Articles

Bleeding complications of oral anticoagulant treatment: an inception-cohort, prospective collaborative study (ISCOAT)

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Summary

Background Bleeding is the most serious complication of the use of oral anticoagulation in the prevention and treatment of thromoboembolic complications. We studied the frequency of bleeding complications in outpatients treated routinely in anticoagulation clinics.

Methods In a prospective cohort from thirty-four Italian anticoagulation clinics, 2745 consecutive patients were studied from the start of their oral anticoagulation (warfarin in 64%, acenocourmarol in the rest). The target anticoagulation-intensity was low (international normalised ratio [INR] ⩽2·8) in 71% of the patients and high (> 2·8) in the remainder. We recorded demographic details and the main indication for treatment and, every 3-4 months, INR and outcome events. Such events included all complications (bleeding, thrombosis, other), although only bleeding events are reported here, and deaths. We divided bleeding into major and minor categories.

Findings 43% of the patients were women. Nearly three-fifths of the patients were aged 60-79; 8% were over 80. The main indication for treatment was venous thrombolism (33%), followed by non-ischaemic heart disease (17%). Mean follow-up was 267 days. Over 2011 patient-years of follow-up, 153 bleeding complications occurred (7·6 per 100 patient-years). 5 were fatal (all cerebral haemorrhages, 0·25 per 100 patient-years), 23 were major (1·1), and 125 were minor (6·2). The rate of events was similar between sexes, coumarin type, size of enrolling centre, and target INR. The rate was higher in older patients: 10·5 per 100 patient-years in those aged 70 or over, 6·0 In those aged under 70 (relative risk 1·75, 95% CI 1·29–2·39, p<0·001). The rate was also higher when the indication was peripheral and/or cerebrovascular disease than venous thromboembolism plus other indications (12·5 *vs* 6·0 per 100 patient-years) (1·80, 1·2–2·7, p<0·01), and during the first 90 days of treatment compared with later (11·0 *vs* 6·3, 1·75, 1·27–2·44, p<0·001). A fifth of the bleeding events occurred at low anticoagulation intensity (INR<2, rate 7·7 per 100 patient-years of follow-up). The rates were 4·8, 9·5, 40·5, and 200 at INRs 2·0–2·9, 3–4·4, 4·5–6·9, and over 7, respectively (relative risks for INR>4·5, 7·91, 5·44–11·5, p<0·0001).

Interpretation We saw fewer bleeding events than those recorded in other observational and experimental studies. Oral anticoagulation has become safer in recent years, especially if monitored in anticoagulation clinics. Caution is required in elderly patients and anticoagulation intensity should be closely monitored to reduce periods of overdosing.

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Introduction

Oral anticoagulant therapy is increasingly used for the prevention and treatment of thromboembolic complications of vascular disease.[1] Bleeding is the most important complication. In a review of observational studies,[2] average annual rates of fatal, major, and major/minor bleeding were 0·8, 4·9, and 15%, respectively. In another review,[3] bleeding rates ranged from 0 to 4·8% for fatal bleeding and from 2·4 to 8·1% for major bleeding. Reliable data are lacking on the true frequency of complications in patients on oral anticoagulants because of methodological limitations.[4] Many studies were done before the introduction of the international normalised ratio system (INR) for prothrombin time (PT),[5,6] or calculated INR retrospectively. Most studies that used the INR system were in highly selected patients. The few observational studies were either retrospective or descriptive, and were not in a clearly defined inception cohort (ie, followed up in one clinic from start of treatment).[4,7] Observational studies that included an inception cohort were retrospective and did not use INR[8] or selected patients.[9]

We have prospectively assessed the rate of bleeding complications in outpatients monitored from the beginning of oral anticoagulation.

