Optimal Intensity of Warfarin Therapy for Secondary Prevention of Stroke in Patients with Nonvalvular Atrial Fibrillation

A Multicenter, Prospective, Randomized Trial

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Background and Purpose—The optimal intensity of warfarin therapy for secondary prevention of stroke in nonvalvular atrial fibrillation (NVAF) remains unclear. We studied the efficacy and safety of conventional- and low-intensity warfarin therapy in a prospective, randomized, multicenter trial.

Methods—The study population consisted of patients with NVAF (<80 years old) who had a stroke or transient ischemic attack. The patients were randomly allocated into a conventional-intensity group (international normalized ratio [INR] 2.2 to 3.5) and a low-intensity group (INR 1.5 to 2.1). They were carefully monitored, and the annual rate of recurrent ischemic stroke and major hemorrhagic complications were compared between the groups.

Results—We enrolled 115 patients (mean age 66.7 ± 6.5 years) into the study. Fifty-five and 60 patients were allocated into the conventional- and low-intensity groups, respectively. The trial was stopped after a follow-up of 658 ± 423 days, when major hemorrhagic complications occurred in 6 patients of the conventional-intensity group and the frequency (6.6% per year) was significantly higher than that in the low-intensity group (0% per year, P = 0.01, Fisher’s exact test). All of the 6 patients with major bleeding were elderly (mean age 74 years), and their mean INR before the major hemorrhage was 2.8. The annual rate of ischemic stroke was low in both groups (1.1% per year in the conventional-intensity group and 1.7% per year in the low-intensity groups) and did not differ significantly.

Conclusions—For secondary prevention of stroke in persons with NVAF, especially in old patients, the low-intensity warfarin (INR 1.5 to 2.1) treatment seems to be safer than the conventional-intensity (INR 2.2 to 3.5) treatment. (Stroke. 2000;31:817-821.)

Key Words: atrial fibrillation ■ cerebrovascular disorders ■ prevention ■ randomized controlled trials ■ warfarin

For primary prevention of stroke or transient ischemic attacks (TIAs) in patients with nonvalvular atrial fibrillation (NVAF), an efficacy of anticoagulation was established in 5 prospective, randomized, controlled trials.1-5 A collaborative analysis was performed by the investigators from the 5 trials to assess risk factors for stroke in patients with AF.6 They identified 4 independent risk factors for stroke through multivariate analysis: history of previous stroke or TIA (relative risk [RR], 2.5), diabetes mellitus (RR 1.7), hypertension (RR 1.6), and increasing age (RR 1.4 for each decade). Associated cardiac disorders, congestive heart failure, and coronary artery disease were also shown to influence stroke risk. In patients with NVAF with any of these stroke risks, warfarin treatment with an international normalized ratio (INR) of 2.0 to 3.0 is recommended.7,8 Two of the 5 studies used lower target ranges of INR (from 1.5 to 2.7 and from 1.4 to 2.8) and demonstrated the efficacy of anticoagulation therapy for primary prevention. These results suggested that low-intensity warfarin treatment was an alternative method for stroke prevention in patients with NVAF.2,5

For secondary prevention of stroke in patients with NVAF, however, efficacy has been evaluated only in a single prospective study of the European Atrial Fibrillation Trial (EAFT).9 The investigators reported the efficacy of warfarin treatment for secondary prevention with an INR range from 2.5 to 4.0 based on the risk reduction for stroke from 12% to 4% per year and a low incidence of major hemorrhagic events (2.8% per year). All hemorrhagic complications, however, were observed more frequently in the anticoagulation group than in the control group (hazard ratio 3.4, 95% CI 1.9 to 6.0, P < 0.001). Although the risk of stroke is high in patients with NVAF with a past history of stroke, the INR range used in the

