We retrospectively studied 79 patients from three centers who suffered an intracerebral hemorrhage during treatment with anticoagulants and compared them with 84 patients from one center who suffered a spontaneous intracerebral hemorrhage without anticoagulant treatment. Mortality after 30 days was slightly higher in patients with anticoagulant treatment (67%) than in those without (55%), and the proportion of patients who attained moderate or complete recovery was slightly smaller in the treated group (22% and 36%, respectively); neither difference was statistically significant. Volume of the supratentorial hematoma was measured from computed tomograms in 70% of the patients in both groups and was significantly greater in the 55 patients treated with anticoagulants than in the 59 patients not so treated. Volume was not related to the degree of anticoagulation. Based on the total number of patients treated with anticoagulants in the Heerlen region, we conclude that for patients older than 50 years of age the risk of intracerebral hemorrhage during anticoagulant treatment is increased approximately eightfold but is unrelated to the degree of anticoagulation. Our results suggest that intracerebral hemorrhage is more frequent and more extensive in patients treated with anticoagulants but that once it has occurred in such patients intracerebral hemorrhage is not significantly more serious than in untreated patients. (Stroke 1990;21:726–730)

The occurrence of intracerebral hemorrhage (ICH) in patients treated with anticoagulants is a serious complication, often fatal. The risk of ICH in patients >50 years of age who have been treated with anticoagulants is estimated to be 10 times that in untreated subjects of the same age. In that study, outcome in treated patients was not different from that in untreated patients, but ICH was diagnosed mainly on clinical grounds. Additionally, it is uncertain whether the risk of ICH is related to the duration and degree of anticoagulation. According to some studies the risk is greatest during the first 6 months, whereas other workers have found that most ICHs occur after at least 1 year of anticoagulation. Though ICH in patients receiving anticoagulants often results from overtreatment, many authors have reported a therapeutic degree of anticoagulation at the moment of the bleeding. Finally, the volume of the hematoma, an important prognostic factor in most studies, has not yet been studied in relation to the use of anticoagulants.

The purpose of our retrospective study, which we believe is the largest of its type, was to examine the influence of anticoagulation treatment on the risk of ICH, the volume of the hematoma, and the clinical course compared with patients suffering an ICH who were not treated with anticoagulants.

Subjects and Methods

We studied the records of 79 patients with ICH who were being treated with anticoagulants. The treated patients had been admitted during 6.5 years (from July 1980 to December 1986) to the De Wever Ziekenhuis in Heerlen (n=38), the University Hospital in Utrecht (n=10), or the St. Elisabeth Ziekenhuis in Tilburg (n=31). The selection criteria for referral to the three hospitals were similar. The treated patients comprised 13 women and 66 men. Their ages ranged from 35 to 82 (mean 67.2) years; two were <50 years old. The indication for anticoagulant treatment was always cardiac or peripheral vascular disease.

The diagnosis of ICH was confirmed by computed tomography (CT) in 63 treated patients and by autopsy in 10; in the other six treated patients the diagnosis was based on clinical grounds, namely, the sudden onset of hemiparesis with rapid
loss of consciousness, followed by death within 1 day (four patients) or 5 days (two patients). The hematoma was located supratentorially in 72 of the treated patients and the localization was based on CT in 57 patients (in two cases the films were lost), on autopsy in nine patients, and on the clinical picture alone for the six patients mentioned above. Infratentorial bleeding occurred in five of the treated patients (in the pons in four and in the cerebellum in the other), and bleeding was confined to the ventricular system in the two remaining treated patients (Table 1). Except for two patients who were given heparin, all patients were treated with oral coumarin preparations (fenprocoumon or acenocoumarol). Bleeding was not preceded by head trauma, however slight, in any treated patient.

Most treated patients were given vitamin K intramuscularly immediately after the diagnosis of ICH. Those with large hematomas and a lowered level of consciousness were usually also given a concentrate of the coagulation factors II, VII, IX, and X. Forty-six of the 79 treated patients (58%) were known to suffer from hypertension (treated or untreated).

