A Comparison Between Six- and Four-Week Intervals in Surveillance of Oral Anticoagulant Treatment

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Abstract

We determined whether international normalized ratio (INR) monitoring at 6 weeks rather than 4 weeks would benefit patients and reduce costs. Patients receiving stable oral anticoagulant treatment (target INR, 3.0) with a prosthetic mechanical heart valve for more than 6 months were randomized for a maximum interval between INR determinations of 6 weeks (group 1, n = 59) or 4 weeks (group 2 [control], n = 65). Patients were followed up for 2 years. The primary end point of the study was the biologic risk of overanticoagulation or underanticoagulation, estimated as the rate of values at risk (INR, <1.5 and >5). The rates of INR values at risk for hemorrhagic (INR, >5) or thromboembolic (INR, <1.5) complications were 3.27% in group 1 and 3.09% in group 2 (P = .81). The INRs of patients in group 1 trended toward higher values, but no difference between groups was observed in time spent at various INR ranges by using the method of linear change. The mean time between INR determinations was 24.9 ± 18.1 days (1.20 per month) in group 1 and 22.5 ± 9.5 days (1.33 per month) in group 2 (P < .0003). For patients in stable condition with a prosthetic heart valve who are monitored at an anticoagulation clinic, a 6-week interval between INR determinations does not increase the biologic risk of thromboembolic or hemorrhagic events.

Laboratory control of oral anticoagulant treatment is performed by regularly testing the prothrombin time, and the results are expressed as the international normalized ratio (INR). In patients receiving long-term treatment, the frequency of laboratory testing depends on INR variability, but it usually is recommended at least once or sometimes 2 or 3 times a month for patients in stable condition. On the other hand, the British Society of Haematology in 1990 stated that, for patients in well-stabilized condition, the interval of prothrombin time testing can be extended gradually to 8 weeks. However, efficacy and safety of treatment by prolonging the interval between laboratory determinations has not been tested in an ad hoc clinical trial. Moreover, the “stability” of the INR depends on target intensity of treatment. For example, in patients with prosthetic heart valves, reducing the target INR from 4.0 to 3.0 stabilizes the INR and reduces the rate of laboratory testing from 1.58 to 1.4 times a month (–11%). Less frequent laboratory testing would improve the quality of life of patients and reduce the costs of treatment. However, some authors do not recommend prolonging the interval between laboratory determinations to a maximum of 6 weeks. Therefore, the aim of the present study was to compare the biologic risk in 2 groups of patients with prosthetic heart valves undergoing stable anticoagulant treatment and randomized to have a maximum interval between laboratory tests of 6 weeks (group 1) or the conventional maximum interval of 4 weeks (group 2 [control]).
Materials and Methods

Patients

Starting in 1998, patients followed up at our anticoagulation clinic were considered for inclusion in the study if they met the following criteria: (1) had a prosthetic mechanical heart valve for more than 6 months, (2) were followed up at the clinic for more than 6 months, and (3) were using warfarin and their target INR was 3.0. Patients were excluded if they had major bleeding as defined previously or were using antiplatelet drugs. Eligible patients were randomized when the last and penultimate INRs (determined at least 2 weeks apart) were in the therapeutic range of 2.5 to 3.5 and the warfarin dosage was unchanged during the preceding 2 months. Randomization to group 1 or group 2 was obtained by computer-generated casual numbers. The study design was approved by local health authorities, and patients gave their permission by signed informed consent.

Follow-up

After randomization, each patient was scheduled for the next testing after 6 or 4 weeks, and intervals were confirmed at each visit if the INR was in the therapeutic range. Intervals were shortened to 1 to 3 weeks when the INR was outside the therapeutic range but still between 2.0 and 4.0. If INR values were outside the 2.0 to 4.0 range, the weekly dosage was modified by 1.25 to 2.5 mg, and patients were retested after 1 to 2 weeks. After changing the dosage, the 4- to 6-week intervals between INR determinations were reinstituted only when the initial conditions permitting randomization were met again. In the meantime, intervals between INR determinations were decided arbitrarily but always were less than 4 weeks. For INR values of more than 5 or less than 1.5, major surgery, or hospital admission, variation in the warfarin dosage and the next appointment were determined, taking into account the single case, and intervals of the group were reinstituted when the initial conditions returned. A patient who did not meet the initial condition for more than 6 months was considered a “dropout.” Interruption of treatment for a few days for minor surgery or invasive maneuvers and missing doses were not considered as dosage variation, and the corresponding INRs were not considered in the analysis of data. In the same way, INRs of patients who did not observe the scheduled appointment (outside the ranges of 23-33 days and 37-47 days for groups 2 and 1, respectively) were excluded from the analysis.

