Challenges of Designing Trials for the Primary Prevention of Stroke

Philip B. Gorelick, MD, MPH

Background and Purpose—Prevention of a first stroke is an important strategy to reduce morbidity and mortality associated with cerebrovascular disease. In this discussion, we review challenges to development of clinical trials for prevention of a first stroke.

Summary of Review—We discuss prevention of first stroke in the context of clinical trial design in the ARRIVE trial and a primary prevention trial in development for the elderly.

Conclusions—Stroke is an important outcome in cerebrovascular disease trials in the elderly, but it may be trumped by coronary heart disease as a more common end point. (Stroke. 2009;40[suppl 1]:S82-S84.)

Key Words: clinical trials ■ primary prevention ■ stroke

Stroke is a pervasive disease worldwide.1 It is estimated to be the second leading cause of mortality with approximately 87% of deaths occurring in low- or middle-income regions.2 Whereas acute stroke treatment and recurrent stroke prevention have been emphasized in the Joint Commission primary stroke center certification initiative, in general, first stroke prevention has not received as much overall systemized public health attention in many regions. The importance of first stroke prevention is clear because of the estimated 780 000 strokes annually in the United States, approximately 600 000 are first strokes.3 Furthermore, developed countries have sustained cardiovascular interventions that may reduce stroke mortality by at least 4% each year.2

The primary basis for the approval of new preventatives and treatments for stroke and other cardiovascular diseases is the traditional randomized, blinded, controlled, clinical trial or community studies, which may use methods such as cluster randomization. The design of primary prevention trials for stroke may be subject to certain challenges or barriers. In this discussion, we review challenges to designing such trials.

Lessons From the National Institutes of Neurological Disorders and Stroke Workshop on Future Primary Stroke Prevention Trials

In January 2004, the National Institutes of Neurological Disorders and Stroke (NINDS) sponsored and convened a workshop, “Stroke Risk Assessment and Future Stroke Primary Prevention Trials,” to discuss and elucidate the challenges of designing primary stroke prevention trials.4 Regardless of agents to be tested in a primary stroke prevention trial, panelists made the following recommendations: (1) the agent to be administered in the trial must be applicable to a large number of people who account for a substantial fraction of strokes in the population; (2) there must be current indications for the agent in the target population (ie, contraindications should not be prevalent); (3) there should be a signal of efficacy; (4) there should be a profile of safety and low toxicity; and (5) the agent should be convenient to administer and inexpensive.4

Furthermore, in relation to research needs and opportunities, the following priorities were established to: (1) accurately predict those at high risk for first stroke (eg, by age, novel risk factors/markers, minorities); (2) develop surrogate outcomes (eg, validate MRI and other brain/vessel imaging) for a specific trial; (3) incorporate and apply standardized assessment of cognition; (4) determine quantitative predictors of how likely the target population will adopt the intervention; (5) determine why interventions may not be widely applied; and (6) finally, design the clinical trial with the appropriate developmental information in hand.4

These points are useful guides as one contemplates a clinical trial study design for prevention of first stroke. In the context of this article, we propose a simple 2-tier system in which primary prevention will refer to first stroke prevention and secondary stroke prevention to recurrent stroke prevention. A major challenge in the design of a study that includes primary stroke prevention is to select an appropriate at-risk population.
Illustrative Example: ARRIVE (Aspirin to Reduce Risk of Initial Vascular Events) and the Identification of a Moderate-Risk Population for Primary Prevention

ARRIVE is an international, randomized, double-blind, placebo-controlled, multicenter, parallel group study to assess the efficacy and safety of 100 mg enteric-coated acetylsalicylic acid in patients at moderate risk of cardiovascular disease (CVD). The primary efficacy end point in ARRIVE is the composite of cardiovascular death or myocardial infarction or all stroke. The use of aspirin in the primary prevention of major cardiovascular events has been studied in key trials such as the British Doctors’ Trial, the Physicians’ Health Study, the Hypertension Optimal Treatment study, the Thrombosis Prevention Trial, the Primary Prevention Project, and the Women’s Health Study. Although these studies did not require a minimum number of events to comprise close to 100,000 patients, several of the individual studies did not require a minimum number of events to support the final analysis. Therefore, it followed that the results were not always supportive of aspirin as an efficacious primary preventative. In fact, 5 of the 6 aforementioned primary prevention trials recruited low-risk for coronary heart disease (CHD) subjects (<1% per annum), and therefore, relatively few major CVD outcome events were recorded during these studies. On the other hand, aspirin efficacy has been more consistently demonstrated in high-risk patients (eg, those with a history of ischemic stroke or transient ischemic attack, or myocardial infarction).

To assure an adequate number of major CVD events and to answer an important clinical question in relation to primary CVD prevention, the ARRIVE study has targeted subjects for inclusion with moderate CHD and CVD risk (10% to 20% and 30% 10-year risks, respectively). Therefore, subjects at moderate risk with no known history of CVD are being recruited. How was moderate risk derived in the ARRIVE study design?

