Is it Time for a Cardiovascular Primary Prevention Trial in the Elderly?

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Background and Purpose—Statins have been shown conclusively to reduce the risk of cardiovascular events in subjects with clinical cardiovascular disease or diabetes aged 65 to 80 years of age. However, few data are available for primary prevention of cardiovascular disease in those aged ≥70 years.

Summary of Review—A moderate-dose statin was of little benefit in a population aged 70 to 82 years when given for 3 years in the setting of suboptimally treated blood pressure. More evidence supports the use of blood pressure–lowering medications, but few data are available regarding the appropriate blood pressure target and most effective agents in the elderly. Some evidence also suggests that the elderly could experience higher mortality with antihypertensive treatment. These findings, along with greater safety concerns and an increasing number of competing risks and medical conditions with advancing age, make it imperative to carefully evaluate the risk/benefit balance from treating hypercholesterolemia and hypertension in persons aged ≥70 years.

Conclusions—We propose a 5-year 2×2 factorial trial of primary prevention in the elderly that will (1) evaluate whether statin therapy will reduce the risk of cardiovascular events when added to the treatment of hypertension to achieve a blood pressure <140/90 mm Hg in most patients and (2) determine the most appropriate blood pressure regimen for the prevention of cardiovascular and renal events. (Stroke. 2007;38:441-450.)

Key Words: cardiovascular disease ■ elderly ■ hypertension ■ primary prevention ■ statins

Cardiovascular event rates increase in a curvilinear fashion after age 65 years in men and age 75 years in women. This makes cardiovascular disease by far the leading cause of death and disability in persons aged ≥70 years in the United States and other Westernized countries (Figure 1).1,2 Stroke, one of the leading causes of disability and institutionalization in the elderly, occurs at a rate roughly similar to that of myocardial infarction and sudden death with advancing age. With continuing increases in average life expectancy, preventive efforts will become increasingly important for preventing morbidity, improving quality of life, and reducing healthcare expenditures for older persons.3 The healthcare burden may become potentially staggering as the baby boomer generation, born between 1946 and 1964, ages. Therefore, identification of the most effective, safe, and cost-effective preventive strategies has become increasingly imperative.

Progress in reducing the case fatality rate for coronary heart disease (CHD) and stroke has shifted mortality to increasingly advanced age, with the number of cardiovascular events in those aged ≥80 years having increased by 60% since 1970.2 When we consider whom to treat, it could be argued that a patient should have at least a 5-year life expectancy to benefit from preventive therapies. Significant reductions in cardiovascular events and overall mortality have occurred over this time period in high-risk populations receiving statins or blood pressure–lowering medications.4–6

Almost all women up to age 80 years and men up to age 75 years have a life expectancy ≥5 years, regardless of health status.7 Even those in average health at age 80 years would still be expected to live >5 years (Table 1).

Many questions remain regarding the use of antihypertensive and cholesterol-lowering drugs with advancing age.8 Competing risks, especially from cancer,9 comorbid conditions, polypharmacy and drug interactions, tolerability, safety, and perhaps even differing pathophysiology of cardiovascular disease, may alter the benefit/harm balance in older patients.10–13 More clinical trial data are needed before evidence-based prevention guidelines can be developed for those aged >70 years and especially those aged >80 years.

Overview: Cholesterol

The positive association between total and low-density lipoprotein (LDL) cholesterol and cardiovascular risk becomes attenuated with advancing age, more so in men than in women.14 Nonetheless, treatment of LDL cholesterol with
diabetes and a wide range of cholesterol levels, simvastatin 40 mg reduced the risk of a cardiovascular events by 18% in those aged 70 to 80 years (n=5806) compared with 24% in those aged <65 years, although the difference was not significant.\(^{16}\) It should be noted that even if attenuation of benefit occurred, the elderly had a higher absolute risk of events, and therefore the number of events prevented in those aged <70 years and in those aged ≥70 years was similar.