End Point

The principal end point was the biologic risk of maintaining INR values that expose patients to the risk of hemorrhagic or thromboembolic complications. The rate of INR values above 5 and below 1.5 was compared between groups. The achieved anticoagulation in the groups was analyzed by the method of linear change. Clinical events defined as previously reported also were analyzed.

Drop Out

Patient follow-up was terminated in the following circumstances: (1) major bleeding or cerebral ischemia or peripheral embolism, (2) further substitution of heart valves, (3) poor compliance with the study or inability to meet the initial condition for more than 6 months (see “Follow-up”), or (4) INR determinations done in another laboratory.

Statistics

The number of INR values to disclose a difference among groups was calculated assuming that the standard rate of INRs more than 5 plus the rate of INRs less than 1.5 was 2.9% and that group 1 would have at worst a total rate of 5.5%. By using a 1-tailed test with a significant difference at \( P < 0.05 \) and a potency of 0.8, at least 811 INR values per group are necessary. If one third of the INR values must be excluded from the analysis, the number of INR values needed per group is 1,216. As the rate of INR determination in our center is 1.4 per month, and this rate, at best, could be 1 per month, a minimum of 101 patient-years of follow-up per group are necessary (ie, approximately 50 patients per group with 2 years of follow-up).

Results

For the present study, 135 patients were eligible; 11 were excluded (4 because of previous major bleeding and 7 because of the use of antiplatelet drugs in addition to warfarin). As shown in Table 1, 59 patients were randomized to group 1 and 65 patients to group 2. Age and sex were similar in the groups. Most prosthetic valves were in the aortic position, and valves were distributed equally with respect to type (tilting disk and bileaflet). The mean daily warfarin dosage was at or near 5 mg. The mean follow-up for group 1 was 114 patient-years and for group 2, 126 patient-years.

We excluded 96 and 104 INR determinations from analysis in groups 1 and 2, respectively. These INR measurements were those during the weeks preceding and following surgery or invasive maneuvers and those for patients who did not observe the scheduled appointment. At the end of follow-up, the numbers of INR determinations were substantially higher than the calculated sample size required to demonstrate the difference between groups in the primary end point of biologic risk for hemorrhagic or thromboembolic complications (group 1, 1,741; group 2, 2,137).
Regarding the biologic risk of hemorrhagic complications, INR values of more than 5 were recorded 29 times (1.67%) in group 1 and 20 times (0.94%) in group 2 ($P = .06$). On the other hand, INR values associated with an increased risk of thromboembolism (INR, <1.5) were observed 28 times in group 1 (1.61%) and 46 times in group 2 (2.15%) ($P = .26$). Overall, the total rate of INR values at risk for hemorrhagic or thromboembolic complications was 3.27% in group 1 and 3.09% in group 2 ($P = .81$).

Oral vitamin K (2 mg) to reverse excessive anticoagulation (INR, >6) was administered more often in group 1 than in group 2 (14 vs 4 times, respectively; $P = .01$), while subcutaneous heparin was administered more frequently in group 2 than in group 1 (34 vs 20 times, respectively; $P = .30$) in high-risk patients with low INR values. The time spent at various INR ranges according to the method of linear change among INR determination is shown in Figure 1. No difference among groups was observed in the time spent at various INR ranges.

The mean time between INR determinations was 24.9 ± 18.1 days (1.20 per month) in group 1 and 22.5 ± 9.5 days (1.33 per month) in group 2 ($P < .0003$). Fifty-two patients in group 1 and 57 in group 2 completed the 2-year follow-up period. Three patients in group 1 (2.6% patient-years) and 1 patient in group 4 (0.8% patient-years) experienced major bleeding. On the other hand, no patients in group 1 had an ischemic stroke, but 2 patients in group 2 (1.6% patient-years) had a stroke (1 complete and 1 minor). Three patients in each group had an episode of transient cerebral ischemia. One patient in group 1 died of sudden death of unknown cause. Two patients in group 2 underwent a substitution of their prosthetic valves.