Risk calculators were used to model the impact of different numbers and combinations of risk factors to derive a moderate risk study population. The European PROCAM and US Framingham risk calculators were used. Sensitivity analyses were developed to evaluate mean risk for the overall study population when different types of subjects were to be enrolled. For example, men who had one of each type of risk factor or different combinations of risk factors and women with similar characteristics were modeled for risk. Age was varied separately in the analyses. Analyses took into account different risk thresholds and parameters in the European and US risk calculators to accommodate both models. Risk in country of origin was also considered. PROCAM and Framingham data sources are from higher-risk countries (eg, United States, United Kingdom, Germany). For low-risk countries (eg, Spain and Italy), CHD risk was set equal to the stroke risk based on epidemiological conventions that indicate CHD and stroke occur in a 1:1 ratio in these countries. The resulting CHD risk in low-risk countries was therefore approximately half of the composite risk in the higher-risk countries. A similar type of analysis was carried out for both stroke and cardiovascular death risk to arrive at appropriate risk for high- and lower-risk countries for these disease states. SCORE charts from the European Society of Cardiology were used to assist in the CVD death risk assessments.

The result of these calculations led to inclusion criteria listed in Table 1. It should be noted that patients enrolling in the study based on the risk calculations could be at lower risk than was shown in the modeling because they might receive treatment for hypercholesterolemia, for example. However, some subjects may develop risk factors (eg, diabetes mellitus) during the study period and actually be at higher risk during follow-up. Given that both higher- and lower-risk countries are involved in ARRIVE, the overall mean expected risks by key outcomes in the study are: CHD 12.9%, stroke 9.1%, CVD death 4.1%, and a total for the composite of outcomes of 26.1%.

### Illustrative Example: Challenges in Developing a Primary Prevention Trial in the Elderly

The elderly are an important segment of the population because the elderly population is growing at a rapid rate, and many of our clinical trials have not been geared to answer germane clinical questions regarding CVD prevention in this group. Also, some elderly may be at higher risk of stroke than CHD. Table 2 lists some challenges that may occur when carrying out a clinical trial in the elderly.

### Conclusion

Stroke is an important outcome in relation to CVD morbidity and mortality in the construct of a primary prevention trial. In

| Table 1. Inclusion Criteria for Moderate Risk in the ARRIVE Study
<table>
<thead>
<tr>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Men aged 50 years and older with 2 or 3 risk factors</td>
</tr>
<tr>
<td>Risk factors in men: aged 60 years and older, elevated cholesterol, current smoker (current smoking status cannot be the sole risk factor for men 60 years and older), low HDL cholesterol, elevated blood pressure, currently on medication for hypertension, and positive family history of early CHD</td>
</tr>
<tr>
<td>Women aged 60 years and older with 3 or more risk factors</td>
</tr>
<tr>
<td>Risk factors in women: elevated cholesterol, current smoking, low HDL cholesterol, elevated blood pressure, currently on any medication to treat high blood pressure, and positive family history of early CHD</td>
</tr>
</tbody>
</table>

HDL indicates high-density lipoprotein.

<table>
<thead>
<tr>
<th>Table 2. Challenges to Carrying Out a Clinical Trial in the Elderly and Means to Overcome Challenges</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recruitment, retention, follow-up, and compliance: ease of access to local study site/personnel by home study visit program, flexible study hours, and provision for travel reimbursement or pick-up service to the study site</td>
</tr>
<tr>
<td>Heightening awareness of trial: network with community organizations and churches that interact with the elderly and develop a high-profile elderly study champion</td>
</tr>
<tr>
<td>Accounting for potentially high attrition rates based on age-related factors (eg, major competing causes of mortality [noncardiovascular death], frailty, depression and other neuropsychiatric conditions, and social isolation); insightful statistical power calculations and establishment of monitoring systems to identify psychosocial problems</td>
</tr>
</tbody>
</table>
many study populations, however, it will be trumped by CHD based on frequency of occurrence of specific outcome events. Some elderly populations may be prone to an excess of stroke compared with CHD. Clinical trials in the elderly have unique challenges that need to be considered.16

Disclosures
P.B.G. serves on and receives honoraria for participation on a safety committee for Novartis (Aliskiren); steering committees for Bayer for the ARRIVE trial; for Boehringer Ingelheim for the PROFESS trial; for Brainsgate (sphenopalatine ganglion stimulator for acute ischemic stroke); adjudications committees for Myriad, TAP, and Pfizer; and has lectured for and received honoraria from diaDexus and Boehringer Ingelheim.

References
Challenges of Designing Trials for the Primary Prevention of Stroke
Philip B. Gorelick

Stroke. 2009;40:S82-S84; originally published online December 8, 2008;
doi: 10.1161/STRKEAHA.108.526947

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/40/3_suppl_1/S82