total patient-time spent in that class. The relationship between INR class and event rates was quantified by rate ratios calculated in a Poisson regression model.**
Results: **In 1326 patients (mean age, 69 years) 41,928 INR measurements were recorded in 1698 patient-years. Patients spent 50% of the total time within the target range of 3.0 to 4.5 INR. Most of the patient-time (60%) was spent between 2.5 and 3.5 INR. For each increasing class of 0.5 INR, the incidence of ischemic events (n = 154, INR data on event available in 49%) decreased by a factor of 0.97 (95% CI, 0.87-1.08). The incidence of major bleeding (n = 123, INR data on event available in 65%) increased significantly by a factor of 1.27 (95% CI, 1.19-1.34) for each increasing 0.5 INR category. The optimal target range was 3.0 to 4.0 INR, with an incidence of 3.8 events (0.9 ischemic and 2.9 hemorrhagic) per 100 patient-years.**
Conclusions: **The target range of 3.0 to 4.0 INR is the optimal range of achieved anticoagulation intensity and is safe for the prevention of ischemic events in patients after infrainguinal bypass graft surgery. (J Vasc Surg 2001;33:522-7.)**

Until recently, the optimal medical treatment for the prevention of infrainguinal bypass graft occlusion was a matter of debate. Most Dutch vascular surgeons prescribed oral anticoagulants,[1] supported by a well-organized system of thrombosis centers. In other countries, aspirin was the most frequently used antithrombotic treatment.[2]

The recently performed Dutch Bypass Oral anticoagulants or Aspirin (BOA) Study demonstrated beneficial effects of oral anticoagulants with regard to the prevention of venous bypass graft occlusion, whereas aspirin proved to be more effective in the prevention of nonvenous graft occlusion.[3] Oral anticoagulant treatment prevented more myocardial infarctions and ischemic strokes compared with aspirin. On the other side, an increased risk of hemorrhagic complications was demonstrated in the patients treated with oral anticoagulants. The target range of anticoagulation, as recommended by the Federation of Dutch Thrombosis Centers, was 3.0 to 4.5 international normalized ratio (INR).[4] Similar intensities, between 2.5 and 4.8 INR, had been used in other prevention trials in patients after coronary bypass graft surgery, atrial fibrillation, myocardial infarction, and cerebral ischemia.[5-8] The optimal intensity of anticoagulant treatment offers the best risk-benefit ratio (ie, the optimal balance of ischemic and hemorrhagic events). This optimum has been determined for several indications: after myocardial infarction between 2.0 and 4.0 INR,[7] after cerebral ischemia of cardiac origin between 2.0 and 4.0 INR,[6] and in patients with prosthetic heart valves between 2.5 and 5.0 INR.[9] For patients who had cerebral ischemia of presumed arterial origin, anticoagulation intensities with INR above 3.0 resulted in an excess of bleeding complications.[8]

The exact date of most of the graft occlusions is unknown, which makes this primary end point of the Dutch BOA Study unsuitable for analysis of anticoagulation intensity at the time of occlusion. The date of onset of secondary outcome events, such as myocardial infarction and hemorrhage, is exactly known. To determine the optimal intensity of oral anticoagulant treatment in patients after infrainguinal bypass graft surgery, we quantitatively analyzed the occurrence of arterial thromboembolic and hemorrhagic events with respect to the level of anticoagulation preceding the events in 1326 patients randomized to oral anticoagulant treatment in the Dutch BOA Study.

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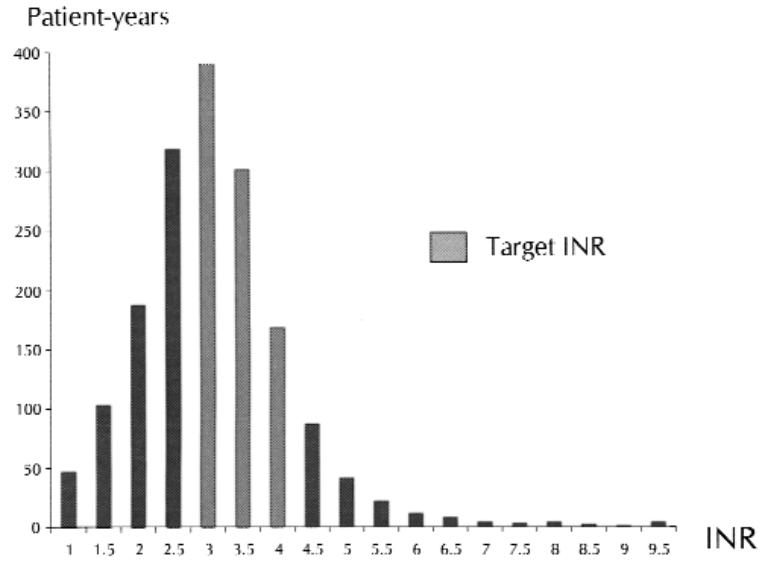