Patients and methods

Centres

This study was done in thirty-four centres of the Italian Federation of Anticoagulation Clinics. Each centre is required to: give extensive instructions to all new patients enrolled; follow-up patients by INR; fix the date for next visit and meanwhile

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	All patients	Target INR	
		Low	High
Demography	2745	1954	791
Males	1561	1029	532
Females	1184	925	259
Age (years, mean and range)			
Males	63·6 (8–91)	. .	. .
Females	61·5 (11–93)	. .	. .
Follow-up			
Patient-years	2011	1381	630
Males	1137	729	408
Females	874	652	222
Age (years)			
<70	1779	1225	554
⩾70	966	729	237
Withdrawals	829	669	160
Subjects who moved from centre	134	84	50
Died	102	86	16
Males	54	45	9
Females	48	41	7

Low INR=⩽2·8, high=>2·8.

Table 1: **Demography and follow-up**

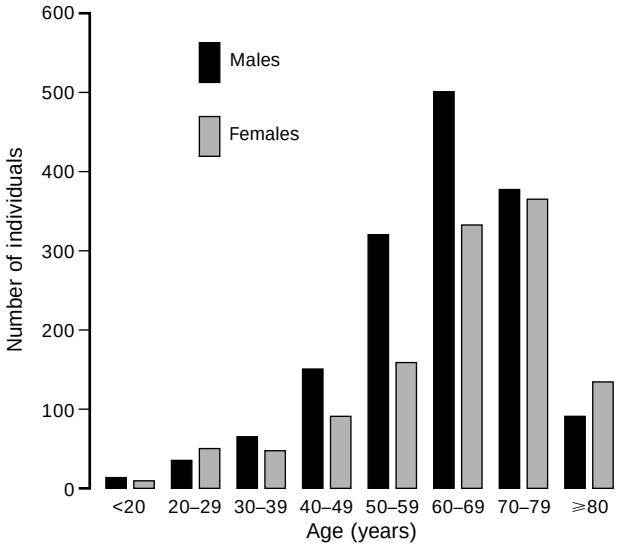

Figure 1: **Distribution of patients by age and sex**

prescribe daily anticoagulant dose; monitor changes in patients' habits, diet, and co-medication, illnesses, bleeding complications and scheduled surgical or invasive procedures; and take part in external laboratory quality-control.

Design and patients

This was an inception cohort study. In each centre, consecutive patients receiving for the first time and within 30 days of admission either warfarin or acenocoumarol (the only two anticoagulant commercially available in Italy) were included, independently of age, indication for anticoagulation, intended therapeutic range, or expected treatment duration. The two exclusion criteria were pregnancy and expected difficulty (usually geographic) in obtaining appropriate follow-up.

Recruitment began in May, 1993, and stopped at the end of October, 1994. The observation period started the day of inclusion in the study and ended on March 31, 1995, or sooner if a major bleeding or thrombotic event occurred, if treatment was discontinued for any reason, or if the patient stopped attending.

For each patient the main indication for oral anticoagulation was recorded. The therapeutic ranges recommended by the Italian Federation of Anticoagulation Clinics were: venous thromboembolism, INR 2–3; non-ischaemic heart disease (including atrial fibrillation and cardiomyopathy), 2–3; ischaemic heart disease (including coronary bypass surgery or coronary angioplasty), 2·5–4·5; cerebral/peripheral artery disease or after arterial surgery, 2·5–4; heart valve disease or biological valve replacement, 2–3; and prosthetic heart valves, 2·5–4·5.

Data collection and monitoring

All centres sent records every 3-4 months of all enrolled patients. Each centre was required to fill in an admission form, including demographic data, indication for anticoagulation (from a standard list), drug used, the start day, the targeted therapeutic range, important co-diseases, and other drugs. Also collected were date of visit, INR, dose (mg per week), date of next visit, log of events. Centres were asked to contact the patient, his or her family, or doctor if an appointment was missed by 20 days.

Twenty-five centres used compatible computerised systems for results and prescriptions. Sixteen used the same system.[10]

The results of all visits were checked by the coordinating centre for inconsistencies. When necessary the centres were asked to provide further information, mainly to avoid loss of follow-up.