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European study seems inappropriately high compared with the recommended INR range for primary prevention and compared with the usual INR level applied to elderly patients. The investigators indicated that no treatment effect was apparent with anticoagulation below an INR of 2.0. However, they analyzed the efficacy by comparing an event rate in a group with an INR of 1.0 to 1.9 with those in the other groups with an INR of >2.0. They did not consider the efficacy by further dividing the group with an INR between 1.0 and 1.9 according to the intensity of the INR. It was demonstrated in the third Stroke Prevention in Atrial Fibrillation (SPAF III) trial that an annual event rate for ischemic stroke or systemic embolism in a group with an INR between 1.5 and 1.9 was lower than that in groups with an INR of <1.5.11

We retrospectively investigated the frequencies of recurrent brain embolism and hemorrhagic complications in 68 patients with NVAF and cardioembolic stroke who were treated with warfarin.12 During the follow-up period of 39±27 months, a brain embolism recurred in 3 patients (1.4% per year) and major bleeding occurred in 12 patients (5.5% per year). The mean INR value in patients with bleeding (3.0) was higher than that in patients with recurrence (2.2) and in the remaining patients without accidents (2.3).

The optimal intensity of anticoagulation therapy in the secondary prevention of stroke in patients with NVAF remains unclear. We compared the efficacies of low- and conventional-dose warfarin treatment for the secondary prevention of stroke and TIA in patients with NVAF in a prospective, randomized, dose-controlled, multicenter trial.

**Subjects and Methods**

Patients younger than 80 years were eligible if they had definite or possible cardioembolic stroke or TIA due to NVAF at 1 to 6 months before study entry. The diagnostic criteria for cardioembolic stroke/TIA due to NVAF are given in Table 1.

We excluded from the current study patients with intracardiac thrombus, left ventricular aneurysm, severe congestive heart failure (NYHA functional class IV), infective endocarditis, acute myocardial infarction in the previous month, coronary artery bypass graft surgery in the previous year, percutaneous transluminal coronary angioplasty in the previous 3 months, dilated cardiomyopathy, mitral valve prolapse, sick sinus syndrome, hyperthyroidism, severe renal or liver diseases, any other thrombotic diseases, past history of intracerebral hemorrhage, pregnancy, or cancer.

Nineteen institutions in Japan participated in the trial. The study was approved by each institutional review committee, and informed consent was obtained from all study patients. After informed consent was obtained from patients or their families, a registration form for each patient was sent to the central trial office by facsimile, where it was determined whether the patient met the criteria. After the patient’s eligibility was confirmed, he or she was randomly assigned to receive either conventional- or low-intensity warfarin therapy, which was open labeled. Patients were administered warfarin, and the prothrombin time was examined at least once a month for adjustment of INR control from 2.2 to 3.5 (target value 2.5) for the conventional-intensity group and from 1.5 to 2.1 (1.9) for the low-intensity group. No antiplatelet agents were administered with the warfarin.

To avoid an inaccurate measurement of prothrombin time, we used commercially available thromboplastin, which has a low international sensitivity index value (range 1.02 to 1.10).13,14

**TABLE 1. Diagnostic Criteria for Cardioembolic Stroke/TIA Due to NVAF**

| A. NVAF diagnosis based on physical, ECG, and transthoracic echocardiographic findings |
| B. Main diagnostic items |
| 1. Abrupt onset, with maximal neurological deficit at onset |
| 2. Embolism to other parts of the body |
| 3. Angiographic findings of intraluminal filling defects (embolus shadow) or reopening of the previously occluded arteries |
| 4. Atrial thrombus |
| C. Other diagnostic items |
| 1. TIA of different arterial territory within 1 month before the index stroke or TIA |
| 2. Consciousness disturbance of somnolence or worse at onset |
| 3. CT or MRI findings; 1 of following 3 items: |
| a. Multiple cortical or cerebellar infarctions in different arterial territories |
| b. Hemorrhagic transformation |
| c. Hyperdense middle cerebral artery sign |
| 4. Angiographic findings of occlusion at arterial bifurcation, branch occlusion, multiple occlusion, absence of atherosclerotic findings |
| D. Exclusion items: Atheromatous lesions with ulcer, severe stenotic lesion, or dissection in the responsible arterial system |