We also studied the number of patients receiving anticoagulants from the Thrombosis Center located in the De Wever Ziekenhuis in the Heerlen region. This is one of the 70 so-called Thrombosis Centers in the Netherlands, which provide 95% of outpatient treatment with anticoagulants. During the entire study period (from July 1980 to December 1986) approximately 2,150 patients per year were under the care of this Thrombosis Center, and the total number of treatment-years was therefore approximately 14,000. The degree of anticoagulation was measured with the thrombotest. The Thrombosis Center aimed to prolong the prothrombin time to an internationally normalized ratio (INR) of 2.8–4.8. This corresponds to an activity of the vitamin K-dependent clotting factors (thrombotest) of 10–5%, or a prothrombin time 1.6–2.0 times the control value. For patients with an increased risk of ICH and those >65 years of age, the target value was an INR of 2.5–3.3 or a thrombostest activity of 12–8% (prothrombin time 1.5–1.7 times the control value). The average duration of anticoagulant treatment for all patients at the Thrombosis Center was 3.3 years.

We used the paired t test and the χ² test to compare the treated and untreated groups; p<0.05 was considered significant. Hematoma volumes were measured either from CT scans or roentgenograms by means of the best-fit method. We used the Rankin Scale, rated approximately 6 months after ictus, as a measure of outcome. Rankin grades 4 and 5 were grouped together as indicating severe handicap and Rankin grades 3, 2, 1, and 0 as indicating moderate to complete recovery.

Results

Duration of the anticoagulant treatment could be determined in 70 of the 77 treated patients who had been followed as outpatients (Figure 1). One patient had used anticoagulants for 18 years. On average, the ICH occurred 4.3 years after the start of anticoagulant treatment. Of the 79 treated patients, 36 (46%) died early (±2 days after the ictus); supratentorial hemorrhage had occurred in 31 (Table 1). Of the 84 untreated patients, 32 (38%) died early. Within 30 days, 67% (53) of the 79 treated patients had died.
compared with 55% (46) of the 84 untreated patients. None of these differences was significant. In addition, there was no significant difference in the proportion of patients who showed moderate or complete recovery (22% [17] of the 79 treated patients and 36% [30] of the 84 untreated patients).

Hematoma volume was measured from the first CT scan or roentgenogram, which was usually made ≤2 days after the ICH, in 55 of the 72 treated and in 59 of the 82 untreated patients with supratentorial hemorrhages (Table 1). The volume varied between 3 and 132 (mean 49.9) cm$^3$ and 1 and 91 (mean 27.6) cm$^3$, respectively. The difference between groups was significant ($p<0.001$). This difference might, however, have been biased as fewer treated than untreated patients who died early had not undergone CT before death (14 of 31 [45%] and 21 of 32 [66%], respectively). Nevertheless, the mean hematoma volume of the 38 treated patients was still significantly greater than that of the 48 untreated patients when the analysis was restricted to those who had survived for >2 days after the ictus (42 [range 3–103] cm$^3$ and 21.8 [range 1–71] cm$^3$, $p<0.001$). In two treated patients (who had thrombotest values within the therapeutic range), CT was repeated because of clinical deterioration. The hematoma volume had increased from 20 to 73 cm$^3$ during 12 hours in one patient and from 35 to 109 cm$^3$ during 3 days in the other. Eleven untreated patients were also examined a second time because of a progressive decrease in level of consciousness, but their hematoma volumes had not increased. Mean hematoma volume of the 28 patients (regardless of group) with supratentorial hemorrhages who died early (63 cm$^3$, 71 cm$^3$ in the treated group and 53 cm$^3$ in the untreated group) was almost twice that of the 86 patients who survived >2 days (32 cm$^3$, 41 cm$^3$ in the treated group and 21 cm$^3$ in the untreated group). The 47 patients who showed moderate or complete recovery had a small mean hematoma volume (18.7 cm$^3$ for both groups together). Of the 41 patients with a hematoma volume of >50 cm$^3$ (regardless of group) all but three either died within 30 days or remained severely handicapped.