Fig 1. Distribution of patient-years spent in each INR unit. *INR,* International normalized ratio.

METHODS

Patients

All patients studied were included in the Dutch BOA Study, a multicenter randomized trial to compare the effectiveness of oral anticoagulants with that of aspirin in preventing occlusions of infrainguinal bypass grafts and other thrombotic events. Background, design, and results of the trial have been reported elsewhere.[3] The study was approved by the ethics committees of all participating hospitals and by the Dutch Health Insurance Council. All patients who were enrolled in the study gave written informed consent. Between April 1995 and March 1998, 1326 patients were randomized to oral anticoagulant treatment. All patients who were receiving active treatment were subjects of the current study, which resulted in 1698 patient-years of follow-up in the current study.

Anticoagulant treatment

Oral anticoagulant treatment consisted of phenprocoumon or acenocoumarol, depending on the surgeons' preference. Calculation of dosage adjustment to achieve the target INR of 3.0 to 4.5 was performed at the anticoagulation clinics according to their own protocol. INR data of all follow-up visits were reported to the BOA Trial Office.

Calculation of INR-specific events rates

Data on the occurrence of events (the numerator) and data on patient-time spent in various categories of anticoagulation intensity (the denominator) are required to calculate INR-specific events rates.

Definition of events. The primary outcome event of the Dutch BOA study was graft occlusion; secondary outcome events were (vascular) death, nonfatal myocardial infarction, nonfatal stroke, amputation, vascular intervention, and major hemorrhage. The date of detection of graft occlusion is not necessarily the true date of graft occlusion. Unfortunately, this makes this end point unsuitable for analysis of INR values at these presumed dates of graft occlusion. For the current study we analyzed data on the occurrence of vascular death, myocardial infarction, stroke, and hemorrhage only, because the date of onset of these events is exactly known. All of these events (including sequential events in the same patients) were eligible for the analysis.

Death from vascular disease included sudden death (reliable observation of the time between onset of symptoms and death, or the patient was found dead) or death from stroke, myocardial infarction, congestive heart failure, peripheral vascular disease, hemorrhage, or other vascular causes. If no clear data on the cause of death were available, the case was classified as vascular death. Myocardial infarction was defined by at least two of the following: a history of chest discomfort for at least half an hour, specific cardiac enzyme levels more than twice the upper limit of normal, or the development of new Q waves on the standard 12-lead electrocardiogram. Stroke was defined as focal neurologic deficit of sudden onset, persisting for more than 24 hours, with an increase in handicap of at least one grade on the modified Rankin scale.[10,11] Findings from computed tomography brain scanning, if performed, were recorded. Major hemorrhage included fatal bleeding, intracranial hemorrhage, or any bleeding requiring hospital attendance, regardless of interventions. Postoperative bleedings (within 30 days after surgery) were excluded from this analysis. Events were adjudicated and classified by an independent panel of two neurologists, cardiologists, vascular internists, or vascular surgeons, who were unaware of treatment allocation. Discrepancies were resolved with the involvement of a third reviewer. If this resulted in three different classifica-

Table I. Occurrence of first ischemic and hemorrhagic outcome events among the 1326 patients allocated to oral anticoagulants

Death from ischemic causes	121
Death from hemorrhagic causes	16
Myocardial infarction (fatal and nonfatal)	29
Stroke (fatal and nonfatal)	35
Ischemic stroke	17
Hemorrhagic stroke	14
Undefined stroke (no CT scan available)	4
Hemorrhage (including intracranial)	108

CT, Computed tomography.

Table II. Types and total numbers of hemorrhage (number of fatalities)

Gastrointestinal	51 (5%)
Urinary tract	17 (0%)
Intracranial	18 (8%)
Other	33 (3%)
Total	119 (16%)

tions, consensus was reached through discussion. The INR at the time of the occurrence of an event was obtained from hospital records. If this INR measurement was not performed or unavailable, we used the last INR measured in the thrombosis center within 8 days before the event. If this measurement was unavailable, the event was excluded from the analysis.

