See related article, pages 441–450.

In this issue of Stroke, Robinson et al provide a thoughtful, logical, and concise review of the rationale for and clinical trial design of a primary cardiovascular disease prevention study in the elderly. As the authors point out, cardiovascular diseases are the leading cause of death and disability in the elderly who reside in developed countries. Yet, there is a paucity of evidence-based data from which to guide us in determining which medical interventions, such as statin and blood pressure–lowering therapies, to use among those ≥70 years of age. With diabetes mellitus incidence and mortality on the rise and as a significant concern in many parts of the world, and stroke mortality a prevalent problem in developing countries, this is not a time to be complacent about cardiovascular disease and, specifically, stroke prevention. Stroke incidence rises exponentially with age and has become an increasingly important cause of mortality and morbidity in the community as heart disease mortality has continued to drop steeply over time, and there are more elderly at risk. The Oxford Vascular Study places the importance of stroke in a community context by showing that of 2024 acute vascular events in this population during the time period 2002 to 2005, 45% were cerebrovascular (618 stroke, 300 transient ischemic attack) and 42% were coronary vascular (159 ST-elevation myocardial infarction, 316 non-ST-segment myocardial infarction, 218 unstable angina, and 163 sudden cardiac death). Furthermore, event and incidence rates rose steeply with age in this study. Therefore, acute cerebrovascular events may be common in a community and on par in frequency with acute coronary events.

Robinson et al provide a proposal for a primary prevention trial in the elderly featuring cholesterol- and blood pressure–lowering therapies in a 2×2 factorial design. We now review the rationale, design, and challenges of their approach.

Rationale for a Primary Prevention Trial in the Elderly

Robinson et al argue cohesively for a primary prevention trial of cardiovascular disease in those ≥70 years of age and recommend featuring treatment of cholesterol and blood pressure based on clinical equipoise regarding these therapies in the aged. In the background section of the article, the authors conclude that statins are of greater benefit in preventing coronary heart disease than stroke in those with a history of cardiovascular disease, whereas blood pressure lowering has been shown to prevent stroke, congestive heart failure and renal disease, but is of less benefit for preventing coronary heart disease and possibly total mortality. Also, they note that the most effective regimen for lowering blood pressure and optimal blood pressure level has not been previously established for the elderly.

Overview of a Primary Prevention Trial in the Elderly

A 2×2 factorial trial design is proposed whereby elderly ≥70 years of age and without clinical evidence of cardiovascular disease, diabetes, and comorbidities limiting survival to <5 years will be randomized in a double-blind study to receive placebo or a statin (or a statin in combination). Subjects are then randomized a second time to receive 1 of 2 blood pressure–lowering regimens aiming for a systolic blood pressure <140 mm Hg or in those with a wide pulse pressure (>80 mm Hg) a systolic blood pressure level <140 mm Hg if tolerated with the systolic blood pressure goal of <160 mm Hg for all participants. The choice of blood pressure treatments will depend on the most recent clinical trial data, and multiple antihypertensive agents are anticipated to be required for many. The authors project a sample with 50% over age 80 years, a balanced sex distribution, and 40% of black descent to be followed over 5 years. The projected sample size could be as small as 1800 subjects or reach 19 000 or more subjects based on statistical power requirements and prespecified interaction tests. In addition to the primary outcome composite of myocardial infarction, coronary heart disease death, congestive heart failure, and fatal and non-fatal stroke (and renal death and endstage renal disease in the case of the blood pressure–lowering regimen arm), the authors propose a host of important secondary outcomes.

Challenges

Many of our large cardiovascular clinical trials have focused on persons in their early or mid 60s and who have had recent cardiovascular events or who have multiple risk factors. Such persons when selected for clinical trials are likely to be at least somewhat motivated to prevent another vascular event, reasonably fit at the time of entry into the trial to
optimize the likelihood of completing the study, and able to attend visits at the local study site. This set of circumstances always challenges the representativeness of the study subjects. A trial among the elderly, however, may be more complicated to complete based on logistical and medically related factors associated with being older. Having recently completed a challenging recurrent stroke prevention study, the National Institute of Neurological Disorders and Stroke (NINDS)/National Institutes of Health (NIH)—sponsored African American Antiplatelet Stroke Prevention Study (AAASPS),6 among a traditionally underserved group, I can attest to the energy and creativity which will likely be needed to recruit and retain subjects who enter into a trial exclusively dedicated to older adults.

Adaptation of lessons learned from AAASPS might prove useful for a primary prevention trial in the elderly.7–9 For example, the following features may be necessary to build into the study design: a plan for a home visitation program carried out by the local study site teams or provision of reimbursement for travel to local study sites or a travel pick-up service for study subjects and their family member(s) to assure high recruitment, retention, follow-up and compliance rates; flexible hours to allow family members to bring subjects to the study office after work; development of a community network composed of organizations which interact with or champion the elderly (eg, church-based organizations, American Association of Retired Persons, local city or state nursing organizations) to heighten awareness of the study and its importance; establishment of a high profile celebrity champion for the study; and other measures.

In addition, one may anticipate a high attrition rate in the study based on age-related factors such as major competing medical conditions (eg, noncardiovascular causes of death) and fragility of the elderly, depression and other neuropsychiatric conditions which are common to this group, and women in China. N Engl J Med. 2005;353:1124–1134.


Key Word: prevention

Conclusion

A cardiovascular primary prevention trial like the one proposed by Robinson et al10 holds promise to provide important answers in relation to the safety and benefit of statin therapy in the elderly and the proper blood pressure–lowering regimen and blood pressure target. Clinicians are in a state of equipoise in relation to the questions posed by the authors and do deserve evidence-based answers to critical patient-management decisions which affect the elderly. A thoughtful review of needs, opportunities, and challenges of clinical research in primary stroke prevention is provided by Radziszewska et al based on proceedings from a recent NINDS/NIH workshop.11

Acknowledgments

I acknowledge David Nye, PhD for providing helpful suggestions.

Disclosures

In the past 12 months, Dr Gorelick has been a consultant to Boehringer Ingelheim, Pfizer, and the Discovery Institute of Medical Education (DIME) and has received honoraria for serving on a speaker’s bureau for Boehringer Ingelheim.

References


Key Word: prevention
Uncertainty of Management of Blood Pressure and Lipids in the Elderly: Time for a Primary Prevention Trial
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Stroke. 2007;38:212-213; originally published online December 28, 2006;
doi: 10.1161/01.STR.0000254557.17193.ab
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

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/38/2/212

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