The degree of anticoagulation was determined immediately after admission in 71 of the 77 treated patients on oral anticoagulants. Their mean thrombotest value was 7.4% (range 21–3.5%), corresponding to an INR of 3.5 (range 1.8–6.5) and a prothrombin time of 1.7 (range 1.3–2.3) times the control value. Fifteen treated patients had thrombotest values of <5% (INR >4.8), and 11 had a thrombotest value of >10% (INR 2.8); the 45 remaining patients had thrombotest values within the therapeutic range. Hematoma volume and thrombotest values were available for 50 of the 70 treated patients with supratentorial hemorrhages who were receiving oral anticoagulants. There was no relation between thrombotest values and hematoma volumes (Figure 2). Both small and large hematomas occurred with both low and high thrombotest values. This finding was not biased by the circumstance that hematoma volumes could not be measured in 17 treated patients with supratentorial hemorrhages as only two had anticoagulated too much.

Thirty of the 79 treated patients were anticoagulated by the Thrombosis Center Heerlen; all 30 were >50 years old. As patients aged >50 years constitute 90% of the patients treated by the Thrombosis Center, the 30 ICHs occurred during a total of 12,600 anticoagulant treatment-years, or one ICH per 420 treatment-years. Seventy-five of the 84 untreated patients were >50 years old. As the Heerlen region has 200,000 inhabitants, of whom 30% (60,000) are >50 years old, there were an average of 18.75 spontaneous ICHs/yr/60,000 people over age 50, which corresponds to a risk of 1 ICH/3,200 person-years. The relative risk of ICH in patients >50 years of age on oral anticoagulants (1/420 treatment-years) was therefore 7.6 (95% confidence interval 5–11) times that of patients without anticoagulants. The calculation in age-specific person-years gave approximately the same results; the relative risk was 8.7 for the age group 50–59, 8.0 for the age group 60–69, 4.0 for the age group 70–79, and 7.6 for the age group ≥80 years.

An inappropriately high degree of anticoagulation (thrombotest value of <5%) was found in 10% (three) of the 30 patients with ICH treated by the Thrombosis Center Heerlen, whereas 27% (eight of 30) were insufficiently anticoagulated (thrombotest value of >10%) (Table 2). On the basis of 2,000 randomly chosen samples (four times a year) from patients without ICH, 69% of all patients had been optimally anticoagulated by the Thrombosis Center (thrombotest values of 5–10%), 27% had thrombotest values of >10%, and 4% had thrombotest values of <5%. There was, therefore, no significant difference between the degree of anticoagulation in patients with or without ICH.
Discussion

Our study shows that the outcome of ICH in patients treated with anticoagulants is only slightly worse than in those without, despite the significantly larger hematoma volumes in treated patients. The degree of anticoagulation was not related to the occurrence of ICH or to the hematoma volume. Mortality in our study, in patients with or without anticoagulants, was similar to that reported earlier and was closely related to the hematoma volume. Only one other study has reported larger hematoma volumes in patients treated with anticoagulants (59 cm$^3$) than in those without (38 cm$^3$); however, there were fewer patients in that study and the differences in volume were not statistically significant.

We did not systematically investigate whether the hematomas increased in volume after the first CT examination. CT was repeated in two of our treated patients because of clinical deterioration; hematoma volume had increased greater than threefold in both patients. We did not observe such an increase in the 11 untreated patients who were scanned a second time. A possible explanation for this difference is that patients treated with anticoagulants who suffer an ICH are not only scanned more often than other patients (as was the case in our series), they are also admitted to a hospital sooner, while the hematoma is still enlarging. Other studies have reported expansion of intracerebral hematomas unrelated to anticoagulation treatment.

The relation between the degree of anticoagulation and the hematoma volume has not been studied before. We found no such relation. We also failed to find a direct link between the degree of anticoagulation and the risk of ICH. When the proportion of patients with ICH who had been overtreated with anticoagulants was compared with the total group of anticoagulated patients in the area, only a slight excess of ICH in overtreated patients was found, with a wide confidence interval.

