The Challenge of Designing a Treatment Trial for Warfarin-Associated Intracerebral Hemorrhage

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Background and Purpose—Warfarin-associated intracerebral hemorrhage (WICH) became more frequent in the past 2 decades. Interest in potential WICH treatment trials has grown, but the practicality of such trials has received less attention. We determined the number of patients that would be eligible for enrollment in hypothetical treatment trials for WICH using a population-based study.

Methods—We identified all patients aged 18 years or older from the Greater Cincinnati/Northern Kentucky region with nontraumatic intracerebral hemorrhage in 2005. Three hypothetical WICH treatment trial criteria sets were used to determine eligibility for enrollment, varying from relatively strict to broadly inclusive. For the hypothetical trials, we assumed the comparison of a standard therapy to an alternative therapy. Sample size calculations assumed different rates of poor outcome depending on the criteria set, various effect sizes, a 2-sided alpha of 0.05, and 80% power. Given 5 years of trial enrollment, the population base needed to enroll the required subjects was then calculated.

Results—Warfarin-associated intracerebral hemorrhage accounted for 54 of 286 (19%) cases of intracerebral hemorrhage within the Greater Cincinnati/Northern Kentucky region in 2005. Eligibility rates ranged from 2 of 54 WICH patients (4% of cases, strictest set) to 11 of 54 WICH patients (20% of cases, most inclusive set). Given these rates, a population base of at least 67 million persons would be required to conduct a 5-year trial for WICH with a 10% effect size using a moderately strict criteria set.

Conclusions—Any planned treatment trial for WICH should anticipate significant challenges in successfully enrolling adequate numbers of patients. (Stroke. 2009;40:1738-1742.)

Key Words: anticoagulants ■ epidemiology ■ intracerebral hemorrhage ■ randomized controlled trials ■ warfarin ■ treatment

Warfarin anticoagulation is increasingly relevant to the care of patients with intracerebral hemorrhage (ICH). Warfarin use quadrupled in the United States during the 1990s after publication of treatment trials showing warfarin is more effective than aspirin for prevention of stroke in most patients with atrial fibrillation.1-5 However, as a consequence of increased warfarin use, the incidence of anticoagulant-associated ICH quintupled during the same period.5 There have been no randomized treatment trials to determine the best method of warfarin reversal after ICH. Although the increasing incidence of warfarin-associated ICH (WICH) and the lack of randomized evidence about its management have stimulated interest in clinical trials for this condition, the design and feasibility of such trials have received less attention.6-7 We determined the number of patients that would qualify for enrollment in hypothetical treatment trials for WICH using a population-based study.

Subjects and Methods

This report analyzes a group of patients with ICH identified as part of the Genetic and Environmental Risk Factors for Hemorrhagic Stroke study. The institutional review board for each participating hospital system approved the Genetic and Environmental Risk Factors for Hemorrhagic Stroke study. We attempted to ascertain all persons age 18 years or older from the 5-county Greater Cincinnati/Northern Kentucky region (population ~1.3 million) evaluated in an emergency room or hospitalized with ICH between January 1, 2005 and December 31, 2005. Cases were identified by retrospective review of primary and secondary ICD-9 codes 430 to 438.9. Study nurses also maintained active surveillance (“hot pursuit”) at several hospitals that treat most ICH in the area.8 All potential cases were abstracted by study nurses and reviewed in detail by study physicians. Patients living outside the 5 counties of interest were excluded by zip code of residence. Other exclusion criteria were previous ICH, traumatic ICH, hemorrhagic cerebral infarction, and hemorrhage associated with brain tumor, encephalitis, recent endarterectomy, and thrombolytic treatment of ischemic stroke. Patient demographics and putative risk factors for ICH, including warfarin use before stroke...
onset, were recorded by chart review. The first available international normalized ratio value was recorded. For all patients, the first available CT or MRI scan was reviewed by 1 of 2 authors (H.T. or M.L.F.). Hemorrhage volumes were measured using the abc/2 method. The degree of intraventricular hemorrhage was documented using an ordinal scale described by Graeb, in which the amount of blood in each ventricle is graded and the scores from each ventricle are summed.

Three hypothetical trial criteria sets were used to determine eligibility for enrollment, with requirements varying from relatively stringent to broadly inclusive (Table 1). This represents the practical difficulty in trial design of balancing the greatest chance of finding a difference in treatment strategies (strict criteria) with the desire to produce widely applicable results and enroll the necessary subjects within a reasonable time frame (inclusive criteria). Eligibility rates in the Greater Cincinnati/Northern Kentucky region were determined for each criteria set. For the hypothetical trials, we assumed the comparison of a standard therapy (such as fresh-frozen plasma) to an alternative therapy (such as prothrombin complex concentrate).