Patients are diagnosed as having definite cardioembolic stroke/TIA due to NVAF if they meet the following criteria:

A+ ≥2 items of B
A+1 item of B+≥2 items of C

Patients are diagnosed as having possible cardioembolic stroke/TIA due to NVAF if they meet the following criteria:

A+ ≥3 items of B+D (see below*)
A+1 item of B+1 item of C
A+ ≥3 items of C

*Diagnosis of cardioembolic stroke/TIA is not made in the other patients with 1 item of D.

point events (occurrence of stroke, TIA, and adverse effects) were assessed and recorded by the stroke specialists. A brain CT scan, MRI examination, or both were performed once a year, regardless of the patient’s outcome. Patient follow-up continued for 2 years or longer or until end point events occurred.

Primary end points included brain infarction, embolism to other parts of the body, TIA, amaurosis fugax, or asymptomatic brain infarction confirmed with CT scanning or MRI. Secondary end points were brain hemorrhage, retinal hemorrhage, or other severe hemorrhagic complications that were fatal; hospital admission for emergency treatment; or blood transfusion.

A sample size of 260 patients was estimated on the basis of an anticipated event rate for both the primary and secondary end points in the conventional-intensity group of 5.7% per year and in the low-intensity group of 1.6% with 90% power and a 2-sided α-level of 5%.12

To safely maintain the trial, information about primary and secondary end points was collected, and the incident ratio of the end points was analyzed every 6 months at the central trial office with the use of χ² tests and log-rank test with Kaplan-Meier survival curve analysis. In case of low cell counts (<5), Fisher’s exact test was used instead of the χ² test. We used an unpaired t test for analysis of continuous variables. If a statistically significant difference in primary or secondary end points between the groups was obtained.

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**A. NVAF diagnosis based on physical, ECG, and transthoracic echocardiographic findings**

**B. Main diagnostic items**

1. Abrupt onset, with maximal neurological deficit at onset
2. Embolism to other parts of the body
3. Angiographic findings of intraluminal filling defects (embolus shadow) or reopening of the previously occluded arteries
4. Atrial thrombus

**C. Other diagnostic items**

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   a. Multiple cortical or cerebellar infarctions in different arterial territories
   b. Hemorrhagic transformation
   c. Hyperdense middle cerebral artery sign
4. Angiographic findings of occlusion at arterial bifurcation, branch occlusion, multiple occlusion, absence of atherosclerotic findings

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Patients are diagnosed as having definite cardioembolic stroke/TIA due to NVAF if they meet the following criteria:

A+ ≥2 items of B
A+1 item of B+≥2 items of C

Patients are diagnosed as having possible cardioembolic stroke/TIA due to NVAF if they meet the following criteria:

A+ ≥3 items of B+D (see below*)
A+1 item of B+1 item of C
A+ ≥3 items of C

*Diagnosis of cardioembolic stroke/TIA is not made in the other patients with 1 item of D.
before completion of the trial, the safety committee members were to be called to discuss study continuation.

## Results

One hundred fifteen patients (83 men and 32 women, mean age 66.7±6.5 years) were enrolled in the study before completion of the trial. We assigned 55 patients into the conventional-intensity group and the remaining 60 patients into the low-intensity group. No significant differences in background characteristics were observed between the 2 groups (Table 2).

Because patient recruitment was slower than expected, the first interim analysis was performed in April 1997, the second one was performed in September 1997, and the last one was performed in March 1998. During a follow-up period of 658±423 days, major hemorrhagic complications occurred in 6 patients of the conventional-intensity group. The rate of complications was significantly higher in the conventional-intensity group (6.6% per year, 95% CI 1.4% to 11.9%) than in the low-intensity group (0% per year (P<0.01 Fisher’s exact test), although the log-rank test did not show significance (Table 3). The annual rate of ischemic stroke was low in both the conventional-intensity (1.1% per year, 95% CI 1.1% to 3.3%) and the low-intensity (1.7% per year, 95% CI 0.8% to 4.2%) group (P=NS). Eleven patients discontinued participation in the study: 8 due to change of address, 2 due to minor hemorrhagic complications (nasal and hemorrhoid bleeding), and 1 due to suicide.

