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

Gualtiero Palareti, Nicoletta Leali, Sergio Coccheri, Mario Poggi, Cesare Manotti, Armando D’Angelo, Vittorio Pengo, Nicoletta Erba, Marco Moia, Nicola Ciavarella, Gianluigi Devoto, Mauro Berrettini, Serena Musolesi, on behalf of the Italian Study on Complications of Oral Anticoagulant Therapy*

Summary
Background Bleeding is the most serious complication of the use of oral anticoagulation in the prevention and treatment of thromboembolic 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%, acenocoumarol 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, 33%), followed by non-ischaemic heart disease (17%). 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),5,4 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).6,7 Observational studies that included an inception cohort were retrospective and did not use INR8 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...
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.

The results of all visits were checked by the coordinating centre 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
861 (24.1%)
Dilated cardiomyopathy
136
Atrial fibrillation
462
Endocarditis thrombosis
24
Other
39
Ischaemic heart disease
403 (14.7%)
Post-myocardial infarction
144
After ACP 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

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Table 2: Indication for oral anticoagulation
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 these patients, the cumulative frequency of fatal, major, and minor bleeding events during outpatient anticoagulant treatment is shown in Figure 2.
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 thromboembolic 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

<table>
<thead>
<tr>
<th>Patient-years of follow-up</th>
<th>Bleeding</th>
<th>x100 patient-years</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fatal</td>
<td>Major</td>
<td>Minor</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>874</td>
<td>4</td>
<td>10</td>
</tr>
<tr>
<td>Male</td>
<td>1137</td>
<td>1</td>
<td>13</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50</td>
<td>288</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>50–69</td>
<td>997</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>&gt;70</td>
<td>726</td>
<td>5</td>
<td>16</td>
</tr>
<tr>
<td>Relative risk &gt;70 vs 70</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indication</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Venous thromboembolism</td>
<td>558</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>Arterial disease</td>
<td>223</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>All others</td>
<td>1230</td>
<td>3</td>
<td>11</td>
</tr>
<tr>
<td>Relative risk arterial disease vs others</td>
<td></td>
<td></td>
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</table>

| Centres                  |          |                    |                        |
| <100 recruited           | 820      | 2                  | 6                      | 46                     | 6·6 | 0·79 (1·10-0·57) |
| >100 recruited           | 1151     | 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                      |                        |                |
| 2–9                      | 377      | 0                  | 6                      | 23                     | 7·7 |                        |
| 3–4–4                    | 1116     | 1                  | 8                      | 45                     | 4·8 |                        |
| 4–5–6–9                  | 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 ≤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 |          |                    |                        |

Table 4: Bleeding events stratified by risk factors

Relative risks are univariate.

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. M ultivariate 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).

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</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women vs men</td>
<td>1·21 (0·86-1·70)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (&gt;70 vs &lt;70 years)</td>
<td>1·69 (1·21-2·37, p&lt;0·001)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Target INR (2.8 vs ≥2.8)</td>
<td>0·83 (0·56-1·22)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indication (arterial disease vs others)</td>
<td>1·72 (1·17-2·54, p&lt;0·001)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Actual INR (4.5 vs ≤4.5)</td>
<td>5·96 (3·68-9·67, p&lt;0·0001)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coumarin type (acenocoumarol vs warfarin)</td>
<td>1·20 (0·85-1·69)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Timing of events (&gt;90 vs ≥90 days)</td>
<td>2·5 (1·4-3·3, p&lt;0·001)</td>
<td></td>
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</tbody>
</table>

Table 5: Multivariate risk ratios


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 the 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 anti-diabetics (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-specific 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 of studies of similar design, and lower than those in experimental trials (0·4, 2·4, and 8·5 per 100 patient-years).2 Levine et al.,1 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.2,21–23 Others have reported bleeding rates higher than1,4,13–15 or similar to ours.

van der Meer et al.1 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).2,13–15

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 and optimum therapeutic ranges can be more easily achieved.24 In line with the results of some but not all 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 reports1,8 that many bleedings 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.22–23 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.24–26 In our study patients over 70 had a relative risk of 1·75 compared with all the others. Similar results have been reported,4,5,8,12 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,24–26 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 many4,5,8,9,12 but not all24–27 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 trials5 or observational studies.8
and raise the question of whether the risk of bleeding during anticoagulation outweighs the benefit in such patients. Finally, the quality of anticoagulation obtained over the whole study was high (68% of all the period was within the therapeutic range), 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, supports the switch from low-sensitivity to high-sensitivity reagents.

The following investigators and centres participated in ISCOAT.

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References