Avoiding Central Nervous System Bleeding During Antithrombotic Therapy
Recent Data and Ideas

Robert G. Hart, MD; Silvina B. Tonarelli, MD; Lesly A. Pearce, MS

Background—Approximately 7000 intracerebral hemorrhages (ICHs) annually in the US are caused by use of antithrombotic therapies. We review the incidence, risk factors, and predictors of ICH in patients receiving long-term anticoagulation or antiplatelet therapy.

Summary of Review—ICH rates range from 0.3% to 0.6% per year during oral anticoagulation in recent reports. Major risk factors are advanced patient age, elevated blood pressure, intensity of anticoagulation, and previous cerebral ischemia. Combining antiplatelet agents with anticoagulation and the combined use of aspirin plus clopidogrel appear to increase ICH risk. Modest blood pressure-lowering halves the frequency of ICH during antiplatelet therapy.

Conclusion—ICH is an uncommon, but often fatal, complication of antithrombotic therapy that particularly afflicts patients with previous stroke. Recent data support that keeping international normalized ratio (INR) 3.0, control of hypertension, and avoiding the combination of aspirin with warfarin reduce its frequency. (Stroke. 2005;36:1588-1593.)

Key Words: anticoagulants • antiplatelet • antithrombotic therapy • aspirin • clopidogrel • intracerebral hemorrhage • warfarin

By the best available estimates, carefully regulated anticoagulation with warfarin to international normalized ratios (INRs) between 2 and 3 doubles the risk of intracerebral hemorrhage (ICH).1,2 Aspirin therapy increases the risk of ICH by ≈40%, with estimates ranging from 24% to 84%.3–7 Based on the frequency of antithrombotic therapy use among ICH patients (≈10% receiving warfarin, ≈25% receiving aspirin),7–11 an estimated 7000 of the 60,000 ICHs occurring annually in the US are caused by the use of warfarin (≈3000) and aspirin (≈4000). These “extra” ICHs account for ≈1% of incident strokes and ≈12% of ICHs.

Increased ICH rates of only 1% to 2% per year can negate the benefits of antithrombotic therapy, yet such increases are beyond appreciation by individual clinicians and must rely on large clinical studies for detection. Information about this uncommon, but most serious, complication of antithrombotic therapy is scattered in the literature. We review recent data relevant to minimizing ICH in patients receiving chronic antithrombotic therapy. Although not a formal systematic review, we attempted to collate all available relevant data via computerized search of the English language literature for each subtopic.

Pathogenetic Constructs and Time Trends
Anticoagulation with warfarin and congeners is safer than it used to be. In randomized trials performed a generation ago, oral vitamin K antagonists were associated with 5- to 10-fold increases in ICH, and absolute ICH rates of 1% per year were often reported.12–14 Relative risks and absolute rates in recent studies are considerably lower, probably because of better regulation of anticoagulation using the INR, lower anticoagulation intensities, and improved control of hypertension. Despite the more frequent anticoagulation of elderly patients, ICH rates range from 0.3% to 0.6% per year in recent reports.7,14–23

Pathogenetically, antithrombotic therapies appear to exaggerate the underlying risk of spontaneous ICH,24 and hence risk factors for warfarin-associated ICH overlap those for spontaneous ICH in patients not receiving antithrombotic therapy (Table 1).8 Patients at highest risk for spontaneous ICH are also those at special risk for anticoagulant-associated ICH, with advanced age and elevated blood pressure as salient risk factors. This construct explains why intensities of warfarin anticoagulation that are infrequently complicated by ICH in middle-aged people undergoing anticoagulation for venous thromboembolism result in much higher absolute rates of ICH among anticoagulated octogenarians, particularly if blood pressure is not well-controlled.