The only placebo-controlled trial conducted in a relatively large primary prevention population of individuals aged ≥70 years, the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) trial, included 5804 subjects with and without cardiovascular disease aged 70 to 82 years, more than half of whom were women.\(^{17}\) Overall, those who received pravastatin 40 mg experienced a 15% reduction in the risk of the primary end point of nonfatal myocardial infarction, CHD death, and nonfatal and fatal stroke compared with placebo. This was somewhat less than expected from previous studies that have shown an \(\approx 1:1\) relationship between percent LDL reduction and percent cardiovascular event reduction in predominantly middle-aged populations,\(^ {15,18}\) given that LDL was reduced by 34% in the pravastatin group in PROSPER. When evaluated according to prior cardiovascular disease status, a significant 22% reduction in events occurred in the 2565 subjects with cardiovascular disease at baseline, whereas no reduction in risk was found in the 3239 subjects without such a history. These findings may be attributable to a number of factors. Inadequate sample size is a possibility, although the rate of events was quite high in the placebo group of those without cardiovascular disease, at 12% over 3.2 years or >20% over 10 years, putting these patients in the high-risk category defined by the National Cholesterol Education Program.\(^ {19}\) Further subgrouping was not performed in PROSPER, but it is likely that women constituted the majority of the primary prevention patients given the older age at the time of cardiovascular disease diagnosis in women. These findings could suggest that a sex differential in benefit from cholesterol lowering may occur with advancing age. A lack of benefit was also found in women who received atorvastatin 10 mg for 3.3 years in the Anglo-Scandinavian Cardiac Outcomes Trial–Lipid Lowering Arm (ASCOT).\(^ {20}\) In this placebo-controlled 2×2 factorial primary prevention trial in hypertensive patients aged 40 to 79 years with a baseline mean LDL of 131 mg/dL, few events occurred in women. Women constituted only 19% of the 10 000 participants, and an even lower proportion were elderly, given that the proportion of the entire study population aged >70 years was \(\approx 17\%\). The cardiovascular event rate was not reported for those aged ≥70 years, although a significant 36% reduction in CHD occurred in those aged ≥60 years.

Very few subjects in PROSPER were aged ≥80 years, and therefore the question of whether statin therapy will benefit very elderly persons also remains unanswered. In epidemiological studies, total cholesterol levels become inversely related to CHD mortality for both men and women after age 80 years.\(^ {14}\) Declining serum cholesterol levels are attributable at least in part to increasing comorbidity and weight loss, although declining cholesterol synthesis may also play a role.\(^ {21}\)
For those aged ≥80 years, some evidence of benefit is available from observational studies, although these findings may be subject to several biases.22–24 In the largest cohort to date, 23,000 patients with acute myocardial infarction, no mortality benefit was found over 3 years for those aged ≥80 years who received a statin, whereas those aged 65 to 79 years had a significant 11% reduction in mortality.24 There was evidence, however, of a trend toward benefit in those aged 80 to 85 years versus those aged >85 years.

Further evidence of attenuated efficacy of LDL reduction in older patients may come from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT).25 In ALLHAT, in which 55% of >10,000 subjects were aged ≥65 years (although few were aged ≥75 years), CHD events and stroke rates did not differ between the pravastatin 40 mg and usual care groups. Although the nonsignificant 9% difference in CHD events has been attributed to the less-than-expected 17% difference in LDL between the 2 groups, this degree of risk reduction is still less than the 1:1 relationship between LDL reduction and CHD risk observed in placebo-controlled statin trials.18 These findings may suggest that other pathophysiological processes less amenable to LDL lowering predominate in older patients such that a lack of efficacy may occur in older patients without clinical CHD or diabetes or in women, who constituted almost 50% of ALLHAT participants.

In addition, there were a few more strokes in the pravastatin group (hazard ratio [HR], 1.03; 95% CI, 0.81 to 1.31; \( P = 0.8 \)) of PROSPER, which did not differ for secondary and primary prevention groups. Explanations proposed by the authors include the low number of strokes that could have resulted in adequate power to detect a benefit, which, along with the relatively short trial duration of 3.2 years, may have been inadequate to influence the progress of cerebrovascular disease in older patients. In contrast, in the meta-analysis of 14 statin trials in primarily middle-aged populations, stroke was reduced by 20% to 25% during years 2 through 5 of treatment.15

Type of stroke was not reported for PROSPER. Although statins would be expected to reduce ischemic stroke risk, such a benefit may not have occurred for hemorrhagic stroke and indeed would not have been expected on the basis of the statin trials in middle-aged populations (hemorrhagic stroke in 14 trial meta-analysis: HR, 1.05; 99% CI, 0.78 to 1.41).15 However, the risk of intracerebral hemorrhage dramatically increases after age 75 years for both men and women,1 suggesting changes in underlying predisposition to hemorrhage. Some evidence for this may come from the Stroke Prevention by Aggressive Reduction of Cholesterol Levels (SPARCL) trial.26 In this 5-year trial of 4,731 patients with a history of stroke or transient ischemic attack but without CHD, the risk of hemorrhagic stroke was 64% higher in the group receiving atorvastatin 80 mg compared with placebo, although the overall risk of recurrent stroke was reduced by 16% because of the 21% reduction in ischemic stroke. Mean on-treatment LDL levels in the placebo group were 129 mg/dL compared with 73 mg/dL in the atorvastatin 80 mg group. Characteristics of participants experiencing a hemorrhagic stroke have not yet been elucidated, but it is important to note that the mean age of SPARCL participants was 63 years, relatively young for a population with cerebrovascular disease.