Laboratory monitoring

Oral anticoagulation was monitored by PT expressed as INR. Centres were asked about their thromboplastin reagent used and its international sensitivity index (ISI). In Italy, many of the most widely used thromboplastin reagents are calibrated by Comitato Italiano per la Standardizzazione dei Metodi in Ematologia e Laboratorio. The thromboplastins used had ISIs under 1·2 in twenty centres, between 1·2 and 1·5 in nine, and over 1·5 in five.

Assessment of anticoagulation

A program provided by F R Rosendaal (University Hospital Leiden, Leiden, Netherlands), was used to calculate the observed percentage time spent at different INRs. The program[11] calculates the total number of days accumulated at different INR in intervals of 0·5 regardless of target values. Patient-years accumulated in INR categories can be calculated for all patients or by stratification. The method does not allocate INR when the interval between two consecutive measurements exceeds 8 weeks, and censors patients after the first outcome event.

The same program was used to calculate the frequency of events at different achieved intensities of anticoagulation (INR<2, 2–3·4, 3·5–4·4, 4·5–6·9, ⩾ 7) by dividing the number of events in patients with "temporally related" INR in each category by the total number of patient-years accumulated in that range. INR was defined as temporally related to an outcome event when it was obtained at the time of the event or during the preceding 8 days. The few outcome events without a temporally related INR were excluded from this evaluation.

Venous thromboembolism	892 (32·5%)
Non-ischaemic heart disease	661 (24·1%)
Dilated cardiomyopathy	136
Atrial fibrillation	462
Endocavitary thrombosis	24
Other	39
Ischaemic heart disease	403 (14·7%)
Post-myocardial infarction	144
After ACBP or PTCA	135
Other	124
Atrial vascular disease	281 (10·2%)
Peripheral	48
Cerebral	93
After vascular surgery	80
After peripheral emboli	44
Other	16
Heart-valve prosthesis	296 (10·8%)
Biological	34
Mechanical	262
Heart-valve disease	183 (6·7%)
Other diagnoses	29 (1·1%)
Total	2745

ACBP=aorto-coronary bypass, PTCA=percutaneous transluminal coronary angioplasty.

Table 2: **Indication for oral anticoagulation**

All	153 (7·6)*	**Minor**	125 (6·2)
Fatal (all cerebral, 4 women)	5 (0·25)	32 haematuria 25 proctorrhagia 16 uterine bleeding 14 gastrointestinal bleeding 14 haematoma 13 large bruising 2 epistaxis 9 other or multiple sites 6 with two minor bleeding episodes 4 with three minor bleeding episodes	
Major	23 (1·1)		
7 digestive			
5 ocular (2 with diabetic retinopathy)			
4 cerebral			
3 haemarthrosis			
2 haemoptysis			
1 retroperitoneal			
1 haematuria			

*Per 100 patient-years.

Table 3: **Bleeding events**

Outcomes

The occurrence of all types of complications (bleeding, thrombosis, other) was recorded, although only bleeding events are considered in this report. Deaths for all causes were recorded and coded as: bleeding, cardiovascular (acute myocardial infarction, stroke), underlying or other diseases, or sudden death. We classified major bleeding as: fatal (death due to haemorrhage); intracranial (documented by imaging), ocular (with blindness), articular, or retroperitoneal; if surgery or angiographic intervention was required to stop bleeding; and if bleeding led to haemoglobin reduction of 2 g/dL or more and/or need for transfusion of two or more blood units. Minor bleeding was all cases of bleeding not classified as major. Non-relevant (small) bleeding was bruising, small ecchymoses or epistaxis, occasional haemorrhagic bleeding, or microscopic haematuria.

In the few cases where this classification was not used, the coordinating centre asked for a more detailed description of the event and adjudicated the event. If classification of the haemorrhagic complication was still uncertain, the event was coded as major bleeding.