Microvascular abnormalities predisposing to bleeding can be detected by MRI. “Leukoaraiosis”29,32 and asymptomatic cerebral microbleeds33,34 have been correlated with ICH during anticoagulation and aspirin therapy, respectively.
However, these MRI lesions suffer from variations in definition, acquisition techniques, and interpretation; the positive and negative predictive values are inadequately defined to permit application to individual patient management, in our view.

Anticoagulation Intensity and Central Nervous System Bleeding

There is no lower threshold of anticoagulation intensity that does not accentuate the risk of ICH and noncentral nervous system major hemorrhage to some degree, in our opinion.12,35 Others have proposed “an all-or-nothing phenomenon with a low threshold,”36 with the latter construct supported by 2 time-dependent INR analyses involving elderly patients with atrial fibrillation (Table 2).25,26 Intracranial bleeding was not increased by warfarin anticoagulation until the INR exceeded 3.5 to 4.0, and there was no increase in ICH associated with INRs of 2 to 3 compared with lower INRs. Despite these reassuring observations, anticoagulation intensity invariably fluctuates in real life. Pooled results of randomized trials with mean achieved INRs of 2 to 2.5 show doubling of intracranial hemorrhages, albeit with a small number of intracranial hemorrhages,1,2 but supported by a large longitudinal cohort comparison.17 Considering intracranial hemorrhage, anticoagulation of atrial fibrillation patients in their 70s appears to be relatively safe if the intensity of anticoagulation is carefully regulated. Of note, a target INR range of 2 to 4.5 (mean achieved INR 2.6) in octogenarians coupled with inadequate

### TABLE 1. Risk Factors for Intracerebral Hemorrhage During Warfarin Anticoagulation

<table>
<thead>
<tr>
<th>Firmly established1,2,3,5–29</th>
<th>Possible</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advancing age (especially older than 75 years)</td>
<td>Concomitant use of aspirin30</td>
</tr>
<tr>
<td>Hypertension (especially systolic blood pressure &gt;160 mm Hg)</td>
<td>Cerebral amyloid angiopathy31</td>
</tr>
<tr>
<td>History of cerebrovascular disease</td>
<td>Asian or Mexican-American ethnicity</td>
</tr>
<tr>
<td>Intensity of anticoagulation</td>
<td>Tobacco smoking</td>
</tr>
<tr>
<td>Imaging and genetic markers</td>
<td>Heavy alcohol consumption</td>
</tr>
<tr>
<td>Leukoaraiosis detected by brain CT/MRI28,32</td>
<td>Microbleeds by T2*-weighted MRI</td>
</tr>
<tr>
<td>APOE e II or IV genotype31</td>
<td></td>
</tr>
</tbody>
</table>

CT indicates computed tomography, MRI, magnetic resonance imaging.

### TABLE 2. Intracranial Hemorrhage vs Anticoagulation Intensity in Atrial Fibrillation Patients: 2 Recent Studies*

<table>
<thead>
<tr>
<th>Longitudinal Cohort Study</th>
<th>Case-Control Study‡</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean Age, 71 y</strong></td>
<td><strong>Mean Age, cases=78 years, controls=75 years</strong></td>
</tr>
<tr>
<td><strong>INR</strong></td>
<td><strong>Rate Per 100 Person-Years</strong></td>
</tr>
<tr>
<td>&lt;1.5</td>
<td>0.5</td>
</tr>
<tr>
<td>1.5–1.9</td>
<td>0.3</td>
</tr>
<tr>
<td>2.0–2.5</td>
<td>0.3</td>
</tr>
<tr>
<td>2.6–3.0</td>
<td>0.5</td>
</tr>
<tr>
<td>3.1–3.5</td>
<td>0.6</td>
</tr>
<tr>
<td>3.6–3.9</td>
<td>0.4</td>
</tr>
<tr>
<td>4.0–4.5</td>
<td>2.7</td>
</tr>
<tr>
<td>&gt;4.5</td>
<td>9.4</td>
</tr>
</tbody>
</table>

*These time-dependent INR-based estimates are not directly applicable to clinical target INR ranges, because the invariable fluctuations in INRs are not considered. Intracranial hemorrhages include both primary intracerebral bleeding and subdural hematomas. Blood pressure data were not provided in either study.