Interestingly, the increase in hemorrhagic stroke in SPARCL occurred in a setting of partially controlled blood pressure, which was 138 to 139/81 to 82 mm Hg at baseline. On the other hand, the Treating to New Targets (TNT) trial, which enrolled subjects with CHD with a mean age of 61 years, found no difference in the rate of hemorrhagic stroke between the atorvastatin 10 and 80 mg groups, although incidences were much lower than in SPARCL. Baseline mean blood pressure in TNT was better controlled at 131/78 (±17/10) mm Hg. In the Heart Protection Study, hemorrhagic stroke rates were similar in both the simvastatin 40 mg and placebo groups.27 Although it did not achieve statistical significance, there were more hemorrhagic strokes in those with previous cerebrovascular disease (mean age 65 years and blood pressure 147/83 mm Hg) but fewer in those without (mean age 65 years and blood pressure 144/81 mm Hg). In PROSPER, in which uncharacterized stroke risk rates were higher in the pravastatin group, mean blood pressure at baseline was 154/84 mm Hg. Although there is some suggestion that high-dose statins may increase the risk of hemorrhagic stroke in older patients, it is also possible that even moderate-dose statins could increase the risk of hemorrhage in older patients who have poorly controlled hypertension. Although antiplatelet and anticoagulation therapy rates were not reported in PROSPER, TNT, or SPARCL, their use would not have been expected to influence the results because of the randomized trial design.

Because stroke constitutes more than half of cardiovascular events in elderly women and almost half of such events in men, benefit from statins for overall stroke prevention will therefore need to be confirmed in trials of primary prevention that are at least 5 years in duration. Furthermore, such trials should evaluate LDL reduction in the setting of adequate blood pressure control, although the definition of adequate control will need to be established, as discussed below.

**How Low to Go: LDL?**

Both European and US guidelines identify an optional LDL goal of <100 mg/dL for moderately high-risk primary prevention patients (≥5% risk of fatal cardiovascular disease or 2 risk factors and 10% to 20% 10-year risk of CHD with at least 1 additional indicator of increased risk, respectively).28,29 For moderate-risk patients, these guidelines identify an LDL goal of <115 to <130 mg/dL. However, data are needed to support these recommendations in persons aged >70 years without cardiovascular disease or diabetes, virtually all of whom are at least at moderate risk (≥10% 10-year CHD risk) on the basis of age and blood pressure. Moreover, no recommendations exist for those aged >80 years.

On pravastatin 40 mg, approximately half of subjects in PROSPER had an LDL >100 mg/dL, the target for high-risk patients, and one third had an LDL >130 mg/dL, the National Cholesterol Education Program target for primary prevention patients.19,30 The lack of benefit in PROSPER could also have been attributable to continued atherosclerotic progression and lack of stabilization of existing lesions due to LDL levels.
Only a few drugs lower LDL by ≥50%: atorvastatin 40 to 80 mg, rosuvastatin 20 to 40 mg, and simvastatin 20 to 80 mg in combination with ezetimibe 10 mg.

However, a number of potentially serious safety concerns arise in the elderly from pursuing more aggressive LDL reduction than the 35% that occurred with moderate-dose statin therapy in PROSPER (pravastatin 40 mg) or the Heart Protection Study (simvastatin 40 mg).32 Moderate-dose statins appear to be well tolerated in elderly persons participating in clinical trials, although the risk of serious muscle adverse effects may be slightly higher. In the simvastatin arm of the Heart Protection Study, 6 of the 9 cases of myopathy or rhabdomyolysis were in subjects aged >65 years.33 High-dose atorvastatin and simvastatin, which have slightly different adverse effect profiles, have been shown in long-term studies of primarily middle-aged populations to have low rates of serious musculoskeletal (<0.6%) and hepatic (<1.4%) adverse effects.26,32 In subgroups of subjects aged ≥65 years from short- and long-term trials, both high-dose atorvastatin (80 mg) and simvastatin 20 to 80 mg in combination with ezetimibe appear to have a minimum of adverse effects.34,35 However, the margin of safety may be lower in elderly patients with significant comorbidities, including diminished hepatic and renal function, that would exclude them from clinical trial participation.36,37 Several characteristics have been identified that should enhance the use of statins in patients aged >70 years (Table 2).11,32