The INR during the follow-up period was 2.3±0.4 for the conventional-intensity group and 1.9±0.3 for the low-intensity group. Mean INR in the conventional-intensity group was between 2.2 and 3.5 in 37 (67.3%) patients, <2.2 in 17 (30.9%) patients, and >3.5 in the remaining patient (1.8%). In the low-intensity group, mean INR was between 1.5 and 2.1 in 55 patients (91.7%), <1.5 in 2 patients (3.3%), and >2.1 in the remaining 3 patients (5.0%).

The 6 patients with major bleeding were all elderly (mean age 73.7±3.7 years, which is older than the other 109 patients with a mean age of 66.3±6.4 years, P<0.01 unpaired t test), and their mean INR before the secondary end point was 2.8 (Table 4). Major hemorrhagic complications included gastrointestinal bleeding in 3 patients and hemoptyisis, massive subcutaneous bleeding from an accidental fall, or cerebellar hemorrhage in the other 3 patients.

The characteristics of the 3 patients with recurrent stroke are given in Table 5. Two of the patients were in the low-intensity group, and the other was in the conventional-intensity group. Their INR before the recurrence was within the target range in 2 patients and above the target range in the other patient (low-intensity group). Their outcomes were social independence for 2 patients and independence at home for the third.

Taking into consideration the results mentioned earlier and the benefit for patients entered into the trial, the committee decided to stop the trial on March 20, 1998.

## Discussion

It appears reasonable that we terminated patient recruitment after the disclosure of an increased rate of life-threatening bleeding in the conventional-intensity group compared with the low-intensity group. The frequency of patients with severe bleeding in the conventional-intensity group was significantly higher than that in the low-intensity group, and no difference in stroke recurrence between the 2 groups was observed at the time of premature termination. The P value for the difference in the incidence of severe hemorrhagic complication between the 2 groups was 0.0103, which was still below 0.0170 (1−0.95^3), the significant level when we took into account 3 times of interim analysis.

In a case-control study, Hylek et al15 investigated the lowest intensity of anticoagulation that was effective in the prevention of stroke in patients with NVAF. They found that the risk of stroke rose steeply at an INR of <2.0. Compared with the risk at an INR of 2.0, the adjusted odds ratio for stroke was 2.0, 3.3, and 6.0 at INR values of 1.7, 1.5, and 1.3, respectively. However, their study put focus on only the lowest effective intensity of anticoagulation and not on the hemorrhagic risk of anticoagulation. The risk of hemorrhage has been reported to increase in elderly persons, as shown in the SPAF II trial, in which the efficacy of aspirin was compared with that of warfarin (target range of warfarin INR 2.0 to 4.5) for the prevention of thromboembolism.16 The risk of ischemic stroke was higher in patients older than 75 years than in those aged 75 years or less, and treatment with warfarin appeared to be more effective than treatment with

### Table 2. Background Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Conventional-Intensity Group (n=55)</th>
<th>Low-Intensity Group (n=60)</th>
<th>P</th>
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</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>65.7±6.8</td>
<td>67.6±6.1</td>
<td>0.14</td>
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<tr>
<td>Sex, M/F</td>
<td>42/13</td>
<td>41/19</td>
<td>0.93</td>
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<tr>
<td>Follow-up period, d</td>
<td>605±406</td>
<td>706±445</td>
<td>0.21</td>
</tr>
<tr>
<td>Controlled INR</td>
<td>2.3±0.4</td>
<td>1.9±0.3</td>
<td>0.0001</td>
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<tr>
<td>Hypertension, n (%)</td>
<td>24 (44)</td>
<td>24 (40)</td>
<td>0.65</td>
</tr>
<tr>
<td>Hyperlipidemia, n (%)</td>
<td>7 (13)</td>
<td>14 (23)</td>
<td>0.14</td>
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<tr>
<td>Diabetes mellitus, n (%)</td>
<td>14 (26)</td>
<td>8 (11)</td>
<td>0.099</td>
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<tr>
<td>Hyperuricemia, n (%)</td>
<td>4 (7)</td>
<td>6 (11)</td>
<td>0.75</td>
</tr>
<tr>
<td>Ischemic heart disease, n (%)</td>
<td>2 (4)</td>
<td>8 (15)</td>
<td>0.097</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>23/32</td>
<td>32/28</td>
<td>0.26</td>
</tr>
</tbody>
</table>