†From Table 5 of Hylek et al involving 58 intracranial hemorrhages among 6320 outpatients taking warfarin in a longitudinal cohort study.26

‡Estimated from Figure 2 of Fang et al involving 170 atrial fibrillation patients with intracranial hemorrhage taking warfarin in a case-control comparison.25

### TABLE 3. CNS Bleeding When Aspirin Is Added to Warfarin: Randomized Trials*

<table>
<thead>
<tr>
<th>Trial</th>
<th>Cohort</th>
<th>Aspirin Dosage</th>
<th>INR</th>
<th>CNS Bleeds During Anticoagulation (bleeds/patients)</th>
<th>CNS Bleeds with Anticoagulation Plus Aspirin (bleeds/patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Turpie et al42</td>
<td>Prosthetic cardiac valves</td>
<td>100 mg</td>
<td>3.0</td>
<td>3/184</td>
<td>7/186†</td>
</tr>
<tr>
<td>UK MRC43</td>
<td>Coronary risk factors</td>
<td>75 mg</td>
<td>1.5</td>
<td>1/1277</td>
<td>7/1268</td>
</tr>
<tr>
<td>Cheseboro et al844</td>
<td>Prosthetic cardiac valves</td>
<td>500 mg</td>
<td>4–5‡</td>
<td>0/181</td>
<td>5/170</td>
</tr>
<tr>
<td>Altman et al¶45</td>
<td>Prosthetic cardiac valves</td>
<td>500 mg</td>
<td>2‡</td>
<td>1/65</td>
<td>1/57</td>
</tr>
<tr>
<td>Dale et al¶46</td>
<td>Prosthetic cardiac valves</td>
<td>1000 mg</td>
<td>2–3‡</td>
<td>3/73</td>
<td>2/75</td>
</tr>
<tr>
<td>Aggregate</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>8/1780</td>
<td>22/1756</td>
</tr>
</tbody>
</table>

*Adapted from the systematic review by Hart et al30 and restricted to trials in which aspirin was added to identical intensities of anticoagulation. Additional recent trials did not report CNS bleeds.47–49 In the AFASAK II trial, the INR was not prolonged beyond the normal range by low-dose warfarin, and it is not included.50

†One intracranial bleed per patient was counted.

‡INRs estimated from prothrombin times or thrombotest values.

¶Patients were assigned to receive warfarin plus either aspirin 500 mg/d (n = 170) or dipyridamole 100 mg 4 times daily (n = 181).

Diagnosis of intracranial bleeds was clinical, usually without neuroimaging.

CNS indicates central nervous system.
control of hypertension resulted in an intolerable ICH rate (1.8% per year) in one trial,37 emphasizing the relatively narrow margin of safety.

**Patients with Cerebrovascular Diseases Are at Special Risk for ICH During Anticoagulation**

In the Stroke Prevention in Reversible Ischemia Trial (SPIRIT) trial, patients with recent cerebral ischemia of presumed arterial origin were randomized to receive anticoagulation (target INR 3 to 4.5) versus aspirin 30 mg per day.38 Mean participant age was 65 years old, average blood pressure at entry was 158/91 mm Hg, and the mean achieved INR was 3.3. A 3.7% per year rate of intracranial hemorrhage among anticoagulated patients resulted in early termination and was 4.5-times higher than in those given aspirin.29,38 The high ICH rate likely resulted from combination of 3 risk factors for warfarin-associated ICH (Table 1): a relatively high INR in patients with cerebrovascular disease with poorly controlled hypertension. Trials involving patients with cerebrovascular diseases testing lower target INRs of 2 to 3 and with lower mean blood pressures have reported substantially lower ICH rates during anticoagulation.2,39,40 It is unknown whether those with atherosclerosis have different ICH risks compared with patients with small-artery disease. Silent cerebral microbleeds are particularly frequent in patients with “lacunar” infarcts and have been associated with ICH during aspirin therapy.32,34,41