Some concern has been raised about higher cancer rates in the more aggressive or active treatment statin arms. In the elderly population in PROSPER, there was a trend toward more cancer deaths in the pravastatin 40 mg group (HR, 1.28; 95% CI, 0.97 to 1.68; P=0.08). A subsequent meta-analysis of all pravastatin trials >3 years in duration found no increase in cancer risk (HR, 1.06; 95% CI, 0.96 to 1.17; P=0.20).17 Meta-analysis of the 14 primarily moderate-dose statin trials also found no association between cancer incidence and statin treatment (HR, 1.00; 95% CI, 0.95 to 1.06; P=0.9), nor was there evidence of any increase over time, predominance of any type, or relationship to LDL level, although the majority of participants in these trials were middle-aged.15 More recently, the TNT trial reported more cancer deaths in the atorvastatin 80 mg group than in the atorvastatin 10 mg group, although this was not statistically significant (HR, 1.13; 95% CI, 0.83 to 1.55; P=0.42). This may have been attributable to chance because cancer rates were lower in the atorvastatin 80 mg group than in the simvastatin 20 to 40 mg group in the Incremental Decrease in End Points Through Aggressive Lipid Lowering (IDEAL) study.38 Future studies will need to evaluate cancer incidence as an end point to determine whether this concern is relevant in the elderly. Air

Table 2. Characteristics and Strategies Likely to Enhance the Safety of Statins in Elderly Patients11,32,33,72

<table>
<thead>
<tr>
<th>Category</th>
<th>Guidelines</th>
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<tr>
<td>- Use highest doses of statins with caution because toxicity is dose related</td>
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<tr>
<td>- Because plasma clearance is increased in persons aged &gt;70 y, simvastatin 80 mg should be used with caution until more safety data are available</td>
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<td>- Well nourished (not frail)</td>
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<td>- Small women: start at lowest dose</td>
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<td>- Asian ancestry: start rosuvastatin at 5-mg dose</td>
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<td>- Good renal function</td>
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<td>- Normal creatinine</td>
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<td>- Glomerular filtration rate ≥30 mL/min per 1.73 m² (ideally ≥60 mL/min per 1.73 m²)</td>
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<tr>
<td>- No receiving drugs or having medical conditions that could compromise renal function</td>
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<td>- Normal hepatic function (preferably normal transaminases)</td>
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<td>- Normal thyroid function</td>
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<td>- Few serious comorbidities</td>
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<td>- No concomitant use of P-450 inhibitors, including</td>
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<td>- Macrolide antibiotics (especially erythromycin and clarithromycin)</td>
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<td>- Antiviral drugs (especially HIV protease inhibitors)</td>
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<td>- Systemic azole antifungals (itraconazole and ketoconazole)</td>
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<td>- Verapamil (simvastatin)</td>
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<td>- Diltiazem (lovastatin, atorvastatin)</td>
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<td>- Amiodarone (simvastatin)</td>
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<td>- Nefazodone</td>
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<td>- Grapefruit juice ≥1 quart/d</td>
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<td>- No chronic immunosuppressive therapy (especially cyclosporine)</td>
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<tr>
<td>- No concomitant use of fibrates (especially gemfibrozil)</td>
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<tr>
<td>- Probably no concomitant use of niacin</td>
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<tr>
<td>- Alcohol intake ≥2 drinks/d (no alcoholism)</td>
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<tr>
<td>- If severe illness, major surgery, or major trauma, discontinue lipid-lowering medications until recovered</td>
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<tr>
<td>- Discontinue before intravenous dye administration</td>
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meta-analysis of 61 prospective studies with almost 1 million participants, the risk of stroke was shown to increase in a logarithmic fashion with increasing systolic and diastolic pressure in persons aged 70 to 89 years,41 with two thirds of the burden of stroke attributable to nonoptimal blood pressure (≥115/75 mm Hg)40 (Figure 2).