### Table 3. Outcome of Conventional- and Low-Dose Groups

<table>
<thead>
<tr>
<th></th>
<th>Conventional-Intensity Group (n=55)</th>
<th>Low-Intensity Group (n=60)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discontinuation, n</td>
<td>12</td>
<td>8</td>
<td>0.23</td>
</tr>
<tr>
<td>Primary end point: ischemic stroke, n</td>
<td>1</td>
<td>2</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Secondary end point: major hemorrhagic complication, n</td>
<td>6</td>
<td>0</td>
<td>0.0103</td>
</tr>
<tr>
<td>Minor hemorrhagic complication, n</td>
<td>2</td>
<td>0</td>
<td>0.23</td>
</tr>
<tr>
<td>Residential removal, n</td>
<td>3</td>
<td>5</td>
<td>0.72</td>
</tr>
<tr>
<td>Suicide, n</td>
<td>0</td>
<td>1</td>
<td>&gt;0.99</td>
</tr>
</tbody>
</table>
aspirin. However, the benefits of warfarin were lost because of a higher rate of intracranial hemorrhage, particularly in the group older than 75 years. In patients >75 years old, low-intensity warfarin treatment may be an alternative because the risk of bleeding was low in the present prospective trial, which was consistent with our retrospective study.12

Stroke recurrence rate was low in both the conventional- and low-intensity groups (1.1% and 1.7% per year, respectively) compared with that in the control patients of primary and secondary prevention trials (4.5% and 12% per year, respectively).8,9 The efficacy of low-intensity treatment with warfarin has been suggested in 2 previous trials of primary prevention.2,5 Because the number of patients enrolled in the present study was too small for a definite risk/benefit assessment, the efficacy of low-intensity warfarin treatment must be confirmed with further study.

In a post-hoc analysis of 46 patients aged ≥70 years, when we investigated INR values measured before primary or secondary events, there was 1 ischemic event in a patient with an INR of 1.75 and 5 severe hemorrhagic events in 5 patients with INR values of 2.25 to 3.05. Therefore, anticoagulation with low-intensity warfarin (INR 1.75 to 2.25) seems effective and safe in the prevention of stroke in patients with NVAF aged ≥70 years. Hart et al17 reviewed 13 randomized trials of antithrombotic therapy in patients with NVAF and indicated that the use of the lowest adequate intensity of anticoagulation was particularly important for elderly patients with NVAF, because major hemorrhage during anticoagulation was age related. They discussed that given the uncertainty regarding the safety of INR values of ≥2.5 for patients with NVAF who are older than age 75, a target INR of 2.0 (range 1.6 to 2.5) may be a reasonable compromise between toxicity and efficacy for this age group, pending further data regarding the safety of higher-intensity treatment. It appears that the present data support their suggestion from the standpoint of safe anticoagulation in older patients with NVAF.

On the other hand, in 69 patients younger 70 years, there was severe hemorrhage in only 1 patient (age 67 years) at an INR of 3.55 and ischemic stroke in 2 patients (age 58 years) at INR values of 2.54 and 2.57. An INR range from 2.57 to 3.55 seems effective and safe in the prevention of stroke in patients with NVAF who are younger than 70 years. However, the number of events was too small to form a positive conclusion. According to this post-hoc analysis and the previous recommendation of anticoagulation (INR of 2.0 to 3.0) supported by reports indicating an increased risk of stroke at an INR of <2.0,7,15,17 it seems reasonable that we should avoid anticoagulation control with an INR of <2.0, at least in patients <70 years old.