**Combining Aspirin With Warfarin**

 Approximately 20% of anticoagulated patients with atrial fibrillation also take aspirin.18,25 Adding aspirin to oral

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**TABLE 4. Observed Rates of CNS Bleeding With Warfarin Plus Aspirin***

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>No.</th>
<th>Mean Age/Systolic BP</th>
<th>Mean INR</th>
<th>Aspirin Dosage</th>
<th>CNS Bleeds</th>
<th>Rate (%/y)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shireman et al (2004)</td>
<td>AF</td>
<td>1962</td>
<td>76 y/NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>0.9†</td>
</tr>
<tr>
<td>SPAF III (1996)</td>
<td>AF</td>
<td>521</td>
<td>72 y/144</td>
<td>1.3</td>
<td>325 mg</td>
<td>5</td>
<td>0.9</td>
</tr>
<tr>
<td>Turpie et al (1993)</td>
<td>PHV</td>
<td>186</td>
<td>78 y/NR</td>
<td>3.0</td>
<td>100 mg</td>
<td>7</td>
<td>1.5</td>
</tr>
<tr>
<td>Meschengieser et al (1997)</td>
<td>PHV</td>
<td>256</td>
<td>54 y/NR</td>
<td>3.1</td>
<td>100 mg</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Buresly et al (2005)</td>
<td>Recent MI</td>
<td>~225</td>
<td>&gt;65 y/NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>4.0</td>
</tr>
<tr>
<td>ASPECT II (2002)</td>
<td>Recent MI</td>
<td>332</td>
<td>61 y/NR</td>
<td>2.4</td>
<td>80 mg</td>
<td>1</td>
<td>0.3</td>
</tr>
<tr>
<td>WARIS II (2002)</td>
<td>Previous MI</td>
<td>1208</td>
<td>60 y/124</td>
<td>2.2</td>
<td>75 mg</td>
<td>9</td>
<td>0.2</td>
</tr>
<tr>
<td>CHAMP II (2002)</td>
<td>Recent MI</td>
<td>2522</td>
<td>64 y/NR</td>
<td>1.8</td>
<td>81 mg</td>
<td>14</td>
<td>0.2</td>
</tr>
<tr>
<td>UK MRC (1998)</td>
<td>Coronary risk factors</td>
<td>1268</td>
<td>57 y/139</td>
<td>1.5</td>
<td>75 mg</td>
<td>7</td>
<td>0.1</td>
</tr>
</tbody>
</table>

*Clinical series published since 1990 identified by computerized search combining terms of anticoagulation/warfarin with antiplatelet/aspirin/clopidogrel,” restricted to those with >100 patients that reported CNS bleeds during long-term treatment; estimated rates are annualized (per 100 patient-years). AF indicates atrial fibrillation; BP, blood pressure in mm Hg; MI=myocardial infarct; NR, not reported; PHV, prosthetic heart valve. †Rate reported for the initial 180 days after hospital discharge. No neuroimaging was performed in 27% of strokes, and the CNS bleeding was likely under-detected.