Absolute risk of CHD is somewhat higher than the risk of stroke for a given blood pressure in persons aged 70 to 79 years but more similar for those aged 80 to 89 years.41 With advancing age, isolated systolic hypertension becomes the predominant form of hypertension, although elevated diastolic hypertension still predicts risk in the older population. A meta-analysis of all clinical trials performed through 2004 found that differences in systolic blood pressures between the treatment groups explained almost all of the reduction in cardiovascular risk.42

The first large hypertension trials conducted exclusively in persons aged ≥65 years compared diuretics and/or β-blockers to placebo and demonstrated significant 25% to 47% reductions in stroke and 19% to 27% reductions in CHD.
events. However, the reduction in CHD events was significant in only 1 trial. Total mortality was significantly reduced by 43% in the trial enrolling the oldest participants, aged 70 to 84 years at baseline, with a mean age of 76 years. The next 2 trials exclusively enrolling persons aged >60 years focused on the treatment of isolated systolic hypertension and used the long-acting calcium channel blocker nitrendipine with or without an angiotensin-converting enzyme (ACE) inhibitor with or without hydrochlorothiazide. These trials demonstrated 33% to 42% reductions in stroke and nonsignificant 25% to 30% reductions in CHD events. One study found that the active treatment group had half the incidence of dementia compared with placebo, a difference that persisted after extended follow-up. Baseline systolic blood pressure in all of these trials was >160 to 180 mm Hg, with on-treatment systolic blood pressure reduced by 20 to 35 mm Hg.

Another important study was the Perindopril Protection Against Recurrent Stroke Study (PROGRESS). It was designed to determine the effects of a blood pressure–lowering regimen in hypertensive and nonhypertensive patients with a history of stroke or transient ischemic attack. This international randomized trial studied 6105 individuals with a mean age of 64 years and baseline blood pressure levels of ≈147/86 mm Hg. The primary outcome was total stroke (fatal or nonfatal, of any type). They noted in >4 years of follow-up that active treatment reduced blood pressure by 9/4 mm Hg, and this resulted in a highly significant relative risk reduction of 28% versus placebo. Active treatment also reduced the risk of total major vascular events by 26%. There were similar reductions in the risk of stroke in hypertensive and nonhypertensive subgroups (all P<0.01). Combination therapy with perindopril plus indapamide reduced blood pressure by 12/5 mm Hg and stroke risk by 43%. This blood pressure–lowering regimen reduced the risk of stroke among both hypertensive and nonhypertensive individuals with a history of stroke or transient ischemic attack and an average age of 68 years. Combination therapy with perindopril and indapamide produced larger blood pressure reductions and larger risk reductions than did single-drug therapy with perindopril alone.

The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) recommended that a blood pressure <140/<90 mm Hg be the goal of therapy for all patients, including those aged ≥65 years. Data to support this recommendation include those from the Hypertension Optimal Treatment trial, which sought to identify the optimal blood pressure target in almost 19,000 participants. This study found that the lowest incidence of cardiovascular events occurred with an on-treatment mean systolic blood pressure of 139 mm Hg and a mean diastolic blood pressure of 83 mm Hg. No further benefit accrued from reducing diastolic blood pressure to <70 mm Hg, although there was no increased risk from doing so. The approximately one third of the participants aged >65 years had results similar to those in younger patients, but there were too few subjects to determine the lower blood pressure limit for safety.

JNC 7 also recommended thiazide diuretics as first-line therapy for the treatment of hypertension on the basis of ALLHAT. In this trial, 57% of subjects were aged ≥65 years at baseline (mean age, 67 years). Although CHD events and all-cause mortality did not differ between the treatment groups, chlorthalidone was found to be superior to amlopidine and lisinopril for preventing congestive heart failure and superior to lisinopril for preventing stroke. There was no evidence of heterogeneity in the findings between chlorthalidone-, amlopidine-, or lisinopril-based regimens in older versus younger age groups. Of interest, participants were treated for hypertension with a variety of agents to a mean blood pressure of 136/77 mm Hg; no evidence of interaction between type of blood pressure and cholesterol treatment was found. The Swedish Trial in Old Patients with Hypertension-2 (STOP-2) trial enrolled participants aged 70 to 84 years and also found similar reductions in cardiovascular events in each of the 3 treatment arms: diuretic/β-blocker, the calcium antagonist amiloride, or an ACE inhibitor. On the other hand, the Second Australian National Blood Pressure Study, which enrolled subjects aged 65 to 84 years (mean age, 72 years), showed superiority for enalapril over hydrochlorothiazide. A meta-analysis of 28 trials further found that although ACE inhibitors were superior to calcium channel blockers for the prevention of CHD, calcium channel blockers were superior for the prevention of stroke.