The EAFT reported an incidence of 2.8% per year for major bleeding and of 4% per year for recurrent stroke.9 The incidence of major bleeding (6.6% per year) in the conventional-intensity group seems higher and those of recurrent stroke (1.1% and 1.7% per year in the conventional- and low-intensity groups, respectively) seem lower than those in the EAFT. One of the reasons might be the difference in the entry criteria of the studies. We used the strict diagnostic criterion of cardioembolic stroke in the recruitment of patients for the current study, whereas the inclusion criterion used in the EAFT was simply TIA or recent minor stroke (grade ≤3 on the modified Rankin scale), which may have resulted in a higher incidence of cardioembolic stroke and a lower incidence of atherothrombotic or lacunar infarction in the present study than in the EAFT. Anticoagulant therapy is effective for the prevention of recurrent cardioembolic stroke, but it may be less effective for atherothrombotic or lacunar infarction, which may have been reflected in the present result.

The study population was smaller than that of the EAFT, and there may have been racial difference. The incidence of intracerebral hemorrhage was reported to be higher in Japan than in Western countries,18 so the Japanese may be more prone to experience hemorrhagic events than Western persons.

### TABLE 4. Characteristics of Patients With Major Bleeding

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age, y/Sex</th>
<th>Site of Bleeding (Treatment)</th>
<th>Interval From Enrollment (mo)</th>
<th>INR Before Bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>74/F</td>
<td>Massive subcutaneous hemorrhage with accidental fall (surgical resection)</td>
<td>2</td>
<td>2.80</td>
</tr>
<tr>
<td>2</td>
<td>67/M</td>
<td>Gastrointestinal bleeding (blood transfusion)</td>
<td>4</td>
<td>3.55</td>
</tr>
<tr>
<td>3</td>
<td>73/M</td>
<td>Gastrointestinal bleeding, cholecystic cancer (surgical resection of the cancer)</td>
<td>11</td>
<td>2.59</td>
</tr>
<tr>
<td>4</td>
<td>74/M</td>
<td>Gastrointestinal bleeding (blood transfusion)</td>
<td>15</td>
<td>2.66</td>
</tr>
<tr>
<td>5</td>
<td>77/M</td>
<td>Cerebellar hemorrhage (hospitalized medical care)</td>
<td>33</td>
<td>2.25</td>
</tr>
<tr>
<td>6</td>
<td>77/M</td>
<td>Hemoptysis (hospitalized medical care)</td>
<td>3</td>
<td>3.05</td>
</tr>
</tbody>
</table>

### TABLE 5. Characteristics of Patients With Recurrent Ischemic Stroke

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age, y/Sex (Group)</th>
<th>Site of Lesion (Prognosis)</th>
<th>Interval From Enrollment (mo)</th>
<th>INR Before Recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>58/M (high)</td>
<td>Left anterior choroidal artery territory (socially independent)</td>
<td>11 mo</td>
<td>2.54</td>
</tr>
<tr>
<td>2</td>
<td>70/M (low)</td>
<td>Pons, left, tegmentum (socially independent)</td>
<td>9 mo</td>
<td>1.61</td>
</tr>
<tr>
<td>3</td>
<td>58/M (low)</td>
<td>Left parietal (independent at home)</td>
<td>10 d</td>
<td>2.57</td>
</tr>
</tbody>
</table>
The present study has potential limitations because the trial was terminated prematurely due to an excessive occurrence of major hemorrhage in the conventional-intensity group. Although the primary and secondary end points in this study were rather simple and clear and interim analysis was planned to maintain the safety of the study population, a nonblinded assessment of end points and multiple interim analyses may have influenced the result.

In conclusion, low-intensity warfarin (INR 1.5 to 2.1) treatment may be safer for the secondary prevention of stroke in patients with NVAF with presumed cardioembolic TIA or stroke within the previous 6 months, especially in elderly patients with NVAF, than conventional-intensity (INR 2.2 to 3.5) warfarin treatment, because major hemorrhagic complications are avoided.

Appendix

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References
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