The tendency for more ICHs to occur with excessive anticoagulation has been reported, but ICH with anticoagulation in the therapeutic or subtherapeutic range is also frequently mentioned. It is difficult to compare these studies because the upper limits of therapeutic anticoagulation differ. Our upper limit of a prothrombin time 2.0 times the control value was the same as in other Dutch studies but differs from that in studies in the United States (1.52 and 2.5). One study did not mention the upper limit of anticoagulation at all. The increased risk (eightfold to 10-fold) of ICH in patients with anticoagulant treatment compared with that of the total population (>50 years old) has also been found in other retrospective studies and in one randomized study. We did not find the increased incidence of cerebellar hematomas in patients treated with anticoagulants that was reported in one study, nor did we detect the high incidence of subdural hematomas in patients treated with anticoagulants reported in the pre-CT era as well as in a recent study. We did not include patients with subdural hematomas in our series, but only three such patients were found during the study period. The marked sex difference in the occurrence of ICH with anticoagulation had been found in an earlier Dutch study; the explanation is that more men than women are treated with anticoagulants in the Netherlands.

The total incidence of ICH, with or without anticoagulants, in the Heerlen region (115 during the period 1983–1986, or 14.4/yr/100,000 persons of all ages) was in good agreement with that (14.5) in the Tilburg Epidemiologic Stroke Study, in which the diagnosis was confirmed by CT in 56% of the patients.

In our study the average duration of anticoagulant treatment before ICH (4.3 years) was only slightly longer than the duration of anticoagulant treatment for all patients (3.3 years). The risk of ICH increases with the duration of anticoagulant therapy; one study reported that 70% of ICHs occurred ≤1 year after the start of anticoagulant therapy, but the authors did not mention the average duration of anticoagulant therapy for all patients.

It is not clear how anticoagulants induce ICH. Histologic examination of surgically removed clots has not provided a cause for the bleeding. In patients treated with anticoagulants who suffered an ICH, but hemosiderin was found in six other patients not treated with anticoagulants, indicating a previous ICH. This finding has been confirmed by others. Perhaps elderly subjects often have small ICHs without symptoms. The incidence of ICH increases with age. Cerebral amyloid angiopathy (CAA), which is probably an important factor in the genesis of ICH, is a frequent finding in aged brains. The occurrence of a large ICH during anticoagulant therapy and CAA without dementia

### Table 2. Degree of Anticoagulation in Patients With and Without ICH Under Care of Thrombosis Center Heerlen

<table>
<thead>
<tr>
<th>Thrombostest</th>
<th>Patients with ICH (n=30)</th>
<th>Random samples (n=2000)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>&lt;5%</td>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td>5%–10%</td>
<td>19</td>
<td>63</td>
</tr>
<tr>
<td>&gt;10%</td>
<td>8</td>
<td>27</td>
</tr>
</tbody>
</table>

ICH, intracerebral hemorrhage; CI, confidence interval.
has been described in three patients. In addition, the presence of fibrinoid necrosis in the perforating arteries, which occurs especially in persons with hypertension, is also related to ICH. However, there are no prospective studies on which to base the degree of anticoagulation required to avoid or treat arterial thromboembolism. However, our conclusion, that the use of anticoagulants increases the risk of ICH but that this risk is not directly dependent on the degree of anticoagulation, suggests an all-or-nothing phenomenon with a low threshold.

Acknowledgments

The authors are grateful to H. Frericks, MD, and Mrs. J. Sykes, PhD, for their critical comments and to Miss J. Schmitz for typing this manuscript.

References


KEY WORDS • anticoagulants • hematoma
Intracerebral hematomas during anticoagulant treatment.
C L Franke, J de Jonge, J C van Swieten, A A Op de Coul and J van Gijn

Stroke. 1990;21:726-730
doi: 10.1161/01.STR.21.5.726

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1990 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://stroke.ahajournals.org/content/21/5/726

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org/subscriptions/