The British have issued the most recent hypertension recommendations based on a comprehensive review of hypertension trials through 2005. For those aged ≥55 years, calcium channel blockers or thiazide-type diuretics were recommended as first-line therapy; for second-line agents, ACE inhibitors were considered superior to β-blockers (or at least atenolol). β-Blocks appeared to have less clinical benefit, especially for stroke prevention, compared with other antihypertensive agents.

Limited data are available for those aged ≥85 years. The Hypertension in the Very Elderly Trial (HYVET) Working Group enrolled 1283 patients aged ≥80 years with blood pressure 160 to 219/90 to 109 mm Hg in a pilot study of a diuretic-based (usually bendroflumethiazide) or ACE inhibitor--
based (usually lisinopril) regimen versus placebo.\textsuperscript{58} Blood pressure decreased by 23/11 mm Hg in the active treatment groups. At 13 months, a trend toward increased mortality was found for both the diuretic- and ACE inhibitor–based regimens. Stroke was decreased significantly in the diuretic but not the ACE inhibitor group. In a meta-analysis of 6 double-blind trials that enrolled subjects aged 80 to 99 years, 76\% of the 1670 subjects were women.\textsuperscript{59} Mean systolic blood pressures were 173 to 197 mm Hg, mean total cholesterol levels were 224 to 243 mg/dL, 8\% to 24\% had diabetes, and 6\% to 12\% had a history of cardiovascular disease. Mortality was very high (20\%) over a mean follow-up period of 3.5 years. Stroke was reduced by 36\% (\(P = 0.01\)) and heart failure by 42\% (\(P = 0.01\)), with a nonsignificant trend toward a reduction in major CHD events of 15\% (\(P = 0.15\)). Similar to the HYVET pilot study, there was a trend toward increased total mortality (14\%; \(P = 0.05\)). The benefit-to-risk ratio will be more clearly established in the ongoing main HYVET trial.\textsuperscript{60} This is a randomized, double-blind, placebo-controlled trial comparing placebo with a low-dose diuretic (indapamide sustained release 1.5 mg daily) and additional ACE inhibitor (perindopril) therapy if required. The trial plans to enroll 2100 patients aged ≥80 years with blood pressure 160 to 219/90 to 109 mm Hg for 5 years of follow-up. The primary end point is stroke, with total mortality a secondary end point. Quality of life, cognitive function, and dementia will also be evaluated.\textsuperscript{61} Although data are not yet available for elderly populations, treatment of hypertension has also been shown to reduce progression of renal failure in middle-aged populations, especially blacks.\textsuperscript{51,62}

Treatment of elderly hypertensive patients can be accomplished with acceptable adverse effect profiles and reasonable adherence rates. In the STOP-2 trial of subjects aged 70 to 84 years, discontinuation of the study drug occurred in 6\% of those treated with chlorthalidone versus 15\% with nitrendipine (primarily attributable to lower-extremity edema) and 20\% with enalapril (primarily attributable to cough).\textsuperscript{55} In ALLHAT, rates of symptomatic adverse effects were not too dissimilar across the groups: chlorthalidone (15\%), amlodipine (16\%), and lisinopril (18\%).\textsuperscript{54} At 1 year, 27\%, 26\%, and 33\%, respectively, were also taking a step 2 (atenolol, reserpine, or clonidine) or step 3 (hydralazine) drug. Of note, diabetes may occur more frequently with thiazides than with other antihypertensive regimens.\textsuperscript{63}

### Considerations in the Design of a Primary Prevention Trial in the Elderly

Clinical equipoise remains regarding the treatment of cholesterol and blood pressure for the primary prevention of cardiovascular disease in those aged ≥70 years. Statins appear to be of greater benefit for preventing CHD than stroke in the elderly with previous cardiovascular disease, but no clear benefit was shown for either in a small sample of hypertensive elderly persons without clinical disease. Although lowering blood pressure has been shown to prevent stroke, congestive heart failure, and renal disease, it is less efficacious for preventing CHD, and the benefit for total mortality is unclear. In addition, the most effective regimen or the optimal blood pressure level has not been established in elderly subjects. Furthermore, whether an overall benefit will occur from reductions in cardiovascular and renal events in the face of competing risks, such as cancer, also remains to be determined.