Sample size calculations assumed different rates of poor outcome depending on the criteria set (Table 2), various absolute effect sizes, 1- to 1 randomization, a 2-sided alpha of 0.05, and 80% power. Poor outcome was defined as a modified Rankin scale score of 4 to 6 at 90 days. Rates of poor outcome with standard therapy were estimated based on the limited available literature. Given 5 years of trial enrollment, the population base necessary to enroll the required subjects was then calculated. The software used to calculate sample sizes was NCSS-PASS 2002.

### Results

Warfarin-associated ICH accounted for 54 of 286 (19%) ICH cases within our population in 2005. Compared to ICH patients without coagulopathy, subjects with WICH were more likely to be younger (mean age 77.7 vs 65.9; P<0.001), more likely to be white (93% of WICH cases vs 75% of other ICH cases; P<0.004), and more likely to die from their hemorrhage (90-day mortality 67% vs 43%; P<0.001). There were no significant differences between groups in gender, percent with preexisting disability defined by modified Rankin Scale score >2, time from onset to first brain scan, or admission Glasgow Coma Scale score. Among those with WICH, 26 of 54 (48%) subjects were older than age 80 years.

To better determine if our sample was representative of WICH patients in general, we compared the 54 WICH patients from 2005 to 176 WICH patients ascertained in the same population from May 1998 to July 2001 and August 2002 to April 2003 as part of the Genetic and Environmental Risk Factors for Hemorrhagic Stroke study. Volume of ICH and presence of intraventricular hemorrhage were not rec-

### Table 1. Enrollment Criteria and Reasons for Exclusion for Hypothetical WICH Treatment Trials

<table>
<thead>
<tr>
<th>Variables</th>
<th>Criteria Set 1</th>
<th>Criteria Set 2</th>
<th>Criteria Set 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr (yr)</td>
<td>18–80</td>
<td>18–80</td>
<td>18–80</td>
</tr>
<tr>
<td>≥6</td>
<td>30 (56)</td>
<td>14 (26)</td>
<td>11 (20)</td>
</tr>
<tr>
<td>≥10</td>
<td>15 (28)</td>
<td>12 (22)</td>
<td>100 (17)</td>
</tr>
<tr>
<td>≥60</td>
<td>25 (46)</td>
<td>Allowed*</td>
<td>Allowed†</td>
</tr>
<tr>
<td>≥1.5</td>
<td>7 (13)</td>
<td>7 (13)</td>
<td>7 (13)</td>
</tr>
<tr>
<td>≥2</td>
<td>11 (20)</td>
<td>11 (20)</td>
<td>11 (20)</td>
</tr>
<tr>
<td>Any reason</td>
<td>52 (96)</td>
<td>48 (89)</td>
<td>43 (80)</td>
</tr>
</tbody>
</table>

*Absolute reduction in poor outcome (mRS score 4 – 6) at 90 days.
†No limitations on IVH.
‡Given calculated sample size and eligibility rates, population base needed to complete trial enrollment in 5 years. Assumes enrollment of 50% of eligible subjects.

### Table 2. Eligibility Rates and Necessary Population Base for WICH Treatment Trials

<table>
<thead>
<tr>
<th>Effect Size (%)</th>
<th>Sample Size</th>
<th>Eligible</th>
<th>Area</th>
<th>Sample Size</th>
<th>Eligible</th>
<th>Area</th>
<th>Sample Size</th>
<th>Eligible</th>
<th>Area</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.5</td>
<td>12,500</td>
<td>2</td>
<td>3.4×10⁸</td>
<td>11,620</td>
<td>6</td>
<td>1.0×10⁸</td>
<td>9,720</td>
<td>11</td>
<td>4.8×10⁶</td>
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<tr>
<td>5</td>
<td>3,130</td>
<td>2</td>
<td>8.4×10⁸</td>
<td>2,944</td>
<td>6</td>
<td>2.6×10⁸</td>
<td>2,500</td>
<td>11</td>
<td>1.2×10⁸</td>
</tr>
<tr>
<td>10</td>
<td>784</td>
<td>2</td>
<td>2.1×10⁸</td>
<td>752</td>
<td>6</td>
<td>6.7×10⁷</td>
<td>656</td>
<td>11</td>
<td>3.2×10⁷</td>
</tr>
<tr>
<td>15</td>
<td>346</td>
<td>2</td>
<td>9.3×10⁷</td>
<td>340</td>
<td>6</td>
<td>3.0×10⁷</td>
<td>302</td>
<td>11</td>
<td>1.5×10⁷</td>
</tr>
<tr>
<td>20</td>
<td>192</td>
<td>2</td>
<td>5.2×10⁷</td>
<td>192</td>
<td>6</td>
<td>1.7×10⁷</td>
<td>176</td>
<td>11</td>
<td>8.6×10⁶</td>
</tr>
</tbody>
</table>