**TABLE 5. Rates of CNS Bleeding During Antiplatelet Therapy With Aspirin and Clopidogrel in Recent Randomized Trials***

<table>
<thead>
<tr>
<th>Trial</th>
<th>Population</th>
<th>Aspirin</th>
<th>Clopidogrel/Ticlopidine</th>
<th>Aspirin + Clopidogrel</th>
<th>Rate Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAPRIE</td>
<td>Vascular disease, mean age=63 y</td>
<td>0.3%/y (n=47)</td>
<td>0.2%/y (n=24)</td>
<td>. . .</td>
<td>. . .</td>
</tr>
<tr>
<td>CURE</td>
<td>Acute coronary syndromes, mean age=64 y</td>
<td>0.1%/y (n=5)</td>
<td>. . .</td>
<td>0.15%/y (n=7)</td>
<td>1.4</td>
</tr>
<tr>
<td>AAASPS</td>
<td>Recent ischemic stroke, mean age=61 y</td>
<td>0.2%/y (n=3)</td>
<td>0.3%/y (n=4)</td>
<td>. . .</td>
<td>. . .</td>
</tr>
<tr>
<td>MATCH</td>
<td>Recent ischemic stroke or TIA, mean age=66 y</td>
<td>. . .</td>
<td>0.4%/y (n=25)</td>
<td>0.7%/y (n=40)</td>
<td>1.6</td>
</tr>
<tr>
<td>Atrial Fibrillation Investigators</td>
<td>Atrial fibrillation, mean age=72 y</td>
<td>0.3%/y (n=11)</td>
<td>. . .</td>
<td>. . .</td>
<td>. . .</td>
</tr>
<tr>
<td>CHAMP</td>
<td>Recent myocardial infarction, mean age=64 y</td>
<td>0.2%/y (n=15)</td>
<td>. . .</td>
<td>. . .</td>
<td>. . .</td>
</tr>
<tr>
<td>WARIS II</td>
<td>Previous myocardial infarction, mean age=60 y</td>
<td>0.1%/y (n=4)</td>
<td>. . .</td>
<td>. . .</td>
<td>. . .</td>
</tr>
<tr>
<td>HOT</td>
<td>Well-controlled hypertension, mean age=62 y</td>
<td>0.04%/y (n=14)</td>
<td>. . .</td>
<td>. . .</td>
<td>. . .</td>
</tr>
<tr>
<td>Women's Health Study</td>
<td>Healthy women, mean age=60 y</td>
<td>0.02%/y (n=41)</td>
<td>. . .</td>
<td>. . .</td>
<td>. . .</td>
</tr>
</tbody>
</table>

*Clinical trials identified by computerized search combining “clinical trial” with “vascular disease” with “antiplatelet/aspirin/clopidogrel,” restricted to those reporting CNS bleeding. Rates are based on published results using total patient exposure reported for primary outcome and hence actual rates may be slightly lower. Aspirin dosages: CAPRIE=325 mg/d; CURE=75–325 mg/d; AAASPS=650 mg/d; WARIS II=160 mg/d; MATCH and HOT=75 mg/d; Women’s Health Study=100 mg every other day; Atrial Fibrillation Investigators=75–325 mg/d; and CHAMP=162 mg/d.

TIA indicates transient ischemic attack. CNS bleeds were not reported in the CREDO trial; in ESPS II, the rate of CNS bleeding was reported as 0.4%/y with aspirin 25 mg twice daily and as 0.3%/y with this aspirin dosage combined with extended-release dipyridamole 200 mg twice daily; however, these absolute rates are underestimates because neuroimaging was not performed in 27% of stroke events.53

†All participants were black; number of CNS bleeds has not been published, obtained from Gorelick and Richardson (personal communication), with rates estimated based on mean follow-up of 1.54 years.66
vitamin K antagonists appears to increase the ICH risk. Meta-analysis of 5 randomized trials in which aspirin was added to equal intensities of anticoagulation shows a relative risk of 2.6 (95% CI, 1.3 to 5.4; \( P = 0.009 \)); however, methodological details were incomplete in several of these trials and ICH diagnosis was not always confirmed by neuroimaging or autopsy (Table 3). A retrospective study of a hospital discharge cohort of 10,993 atrial fibrillation patients (mean age, 77 years), use of antiplatelet therapy was associated with a 3-fold increase in ICH (relative risk, 3.0; 95% CI, 1.6 to 5.5 in bivariate analysis; Table 4). In contrast, 2 case-control studies did not find concomitant aspirin use to be a predictor of ICH during anticoagulation.\(^{25,27} \) For atrial fibrillation patients, results of 3 randomized trials appear conflicting, but differences in study design and small numbers of ICHs preclude meaningful comparisons and definite conclusions.\(^{48,51,52} \)