Statistics

The SOLO package (version 4.0) was used. Differences between groups were assessed by χ^2 or two-sample proportion tests as appropriate. Cumulative frequency of fatal, major, and minor bleeding events was analysed separately and altogether with the Kaplan-Meier method. Data were censored after the first bleeding complication, after the cessation of oral anticoagulation, or when a patient stopped being monitored. The independent effect of possible risk factors was investigated with Poisson regression.

Results

2745 patients (43% female) were included (table 1). Twenty-five centres enrolled under 100 cases, and nine enrolled over 100. In the centres that enrolled over 100 patients, the number of anticoagulated patients not included in the study (second anticoagulation course, anticoagulation started after 30 days, geographic inacccessibility) ranged from 6 to 11% of the patients included. The anticoagulant drug used was warfarin in 1752 (63·8%) and acenocoumarol in the remaining 993 (36·2%) patients. During the study, 22 patients changed from warfarin to acenocoumarol and 28 from acenocoumarol to warfarin. Most patients were aged between 60 and 79 (57·8%) but 8% were over 80 (figure 1). The mean length of follow-up was 267 days (range 5-660).

The most frequent indication for oral anticoagulation was venous thromboembolism, followed by non-ischaemic heart disease (mainly atrial fibrillation (table 2). To check the variety of the therapeutic ranges and target values in the participating centres (therapeutic ranges that sometimes differed from those recommended by our federation), we evaluated the effects of the intended anticoagulation intensity by dividing the study population into two groups: INR targets of 2·8 or lower and over 2·8 (low and high intensity, respectively). This cutoff was chosen on preliminary analysis of the patients' inclusion forms which showed good discrimination. The low-intensity group had an intended range between 1·8 and 3·5, and included 1954 patients (71·2%). The high-intensity group (therapeutic range 2·5–4·5) included 791 patients (28·8%), mainly with coronary, cerebral, or peripheral arterial disease and surgery, or mechanical heart-valve prosthesis.

During the study 829 patients (30%) withdrew from anticoagulation. In 756 of these cases, the intended treatment period was completed. In 35 cases, anticoagulation was interrupted because of other diseases that required different medical and/or surgical treatments. Although we cannot exclude that some of the patients who discontinued were given other antithrombotic drugs, 38 patients withdrew from anticoagulants because they were recommended by their family doctor or specialist to shift to antiplatelet drugs (aspirin, 31; ticlopidine, 7). 134 patients (4·8%) changed monitoring centre, thus terminating follow-up. 30 patients, mostly because they were on vacation, spent from 30 to 90 days without being monitored. When they resumed follow-up they were carefully questioned about possible complications. 102 patients (3·7%) died during study.

Control of anticoagulation

The total number of INR results was 51 566, with an average time between two measurements of 15 days. The number of patient-years at different INR categories was calculated for 1980 out of the 2011 patient-years of total follow-up (98·4%). We could not allocate INRs to 31 patient-years.

In the whole study population, patients were within, below, and above therapeutic ranges 68·0, 26·1, and 5·9% of the time, respectively. The proportions of time spent within and below the therapeutic ranges were significantly higher and lower, respectively, in patients with low intended anticoagulation intensity ($p<0·001$). The proportion of time below the therapeutic range was significantly lower ($p<0·05$) when thromboplastins with low ISI values (<1·2) were used (data not shown). No differences were found for sex, age, and anticoagulant drug used.

The quality of anticoagulation treatment control was examined in the 141 patients who had bleeding events. In

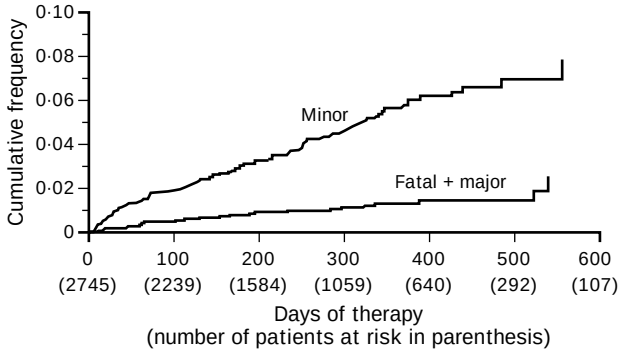

Figure 2: **Cumulative frequency (Kaplan-Meier curves) of fatal plus major and of minor bleeding events during outpatient anticoagulant treatment**