**Discussion**

At present, there little is known about the efficacy and safety of reducing the frequency of laboratory tests in patients receiving oral anticoagulant treatment. Patient comprehension and reliability and the individual thromboembolic and hemorrhagic risk profile always should be considered when making decisions about testing frequency.9,14 However, relatively young and active patients with prosthetic heart valves often request a prolonged period between visits. If the INR is stable, INR determinations could be done less frequently,6 but this is not the advice of some investigators.8

A dynamic stochastic model considering the cost of visits and of complications in 216 patients was developed, with the aim of reducing the number of monitoring visits for these patients.15 To prove the effectiveness of such an approach, we chose patients in stable condition with prosthetic heart valves without previous bleeding or associated antiplatelet therapy to perform a randomized study testing at a 6-week vs the usual 4-week interval between INR determinations.

The reason for choosing this selected patient population was related to their willingness to participate in the study as active members of the local patients’ association receiving oral anticoagulant treatment. The question of the safety of this approach for the “average” anticoagulated patient remains unanswered because the selected patients were not

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**Table I**

Characteristics of Studied Patients

<table>
<thead>
<tr>
<th>Group 1 (n = 59)</th>
<th>Group 2 (n = 65)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ± SD age (y)</td>
<td>62.3 ± 12.6</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>32/27</td>
</tr>
<tr>
<td>Prosthetic valves</td>
<td></td>
</tr>
<tr>
<td>Position</td>
<td></td>
</tr>
<tr>
<td>Aortic</td>
<td>40</td>
</tr>
<tr>
<td>Mitral</td>
<td>14</td>
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<tr>
<td>Mitral and aortic</td>
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</tr>
<tr>
<td>Type</td>
<td></td>
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<tr>
<td>Sorin</td>
<td>18</td>
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<tr>
<td>St Jude</td>
<td>13</td>
</tr>
<tr>
<td>Björk-Shiley</td>
<td>6</td>
</tr>
<tr>
<td>Carbomedics</td>
<td>6</td>
</tr>
<tr>
<td>Other</td>
<td>16</td>
</tr>
<tr>
<td>Follow-up (patient-years)</td>
<td>114</td>
</tr>
<tr>
<td>Mean daily warfarin dosage (mg)</td>
<td>5.15</td>
</tr>
<tr>
<td>No. of determinations</td>
<td>1,741</td>
</tr>
</tbody>
</table>

* Group 1 patients underwent determination of international normalized ratios at 6-week maximum intervals, group 2 (control group) at 4-week maximum intervals. Valve manufacturers were as follows: Sorin and Carbomedics (Sorin Biomedica, Saluggia, Italy), St Jude (St Jude Medical, St Paul, MN), and Björk-Shiley (Pfizer, New York, NY).
average (based on target INR and age). However, high intensity of anticoagulant treatment generally determines increased INR variability, which might be lower in the average patient. Moreover, thromboembolic and hemorrhagic events are more frequent in older patients but were not the end point of the present study. The end point in the present study was a surrogate one (rate of INR values at risk), since using clinical outcomes would require an acceptably high number of randomized patients to achieve sufficient power.

It is well documented that time in the target range is associated strongly with clinical outcomes. We found no difference in the rate of INR values at risk for hemorrhagic or thromboembolic complications and a significant increase in the interval between visits in group 1. However, the INRs of patients scheduled for longer intervals between visits apparently shift toward higher values. This could explain the higher number of major bleeding episodes and the lower rate of ischemic stroke in group 1. Nevertheless, when looking at time spent at various INR ranges, it seems that the 2 groups are quite similar and the differences are minimal; therefore, bleeding and thromboembolic complications in the 2 groups might have occurred by chance. Moreover, time in the therapeutic range (INR, 2.5-3.5) was increased in group 1 (Figure 1), despite the observation that this generally is true with more frequent testing. Therefore, for patients in stable condition with prosthetic heart valves who are compliant with treatment instructions, it seems reasonable to prolong the maximum interval between INR determinations to 6 weeks, thus reducing costs and improving the quality of life for patients. Furthermore, as the time within the therapeutic INR range improves at a lower intensity of treatment, these results might be extrapolated to the majority of patients receiving oral anticoagulant treatment. Further study is needed to confirm that clinical outcomes of bleeding or thrombosis are not increased when extending the maximum INR monitoring time from 4 to 6 weeks.

References