Calculation of patient-time spent in various categories of anticoagulation intensity. The number of patient-years is calculated by multiplying the number of patients by the time of follow-up in years. The total patient-time at different categories of INR was calculated assuming a gradual linear change with increments of 1 day between two measurements, with small steps of 0.1 INR. This method has been described in detail by Rosendaal et al.[12]

Calculation of INR-specific event rates. The incidence of events at various achieved intensities of anticoagulation was calculated by dividing the number of events by the total observation time with categories of 0.5 INR.

Statistical analysis

The precision of the event rate estimates was obtained from a Poisson model and given as 95% CI. The Poisson model was fitted to determine the relationship between the intensity of anticoagulation (in categories of 0.5 INR) and the incidence of thromboembolic and hemorrhagic events. Data analysis was performed with EGRET statistical package (EGRET Software Corp, Seattle, Wash).[13]

RESULTS

From a total of 2650 randomized patients, 1326 were allocated to oral anticoagulant treatment, with 2287 patient-years of follow-up. The mean age of the patients allocated to oral anticoagulants was 69 years (range, 33-93); 65% were male. The indication for surgery was intermittent claudication in 50% of the patients and critical ischemia in the other half. Eighty-one percent of all bypass grafts were femoropopliteal, and 19% were femorocrural or femoropedal. In 59%, an autologous vein was used for bypass grafting; in the other patients a biograft, prosthesis, or composite graft was used.

A total of 182 patients stopped taking their assigned oral anticoagulant medication during follow-up. In the current study, we analyzed 41,928 INR measurements in an on-treatment period of 1698 patient-years. Patients were monitored on average once per 2.1 weeks, resulting in an average of 25 visits to the anticoagulation clinics per year. Fig 1 shows the distribution of patient-years spent in each INR category (0.5 INR unit). The INR was within the target range of 3.0 to 4.5 approximately 50% of the time. The intensity of anticoagulation was below the target range 39% of the time, whereas the intensity was above the target range 11% of the time. Most patient-time (60%) was spent within the range of 2.5 to 4.0 INR.

The incidence of first outcome events is shown in Table I. There were 121 ischemic deaths, whereas there were 16 fatal bleedings. The types of hemorrhage (including repeated events) are shown in Table II.

A total of 154 ischemic and 123 hemorrhagic events occurred during follow-up (this includes repeated events). INR measurements within 8 days before the event were available from 76 (49%) ischemic and 80 (65%) hemorrhagic events. The number of patient-years, events, and INR-specific incidence rates of ischemic and hemorrhagic events is given in Table III. The single INR category of 3.0 to 3.5 had the lowest incidence rate of combined events: 3.3 events per 100 patient-years (95% CI, 1.8-5.7). The incidence of ischemic and hemorrhagic events was 1.0 and 2.3, respectively, per 100 patient-years. The two INR categories with the lowest incidence rates of both ischemic and hemorrhagic events were from 3.0 to 4.0, with a total incidence of 3.8 events (0.9 ischemic and 2.9 hemorrhagic) per 100 patient-years.

The INR-specific incidence rates of ischemic and hemorrhagic events are presented graphically in Fig 2. The incidence of ischemic events hardly decreased with increasing INR in the Poisson model: a factor of 0.97 (95% CI, 0.87-1.08) for each INR unit. The incidence of hemorrhage increased significantly for each 0.5 INR unit by a factor of 1.27 (95% CI, 1.19-1.34). Fig 3 presents the INR-specific incidence rates of all events, with the corresponding 95% CIs.