	Patient-years of follow-up	Bleeding			×100 patient-years	Relative risk (95% CI)
		Fatal	Major	Minor		
Sex						
Female	874	4	10	61	8·6	1·25 (0·91–1·71)
Male	1137	1	13	64	6·8	
Age (years)						
<50	288	0	0	20	6·9	
50–69	997	0	7	50	5·7	
⩾70	726	5	16	55	10·5	
Relative risk ⩾70 *vs* 70						1·75 (1·28–2·39, p<0·001)
Indication						
Venous thromboembolism	558	1	7	30	6·8	
Arterial disease	223	1	5	22	12·5	
All others	1230	3	11	73	7·1	
Relative risk arterial disease *vs* others						1·80 (1·20–2·70, p<0·01)
Centres						
<100 recruited	820	2	6	46	6·6	0·79 (1·10–0·57)
>100 recruited	1191	3	17	79	8·3	
Coumarin						
Acenocoumarol	753	2	7	58	8·9	1·30 (0·95–1·79)
Warfarin	1258	3	16	67	6·8	
Target INR						
⩽2·8	1381	3	17	94	8·2	0·75 (1·08–0·52)
>2·8	630	2	6	31	6·2	
Temporally related INR (not available)		2	1	2		
<2	377	0	6	23	7·7	
2–2·9	1116	1	8	45	4·8	
3–4·4	442	2	3	37	9·5	
4·5–6·9	42	0	2	15	40·5	
⩾7	3	0	3	3	200	
Relative risk values ⩾4·5 *vs* <4·5						7·91 (5·44–11·5, p<0·0001)
Timing of events (days)						
⩽90	566	1	9	52	11·0	
>90	1445	4	14	73	6·3	
Relative risk ⩽90 *vs* >90						1·75 (1·27–2·44, p<0·001)

Relative risks are univariate.

Table 4: **Bleeding events stratified by risk factors**

these patients the proportion of time within, below and above therapeutic ranges was 66·3, 24·1, and 9·6%, respectively; the difference in this distribution compared with the distribution in the whole study population was not statistically significant.

Bleeding complications

Bleeding events are detailed in table 3 and figure 2. The rates of bleeding events were not different according to sex, coumarin type, size of enrolling centre, and target zone (table 4). However, the rate was higher in older patients and when the indication for anticoagulant treatment was arterial disease. Among these patients, bleeding was frequent in those with cerebrovascular disease (n=107: 2 major events [1 fatal] both intra-cranial; 10 minor events, 14·5 per 100 patient-years of follow-up) or peripheral emboli (n=44: 2 major and 6 minor events, 21·6 per 100 patient-years). The risk of haemorrhagic events during therapy was higher during the first 90 days of treatment (table 4).

The frequency of bleeding events at different achieved intensities of anticoagulation was investigated by dividing the number of events in patients with temporally related INR in five increasing INR categories by the total number of patient-years accumulated in these categories (table 4). Many bleeding events (29 out of the 147 [20%] with available related INR) occurred at low anticoagulation intensity. However, in 4 of these 29, the low INR on the day of the event had been preceded (within 3-10 days) by value over 4·5, indicating that erratic anticoagulation may have been a cause of bleeding in these cases. The rate of bleeding was significantly lower (p<0·05) in the 2·0–2·9 INR category which had the lowest frequency of events. With further increase in INR, there was an increase in bleeding. Multivariate analysis confirmed that the risk of bleeding was higher when INR exceeded 4·5, when arterial disease was the indication for anticoagulation, and during the first 90 days of treatment (table 5).