To address some of these questions, we propose a 2×2 factorial trial in a population of elders aged ≥70 years free of clinical evidence of cardiovascular disease, diabetes, and comorbidities likely to limit survival to <5 years. To establish the efficacy and safety of statin treatment for cardiovascular event reduction, subjects would need to be randomized in a double-blind fashion to placebo\textsuperscript{60} or a statin (or a statin in combination). Treatment choice and dose would depend on an established record of safety in those aged ≥70 years as well as the LDL treatment target (<100 mg/dL).

Subjects would then be rerandomized to receive 1 of 2 blood pressure–lowering regimens to achieve a systolic blood pressure <140 mm Hg or, in those with wide pulse pressure, ie, >80, to try to achieve a level <140 mm Hg if tolerated by the patient, with the goal of a systolic blood pressure <160 mm Hg in all participants. Choice of treatment regimens will depend on the most recent data, and multiple agents will be needed for a significant number of patients.

All subjects would receive recommendations according to guidelines for aspirin prophylaxis, diet, physical activity, and smoking cessation advice. Along with a major research infrastructure for screening and baseline assessment, such as used in ALLHAT, special efforts to include elders will be required. These may include provision of transportation and identification and subsidy for substitute caregiving. However, previous studies have demonstrated that large cohorts of elderly black and white women and men can be recruited successfully for clinical trials.\textsuperscript{64–67}

Although the age cut point was chosen to be ≥70 years because of the paucity of data in this population, efforts should be focused on enrolling those aged >75 years, especially among women, whose event rate begins to approach that of men at approximately this age (Figure 1). Because virtually no data are available for persons aged >80 years, persons in this age group should comprise 50\% of the sample, with a sample size sufficient for subgroup analyses. The sex distribution should be balanced, and approximately 40\% should be of black descent, with a sufficient sample size to evaluate the primary end point in each sex-race subgroup. The rates for blacks in the Cardiovascular Health Study were greater than those for similarly aged whites for all cardiovascular events and mortality.\textsuperscript{58} However, the differential beneficial and adverse effect profiles of diuretics and calcium channel blockers for blacks may differ for whites and blacks.\textsuperscript{69}

Important characteristics that could be considered for exclusion are listed in Table 3. Subjects should also be equally distributed between those with high-density lipoprotein cholesterol levels above and below 45 mg/dL for men and 55 mg/dL for women. In PROSPER, those with high-density lipoprotein cholesterol ≥45 mg/dL had no reduction in cardiovascular risk compared with a 33\% reduction in those with lower high-density lipoprotein cholesterol levels.\textsuperscript{30} Both aspirin and anticoagulation therapy should be allowed because the benefits would be expected to be additive to
testing such as carotid ultrasound, coronary calcification, and magnetic resonance imaging are likely to have limited availability in clinical practice and would limit generalizability of the trial findings in addition to the prohibitive cost.

End Points
For the statin comparison, the primary end point should include myocardial infarction, CHD death, congestive heart failure, and nonfatal and fatal stroke. For the comparison of the 2 antihypertensive regimens, the primary end point should include both the same cardiovascular end points as for the statin comparison along with the renal end points of end-stage renal disease and renal death. Important secondary end points should include total mortality; number and duration of hospitalizations for all cardiovascular events, including coronary, cerebral, and peripheral revascularization and unstable angina; renal events; physical and cognitive function; independent living; dementia; cancer; time to major cardiovascular disease event; and individual event categories. Subgroup analyses by age, sex, risk factors, and comorbidities will also be important end points, as will cost/benefit analyses.

With the use of an exponential change in event rates estimated from the Cardiovascular Health Study,68,71 a sample size of ~1800 subjects (50% women, 50% aged >80 years, and 40% black) would detect an 18% reduction in cardiovascular events (based on an assumption of a 15% reduction in CHD and stroke and a 10% decrease in congestive heart failure events with an incident event rate of 42% over 5 years), and ~3400 subjects would have 90% power to detect a more conservative 13% reduction in the composite primary end point of cardiovascular events. This estimate of incident event rates may be conservative if projections are made from the event rate in PROSPER. In PROSPER, subjects were aged 70 to 82 years at baseline, with a projected 5-year event rate of 32%. In the Cardiovascular Health Study, the event rate in those aged >80 years was 64% higher than in those aged 70 to 79 years. Therefore, had PROSPER also included a substantial group of persons aged >80 years, the projected event rate could have been as high as 52%.