DISCUSSION

The optimal intensity of oral anticoagulation with the lowest incidence of ischemic and hemorrhagic events appears to be between 3.0 and 4.0. In this range, the incidence of ischemic events was low: 0.9 event per 100 patient-years. The incidence of hemorrhagic events was higher when this level of anticoagulation was achieved: 2.9 bleeding complications per 100 patient-years. The inci-

Table III. Incidence of ischemic and hemorrhagic events according to INR categories

		Ischemic events		*Hemorrhagic events*		*All events*	
INR	*Patient-years*	*No.*	*No./100 pt-yrs*	*No.*	*No./100 pt-yrs*	*No.*	*No./100 pt-yrs*
< 2.0	150	23	15.4	9	6.0	32	21.4
2.0-2.4	187	11	5.9	5	2.7	16	8.5
2.5-2.9	318	15	4.7	8	2.5	23	7.2
3.0-3.4	390	4	1.0	9	2.3	13	3.3
3.5-3.9	301	2	0.7	11	3.7	13	4.3
4.0-4.4	167	3	1.8	11	6.6	14	8.4
4.5-4.9	87	2	2.3	7	8.0	9	10.3
5.0-5.4	41	4	9.9	5	12.3	9	22.2
5.5-5.9	21	3	14.3	0	0	3	14.3
≥ 6.0	37	9	24	15	41	24	65
Total	1698	76	5	80	5	156	9

dence of all events was 3.8 per 100 patient-years at this level of anticoagulation. The relative risk of ischemic events decreased only 3% with each increasing INR unit, whereas the incidence of bleedings increased markedly with 27% per increasing INR unit.

The level of anticoagulation in patients with arterial occlusive disease is still a matter of debate. Our findings support the use of a target range of 3.0 to 4.0 INR. This is in accordance with results of other studies performed to determine optimal anticoagulant intensity. Two studies in patients with atrial fibrillation and in patients after myocardial infarction demonstrated optimal anticoagulation intensity of 2.0 to 4.0 INR.[6,7] The optimal intensity in patients with mechanical heart valves was slightly higher, between 2.5 and 5.0.[9] These three studies were performed in ways similar to ours.

Obviously, the gold standard to investigate the optimal therapeutic range is a randomized trial. A limitation of such a trial could be the inescapable fluctuation of intensity of anticoagulation, caused by various patient characteristics and extraneous factors, such as various methods of monitoring the intensity of anticoagulation. However, from a pragmatic point of view, an intensity trial of high versus low should be very well feasible. Also this way, the number of graft occlusions in assigned treatment groups can be studied. The methods we used in the current study for calculating INR-specific incidence rates and the relationship between incidence of events and intensity of anticoagulation are useful for the assessment of the optimal therapeutic range. The total number of patient-years of follow-up (2287) was higher than the number of patient-years in which we registered INR measurements (1698). This difference was caused by patients who discontinued their medication and by missing INR measurements due to several other reasons, mainly logistical. Unfortunately, data about the level of anticoagulation were available in only 49% of the ischemic events and in 65% of the bleedings. This was due to the protocol of the trial, which did not require an INR measurement at the time of an event. Obviously, at the time of a bleeding, the level of anticoagulation is measured more often than at the time of an ischemic event. These missing data cause an underestimation of the true incidences. This, however, does not affect the result of estimation of optimal anticoagulation intensity because the distribution of patient-years and events over the INR units is not likely to be changed by missing data. The missing data influence the results only if there is an association with the INR level, which is unlikely. We chose a strict criterion for the inclusion of an event in the analysis. The last INR measure had to be within a maximum of 8 days before the event; otherwise, the event was excluded from the analysis of INR-specific incidences of events. We think that measurements taken more than 1 week before an event represent the INR at the moment of the event insufficiently. Because of the smaller numbers of patient-years in the lowest and highest levels of anticoagulation, the estimated incidence rates of events at these levels are not as precise as the incidence rates at the levels between 2.0 and 4.5. The latter incidence rates, which are the most precisely estimated, are the important ones, given that the target ranges most often used vary between these levels. The achieved anticoagulation intensity varied most of the patient-time from 2.5 to 3.9 INR. Obviously, safety with regard to bleeding complications was the goal during the monitoring and administering of anticoagulant therapy. Caution was probably stimulated because of the advanced age of most of the patients.[14] This caution appeared to be legitimate because the risk of bleeding increases sharply with a factor 1.27 for each increasing 0.5 INR category, whereas the risk of an ischemic event increases only 3% with each decreasing category of 0.5 INR. The increasing risk of ischemic events starts at anticoagulation intensities below 3.0, whereas the risk of hemorrhagic events begins to increase at INR levels above 3.5. Regardless of possible differences in severity and risks of the two types of events, we should attempt to achieve the lowest incidence of both ischemic and hemorrhagic events, at an anticoagulation level between 3.0 and 3.5 INR.