*Graber scale ≤4.
ordered during those years. There were no significant differences between periods in patient age, race, gender, percent with initial international normalized ratio ≤1.5, percent with baseline modified Rankin scale ≥2, admission Glasgow Coma Scale score, time from onset to first head scan, or 90-day survival.

Eligibility results are displayed Table 2. For criteria set 1, only 2 of 54 (4%) patients with WICH were eligible for enrollment; for criteria set 2, 6 of 54 (11%) cases were eligible; for criteria set 3, 11 of 54 (20%) cases were eligible. The major reasons for exclusion are presented in Table 1. Advanced age, delayed time from onset to first scan, and intraventricular hemorrhage were prominent reasons for exclusion. If the upper age limit was increased to 85 years for each criteria set, the number of eligible subjects per year increased by 0 (set 1), 1 (set 2), and 5 (set 3) persons.

Given these eligibility rates within the Greater Cincinnati/Northern Kentucky region, a population base of at least 67 million persons would be required to conduct a 5-year treatment trial for WICH with a 10% absolute effect size using criteria set 2. A population base of 67 million persons represents the entire population of the 145 largest incorporated places in the United States.17

**Discussion**

ICH produces a case fatality rate nearly 3-times greater than ischemic stroke.18,19 Warfarin anticoagulation is independently associated with poor outcome after ICH.16,20,21 In a population-based study of ICH, patients with WICH had greater mortality than other ICH patients beginning 1 day after hemorrhage (33% vs 16%).13 The mechanisms by which warfarin worsens outcome after ICH likely include larger hematoma volumes at medical presentation, more hematoma expansion after medical presentation, and greater age and burden of medical comorbidities among WICH patients.13,21–23

The increased use of warfarin anticoagulation for stroke prevention in the setting of atrial fibrillation reduced rates of cardioembolic ischemic stroke and produced benefit on a population-scale, but also lead to an increased incidence of WICH, which now accounts for ≥20% of all ICH.5,24,25 As Western populations age and rates of atrial fibrillation and warfarin use increase, the number of WICH cases will likely increase. These factors and the lack of randomized data on the best method of warfarin reversal after intracranial hemorrhage are important reasons to undertake a WICH treatment trial. However, our study illustrates the difficulty of such a task. WICH remains uncommon compared to ischemic stroke and its subtypes and the enrollment criteria explored in our study dramatically reduce the available subject pool.

The hypothetical enrollment criteria sets chosen for our analyses represent the conflicting priorities faced by clinical trialists. Restricting enrollment to patients with a reasonable chance of recovery should increase the odds that a superior treatment can be proven effective by removing subjects destined for a poor outcome regardless of intervention because of massive hemorrhage, severe intraventricular hemorrhage, or coma on arrival.26–28 These considerations are balanced by the desire to generate widely applicable data and to enroll the required number of subjects within a reasonable time frame. In this regard, the most important variable in our criteria sets is probably age. Advanced age is associated with other comorbidities and is a predictor of poor outcome after ICH.26,28,29 Although nearly 50% of WICH subjects were older than age 80 years, increasing the maximum allowable age in our hypothetical trials from 80 to 85 had a very modest impact on projected recruitment.

Our study was limited by the need to make assumptions about several key variables. Whereas mortality after WICH has been well-described, data on morbidity after WICH are limited, especially when considering subsets of WICH patients.7,13–16 The targeted absolute effect size for an intervention is critical to trial design and drives sample size calculations. Fresh-frozen plasma remains standard care for WICH in many centers, although some guidelines recommend prothrombin complex concentrates based on reduced time to international normalized ratio reversal.9 However, small case series have not shown differences in clinical outcomes when comparing these treatments.7,14 No randomized pilot data exist to estimate the absolute benefit in outcomes that might be expected when comparing prothrombin complex concentrates or recombinant activated factor VII to fresh-frozen plasma. In the absence of such data, trialists may have to choose an absolute effect size based on clinical judgment and recruitment ability.