During the whole follow-up, 70 thrombotic events (20 fatal, 39 major and 11 minor) occurred in 67 patients, 5 of whom also had bleeding. The rate of thrombotic complications was 3·5 per 100 patient-years of treatment.

About one-third of the patients who had bleeding complications (46/141) had more than one indication for oral anticoagulation. Besides the main one, there was: peripheral and/or cerebral arterial disease (n=22), ischaemic heart disease (8), and atrial fibrillation and venous thromboemobolic disease (6 each). At least one other disease or risk factor was present at the start of treatment in 78 of 141 who had bleeding (table 6). In a few cases we could correlate the occurrence of a bleeding episode with onset of specific pro-haemorrhagic conditions, such as trauma (1 major and 5 minor

	Relative risk (95% CI)
Sex (women *vs* men)	1·21 (0·86–1·70)
Age (⩾70 *vs* <70 years)	1·69 (1·21–2·37, p<0·001)
Target INR (⩽2·8 *vs* >2·8)	0·83 (0·56–1·22)
Indication (arterial disease *vs* others)	1·72 (1·17–2·54, p<0·001)
Actual INR (⩾4·5 *vs* <4·5)	5·96 (3·68–9·67, p<0·0001)
Coumarin type (acenocoumarol *vs* warfarin)	1·20 (0·85–1·69)
Timing of events (⩽90 *vs* >90 days)	2·5 (1·4–3·3, p<0·001)

Table 5: **Multivariate risk ratios**

	Number
Hypertension	25
Cancer	20
Diabetes	10
Renal and bladder disease	7
History of gastrointestinal bleeding	6
Gastrointestinal disease	5
Renal insufficiency	4
Lung disease	4
Lupus-anticoagulant/anticardiolipin-antibody	3
Chronic liver disease	2
Cardiac insufficiency	2
Uterine fibromatosis	2
Thrombocytopenia	1
von Willebrand's disease	1
Psychiatric disease	1

Table 6: **Other diseases and risk factors at start of oral anticoagulation in 78 of 141 patients with bleeding complications**

bleedings), urinary infections and/or nephrolithiasis (4 minor), heparin co-administration (2 minor), thrombocytopenia and lung disease (1 minor each). Finally, cancer was diagnosed in 2 patients after minor events.

Except in venous thromboembolism, many of the other patients received more than one treatment. In 77 of 153 cases drugs other than coumarins were administered near to the bleeding event, mostly antihypertensive drugs (2 fatal, 6 major and 34 minor), vasodilators and nitrates (11 minor), aspirin or other antiplatelet drugs (2 major, 9 minor), amiodarone (6 minor), allopurinol (4 minor), cyproterone acetate (2 major, 1 minor), and antidiabetics (3 minor). Minor bleeding occurred a few days after withdrawal of rifampicin or barbiturates (1 case each).

During the study, 102 patients died, 5 due to bleeding events. The causes of death other than bleeding were: cancer (34), acute myocardial infarction (6), heart failure (22), sudden death (12), post-surgery complications (4), non-specified cardiovascular events (4), ischaemic stroke (3), pulmonary embolism (7, 5 of whom highly probable and 2 confirmed by necropsy), sepsis (2), acute hepatitis (1), and respiratory insufficiency (1).

Discussion

We were able to estimate haemorrhagic risk complications during oral anticoagulation in outpatients monitored by INR in specialist anticoagulation clinics. The results reflect the normal practice of Italian centres. The rate of fatal, major, and minor bleeding events was 0·25, 1·1, and 6·2 per 100 patient-years of follow-up, respectively. These figures are lower than the average annual frequencies of bleeding (0·8, 4·9, and 15 per 100 patient-years for fatal, major, and major/minor bleeding, respectively) in a review[2] of studies of similar design, and lower than those in experimental studies (0·4, 2·4, and 8·5 per 100 patient-years).[2] Levine et al,[3] reviewing randomised controlled trials, reported rates ranging from 0 to 4·8 per 100 patient-years for fatal and 2·4 to 8·1 per 100 patient-years for major bleeding. The rates of bleeding we found are also lower than those in studies in which patients were routinely treated with oral anticoagulation for various indications.[12-15] Others have reported bleeding rates higher than[7,16,17] or similar[9] to ours.