A larger, but still reasonable by modern clinical end point trial standards, sample size would be required to test for interactions. To test for 1 interaction, such as for differential risk reduction for those aged <80 versus ≥80 years for a given treatment, a sample size of ~4900 would have 90% power to detect an 18% reduction in events, and a sample size of 9500 could detect a 13% reduction in events. To test for 2-way interactions, for example, between age and gender, a sample size of 10 000 would have 80% power to detect an 18% reduction in cardiovascular events, as well as a 10% reduction in total mortality. A trial of 19 000 subjects would have 80% power to detect a 5% decrease in total mortality as well as a 13% lower risk of events for 3-way interactions, eg, between age, gender, and race.

Conclusion
Little data are available regarding the benefits and risks of cholesterol and blood pressure lowering in those aged >70 years and especially those aged >80 years without cardiovascular disease or diabetes. Given the demographics of the

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt; 70 y</td>
<td>Clear evidence of benefit from clinical trials in younger primary prevention populations49,74</td>
</tr>
<tr>
<td>Clinical evidence of cardiovascular disease or diabetes (NCEP ATP III CHD equivalent)</td>
<td>Clear evidence of benefit from clinical trials in patients aged &lt; 80 y with these conditions5,16</td>
</tr>
<tr>
<td>Any condition likely to limit survival to &lt; 5 y, including cancer, congestive heart failure, or hemodialysis</td>
<td>Disease course unlikely to be affected by lowering LDL and blood pressure</td>
</tr>
<tr>
<td>LDL &lt; 100 mg/dL</td>
<td>Evidence of excess mortality in elderly persons with untreated LDL level &lt; 100 mg/dL; may represent serious comorbidities or malnutrition</td>
</tr>
<tr>
<td>Untreated systolic blood pressure &lt; 140 mm Hg or systolic blood pressure &lt; 160 if pulse pressure ≥ 100 mm Hg</td>
<td>Although the 5-y rate of death was similar (10%) in Cardiovascular Health Study participants with systolic blood pressure ≥ 128 mm Hg and in those with blood pressure &gt; 128 to 140 mm Hg,21 no lower limit of safety with antihypertensive treatment has been established</td>
</tr>
<tr>
<td>Systolic blood pressure &gt; 200 mm Hg</td>
<td>Will need multiple medications to control and may be secondary to an underlying medical condition</td>
</tr>
<tr>
<td>Underweight men ≤ 142 lb (63.9 kg) or women ≤ 115 lb (51.8 kg) or unexplained weight loss ≥ 10 lb (4.5 kg)</td>
<td>21% mortality at 5 y71 vs 11–14% in higher-weight individuals</td>
</tr>
<tr>
<td>Moderate to severe cognitive dysfunction or dementia</td>
<td>33% mortality at 5 y71 less likely to be affected by lowering LDL and blood pressure</td>
</tr>
<tr>
<td>Nursing home residence or self-reported difficulty with ≥ 3 instrumental activities of daily living</td>
<td>&gt; 30% mortality at 5 y71 less likely to be affected by lowering LDL and blood pressure</td>
</tr>
<tr>
<td>Poor self-assessed health</td>
<td>38% mortality at 5 y71 less likely to be affected by lowering LDL and blood pressure</td>
</tr>
<tr>
<td>Excessive alcohol intake (&gt; 2 drinks/d)</td>
<td>Increased risk of statin myotoxicity</td>
</tr>
<tr>
<td>Known drug contraindications</td>
<td>Increased risk of muscle and liver toxicity</td>
</tr>
</tbody>
</table>

NCEP ATP III indicates National Cholesterol Education Program Adult Treatment Panel III.

Volunteers for the trial may or may not be healthier than the general population. Event rates were actually higher in the PROSPER trial than for a similarly aged population in the Cardiovascular Health Study.68 Although evidence of subclinical atherosclerosis would identify those most likely to benefit from primary prevention, several factors mitigate against its use as a criterion for eligibility. Older individuals without evidence of subclinical disease still have a significant 10-year risk of CHD (13% without versus 16% with evidence of subclinical disease) and stroke (6% without versus 12% with such evidence).70 Furthermore, noninvasive diagnostic
population and the length of life lived after the age of 70 years, a clinical trial is urgently needed to evaluate cardiovascular risk factor interventions in older persons. A trial of cholesterol lowering in the setting of adequate blood pressure control, which would also allow comparison of 2 antihypertensive regimens, of a size similar to those recently reported would be adequately powered to detect reductions in cardiovascular and functional end points as well as total mortality.

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References


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