Although available data are not consistent, accentuation of ICH risk is probable when anticoagulant and antiplatelet therapy are combined.\(^{23} \) In younger patients with prosthetic cardiac valves or coronary artery disease who have inherently low ICH risks, absolute rates of ICH during combined warfarin–aspirin therapy are low (Table 4). In older patients or with target INRs \( > 3 \), addition of aspirin to anticoagulation should be performed only after careful consideration of the benefit/risk ratio because of probable accentuation of ICH, in our view. It remains unclear whether combination therapy is of overall benefit for elderly atrial fibrillation patients who have previous stroke or manifest coronary artery disease.

### Combination Antiplatelet Therapies

The combination of clopidogrel with aspirin increased the rate of central nervous system bleeding by 61% (\( P = 0.06 \)) compared with clopidogrel alone in a recent randomized trial involving patients with recent stroke or transient ischemic attack (Table 5).\(^{57} \) Although a similar trend was observed in a randomized trial involving patients with acute coronary syndromes, there were too few ICHs to meaningfully assess.\(^{59} \) The ICH rate was significantly higher (rate ratio, 4.8; 95% CI, 2.6 to 8.6) among patients given clopidogrel plus aspirin who had recent stroke or transient ischemic attack (Management of Atherothrombosis with Clopidogrel in High-risk Patients [MATCH] trial) versus those with acute coronary syndromes (Clopidogrel in Unstable Angina to Prevent Recurrent Events [CURE] trial), despite similar mean ages, supporting that cerebrovascular patients are different.\(^{57,59} \) Available data support that the combined use of low-dose aspirin plus clopidogrel may accentuate intracranial hemorrhage by a clinically important magnitude for patients with cerebrovascular disease. This hypothesis is based on limited data, estimated absolute rates derived from aggregate data are unstable (Table 5), and results of ongoing randomized trials are needed to refine these constructs.

### Blood Pressure Control

Modest reduction in blood pressure profoundly lowers ICH risk.\(^{64–66} \) In the randomized Perindopril Protection Against Recurrent Stroke Study (PROGRESS) trial involving patients with previous stroke or TIA transient ischemic attack, 72% of participants were receiving antiplatelet therapy and 10% oral anticoagulants.\(^{64} \) Hemorrhagic stroke was reduced 50% (95% CI, 26 to 67) by a mean 9 mm Hg reduction in systolic blood pressure and 76% (95% CI, 55 to 87) by a 12 mm Hg reduction (absolute rates of 0.6% per year to 0.3% per year and 0.2% per year, respectively).\(^{64} \) ICH rates during antiplatelet therapy (and likely during anticoagulation) are exquisitely sensitive to blood pressure control.

### Summary

Central nervous system bleeding is an uncommon but often fatal complication of chronic antithrombotic therapy. Its frequency may be increasing because of more widespread use of these agents in older patients and possibly because of the more frequent use of warfarin combined with aspirin. Relatively small differences in the ICH rate of 1% to 2% per year can shift the balance of therapeutic benefit versus harm.\(^{37,38,57} \) Recent data offer insights about pathogenesis, anticipated absolute rates, and clues to prevention (Tables 6 and 7). This review illustrates the limitations of available data and the need for additional research. The profound influence of blood pressure is notable: the use of antithrombotic therapy in patients with cerebrovascular disease should be contingent on a commitment to careful blood pressure management, in our view.

### References


64. PROGRESS Collaborative Group. Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6,105 individuals with previous stroke or transient ischemic attack. Lancet. 2001;358:1033–1041.


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