van der Meer et al[4] found higher rates of major bleeding events than we did, probably because of higher anticoagulation intensity in the patients. The low bleeding rate we recorded, most likely due to the moderate treatment intensity, did not seem to be counterbalanced by more frequent thrombotic complications, since the rate of such complications was actually lower (3·5 per 100 patient-years) than that in other studies (5·9 to 9·5).[7,17]

The use of INR increases the reliability of anticoagulant control and makes possible inter-study comparisons.[18] Unnecessarily high doses, associated with higher bleeding rates, can be avoided[19] and optimum therapeutic ranges can be more easily achieved.[20] In line with the results of some[4] but not all[3] studies, we found no relation between risk of bleeding and target zone. However, intensity of anticoagulation achieved was related to bleeding. About one-fifth of all bleeding events occurred at very low INR (<2). This confirms other reports[21, 8] that many bleeds during oral anticoagulation are not related to the intensity of anticoagulation but to a local bleeding source that may be unmasked by anticoagulant therapy. A slight but significant increase of risk was recorded for INRs of 3·0–4·4, the risk of bleeding becoming much higher for values over 4·5. Similar results are suggested by other studies.[7,22] Based on these findings it would be prudent to avoid INR of 4·5 or more.

It is debatable whether the risk of bleeding during oral anticoagulation is higher in older patients.[3,23] In our study patients over 70 had a relative risk of 1·75 compared with all the others. Similar results have been reported,[4,8,18,22] although not by Fihn et al.[7] Our results also indicate a relation between older age and intracranial bleeding, as was reported by Landefeld and Goldman.[8] In our study we found no relation between intracranial bleeding and achieved anticoagulation.

Although most physicians are aware of the higher risk of oral anticoagulation in the elderly,[24,25] an increasing number of elderly patients are treated with anticoagulants. Older patients on anticoagulants should be: treated at a low target zone; monitored closely to keep their INRs within the therapeutic zone; and carefully followed up so that conditions which may interfere with oral anticoagulation can be monitored.

In our study more than one-third of all bleeding episodes occurred within the first 90 days of each anticoagulant course; the frequency of bleeding then stabilised. A higher frequency of bleeding early in the course has been reported in many[7,8,14] but not all[26,27] studies. Several factors may contribute to the increased risk of early bleeding. First, anticoagulant therapy can unmask a cryptic lesion. Second, dose adjustment may be less well-controlled at the start of treatment. As clearly pointed out by Landefeld and Goldman,[8] studies that examine non-inception cohort and/or include patients who have resumed anticoagulation are likely to underestimate the true risk of bleeding by either missing early events or excluding from any second course patients who had bled in the first course.

Our patients on oral anticoagulation for arterial vascular disease had a higher frequency of bleeding (12·5 per 100 patient-years of follow-up) than the others; the rate of bleeding was even higher if cerebrovascular patients were considered alone (14·5). Since the arterial vascular disease was also the most frequent secondary indication in the 22 patients who bled, this indication whether main or secondary was most frequently associated with bleeding (50 patients out of 141). These results confirm the particularly high risk of oral anticoagulants in patients with arterial disease, especially cerebrovascular disease, recorded in experimental trials[3] or observational studies,[8]

and raise the question of whether the risk of bleeding during anticoagulation outweighs the benefit in such patients[28, 29]

Finally, the quality of anticoagulation obtained over the whole study was high (68% of all the period was within the therapeutic ranges), especially given that thirty-four centres did the monitoring with a wide range of thromboplastins. The quality of treatment was higher for patients in the low target zone and when thromboplastins with low ISI were used. This result, consistent with our previous findings,[18] supports the switch from low-sensitivity to high-sensitivity reagents.

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