This large prospective study demonstrates that the optimal intensity of anticoagulation is 3.0 to 3.5 INR. A target range of 3.0 to 4.0 INR is safe with regard to hemorrhage and effective with regard to the prevention of ischemic events in patients with an infrainguinal bypass graft.

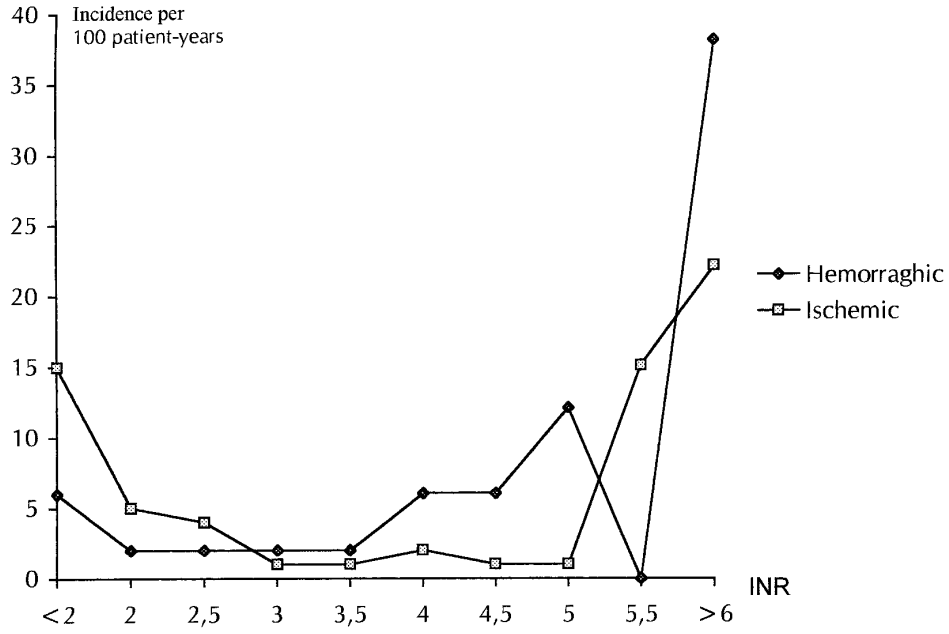

Fig 2. INR-specific incidence rate of hemorrhagic and ischemic events. *INR*, International normalized ratio.

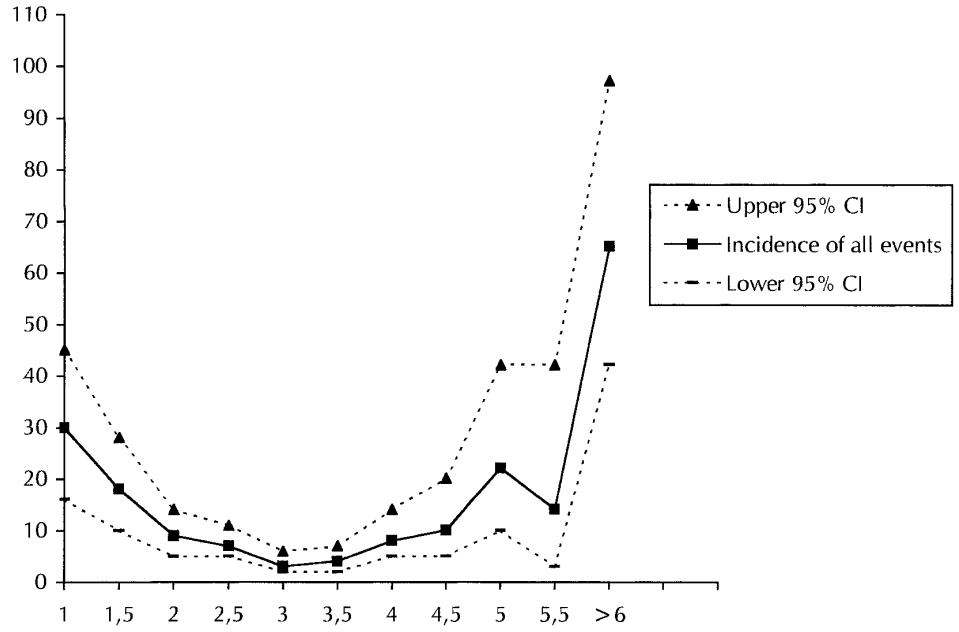

Fig 3. INR-specific incidence rate of all events with corresponding 95% CI.

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