We estimated that 50% of all subjects eligible for a WICH treatment trial would be enrolled, but the true number may be significantly lower. To our knowledge, the percentage of eligible stroke patients in a community who are enrolled into an available treatment trial is unknown; this percentage may vary widely by community and treatment center. Although our data allow estimation of the population base needed for enrollment of eligible subjects, it is also unclear how these numbers will translate into required enrolling centers, because communities have different referral patterns and sometimes multiple competing hospitals or hospital systems.

Our study shows that any planned treatment trial for WICH should anticipate significant challenges in successfully enrolling adequate numbers of patients. There is little chance that a WICH treatment trial could enroll sufficient subjects within the traditional 5-year NIH funding cycle. There are several options for addressing this dilemma, each with limitations.

First, a large pilot trial could be designed to better estimate enrollment rates and provide preliminary data on treatment effect to determine whether a definitive WICH treatment trial is possible. However, the US National Institutes of Health has specifically discouraged early phase trials with a primary intent of providing sample size estimates.30

Second, a large (probably multinational) phase III trial could be designed with anticipated enrollment over several funding cycles, many clinical centers, and several prespecified analyses for feasibility and futility. Hard stopping points would be required for insufficient recruitment or statistical futility for showing a difference between treatment regimens—such a trial could not be allowed to linger for years with inadequate enrollment. Disadvantages of this approach are the high cost, lack of preliminary data to optimally design
the trial, and potential for failure after considerable effort and expense.

Finally, a trial could be conducted with a surrogate endpoint rather than the clinical endpoint of death and disability. The only plausible mechanism by which optimized warfarin reversal could improve outcomes after WICH is limitation of hematoma growth. Early hematoma growth leads to worse clinical outcomes and is more common after WICH than after ICH without coagulopathy. Hematoma growth used as a surrogate endpoint is easy to quantify and should allow a smaller sample size than a clinical endpoint. Furthermore, if the primary trial endpoint was hematoma growth after 24 or 48 hours, use of broader inclusion criteria might be accepted because the radiographic outcome would be less susceptible than 90-day clinical outcomes to being overwhelmed by the poor general health of enrollees. The combination of smaller sample size and broader inclusion criteria would increase the chance that a trial could be completed in a timely and cost-efficient manner. Such a trial, comparing fresh-frozen plasma to another agent (prothrombin complex concentrates or recombinant activated factor VII), would focus on hematoma growth and early safety. If one agent reduced hematoma growth and had a superior or equivalent safety profile, the trial would be considered definitive and the agent would be adopted for use. If no agent had a superior safety profile while the other was more effective at reducing hematoma growth, the trial result could be inconclusive (depending on the magnitude of the safety signal), and a larger trial with a 90-day clinical endpoint would be required. Whereas data from a trial using a surrogate endpoint would be less robust than results from a trial powered for clinical outcomes, it would be a considerable improvement over what is now available, especially given the devastating nature of WICH. Difficulties with this strategy include our limited understanding of what amount of hematoma growth is clinically significant (as demonstrated by the trials of recombinant activated factor VII for ICH without coagulopathy), the problems encountered with surrogate endpoints in trials for cardiovascular disease and diabetes, the fact that surrogate markers have not gained wide acceptance as “hard” endpoints in stroke research, and potential opposition from federal funding and regulatory agencies.

Sources of Funding
Supported in part by NINDS (R-01-NS 36695) and a University of Cincinnati College of Medicine Medical Student Research Fellowship.

Disclosures
Matthew L. Flaherty, MD, received compensation for activities with Novo Nordisk. He is Principal Investigator of a NINDS-funded randomized clinical trial testing recombinant activated factor VII for the treatment of intracerebral hemorrhage. Joseph P. Broderick, MD, received compensation for activities with Ono Pharmaceuticals, Novo Nordisk, Boehringer-Ingelheim, Johnson and Johnson, Hoffman La Roche, and Wyeth Pharmaceuticals. All consulting fees and honorarium are placed in an educational/research fund in the Department of Neurology. He was a member of the steering committee for trials of activated recombinant factor VII for treatment of acute intracerebral hemorrhage. He has received financial/grant support from EKOS Corporation, AstraZeneca, Concentric Inc., Johnson and Johnson, and Genentech. The remaining authors have no disclosures.

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*Stroke*. 2009;40:1738-1742; originally published online March 12, 2009; 
doi: 10.1161/STROKEAHA.108.538462

*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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