

Hypertension

JOURNAL OF THE AMERICAN HEART ASSOCIATION



*Learn and Live*SM

Blood Pressure Lowering for Primary and Secondary Prevention of Stroke

Haifeng Zhang, Lutgarde Thijs and Jan A. Staessen

Hypertension 2006;48;187-195; originally published online Jul 3, 2006;

DOI: 10.1161/01.HYP.0000231939.40959.60

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75214

Copyright © 2006 American Heart Association. All rights reserved. Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://hyper.ahajournals.org/cgi/content/full/48/2/187>

Subscriptions: Information about subscribing to Hypertension is online at
<http://hyper.ahajournals.org/subscriptions/>

Permissions: Permissions & Rights Desk, Lippincott Williams & Wilkins, a division of Wolters Kluwer Health, 351 West Camden Street, Baltimore, MD 21202-2436. Phone: 410-528-4050. Fax: 410-528-8550. E-mail:
journalpermissions@lww.com

Reprints: Information about reprints can be found online at
<http://www.lww.com/reprints>

Blood Pressure Lowering for Primary and Secondary Prevention of Stroke

Haifeng Zhang, Lutgarde Thijs, Jan A. Staessen

Hypertension affects from 20% to 30% of the world population.^{1,2} Blood pressure is the most consistent and powerful predictor of stroke. Population mortality trends for stroke parallel those in hypertension.^{3,4} A systolic blood pressure >115 mm Hg explains 60% of the population-attributable risk of stroke.⁵ In the Framingham cohort,⁶ the lifetime risk of stroke at ages 55, 65, and 75 years was similar, approximating 1 in 5 for women and 1 in 6 for men. In many countries, such as China,⁷ stroke is the third cause of death only preceded by heart disease and total cancer. Two thirds of stroke deaths occur in developing nations.⁸ According to recent estimates published by the World Health Organization, worldwide, ≈15 million people per year fall victim to a stroke, of whom ≈5 million die and another ≈5 million are left permanently disabled.¹ From this vantage point, we reviewed the recent literature to underscore the deadly but reversible link between stroke and blood pressure.

Role of Blood Pressure Among Other Risk Factors

Nonmodifiable Risk Factors

Nonwhite ethnicity, male sex, older age, and a positive family history are among the nonmodifiable risk factors of stroke.^{9,10} Monogenic stroke disorders,¹¹ such as, for instance, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy,¹² are extremely rare. In the vast majority of cases, stroke has a polygenic background associated with proven or suspected variation in the genes contributing to hypertension, carotid intima-media thickness, vascular remodeling, small vessel disease,¹³ inflammation, oxidative stress, dyslipidemia, or the generation of angiotensin II.^{14,15} Small vessel disease of the brain underlies 20% to 30% of ischemic strokes and a larger proportion of intracerebral hemorrhages.¹³

Modifiable Risk Factors

Smoking,^{1,9,10} excessive alcohol intake (>60 g per day),^{9,10,16} obesity,^{9,10} dyslipidemia,^{9,10} diabetes mellitus,^{9,17} carotid artery disease,^{9,10} atrial fibrillation, heart failure, and other forms of heart disease^{1,9} are treatable risk factors for stroke.

However, among the modifiable risk indicators, high blood pressure has by far the largest impact.^{1,9} In a quantitative overview of 61 cohort studies, the Prospective Studies Collaboration demonstrated a strong log-linear relation without threshold between stroke mortality and blood pressure (Figure 1A), starting at levels of 115 mm Hg systolic and 75 mm Hg diastolic and consistent across the age range (50 to 89 years).¹⁸ At ages 40 to 69 years, each difference in blood pressure of 20 mm Hg systolic or 10 mm Hg diastolic was associated with a >2-fold difference in stroke mortality.¹⁸ More recently, the Asian Pacific Cohort Studies Collaboration reported that in both sexes systolic blood pressure (Figure 1B) tended to be more predictive than diastolic blood pressure in all age groups with the exception of men <50 years.^{19,20}

Stroke Prediction From Automated Blood Pressure Measurements

Prospective observational^{21,22} and intervention²³ studies consistently noticed that blood pressure recorded either by ambulatory monitoring^{21,23} or by self-measurement²² predicted cardiovascular complications, in particular, stroke, over and beyond the office blood pressure. In the Ohasama study,²² each increment in the self-measured blood pressure by 10 mm Hg systolic or 5 mm Hg diastolic resulted in an increase in the risk of total stroke by 30% and 20%, respectively. Already in 1988, O'Brien et al²⁴ reported that an abnormal circadian blood pressure profile with decreased nighttime dipping (<10 mm Hg systolic or 5 mm Hg diastolic) was associated with a high risk of cerebrovascular complications. More recent studies^{25,26} not only substantiated these initial observations²⁴ but investigated other characteristics of the diurnal blood pressure profile as well. Kario et al²⁵ dichotomized 519 hypertensive Japanese with mean age of 72 years into those whose morning surge in systolic blood pressure (average over 2 hours after awakening minus average over 1 hour including the lowest level during sleep) was ≥55 mm Hg (top decile) and the remainder of the participants. Patients belonging to the top decile had a higher baseline prevalence of multiple

Received February 26, 2006; first decision March 17, 2006; revision accepted June 2, 2006.

From the Studies Coordinating Centre (H.Z., L.T., J.A.S.), Division of Hypertension and Cardiovascular Rehabilitation, Department of Cardiovascular Diseases, University of Leuven, Belgium; and the Department of Cardiology (H.Z.), First Affiliated Hospital, Nanjing Medical University, Nanjing, China.

The corresponding author had full access to all data and had final responsibility for the decision to submit the manuscript for publication.

Correspondence to Jan A. Staessen, Studies Coordinating Centre, Division of Hypertension and Cardiovascular Rehabilitation, Department of Cardiovascular Diseases, Campus Gasthuisberg, University of Leuven, Herestraat 49, Box 702, B-3000 Leuven, Belgium. E-mail jan.staessen@med.kuleuven.be

(*Hypertension*. 2006;48:187-195.)

© 2006 American Heart Association, Inc.

Hypertension is available at <http://www.hypertensionaha.org>

DOI: 10.1161/01.HYP.0000231939.40959.60

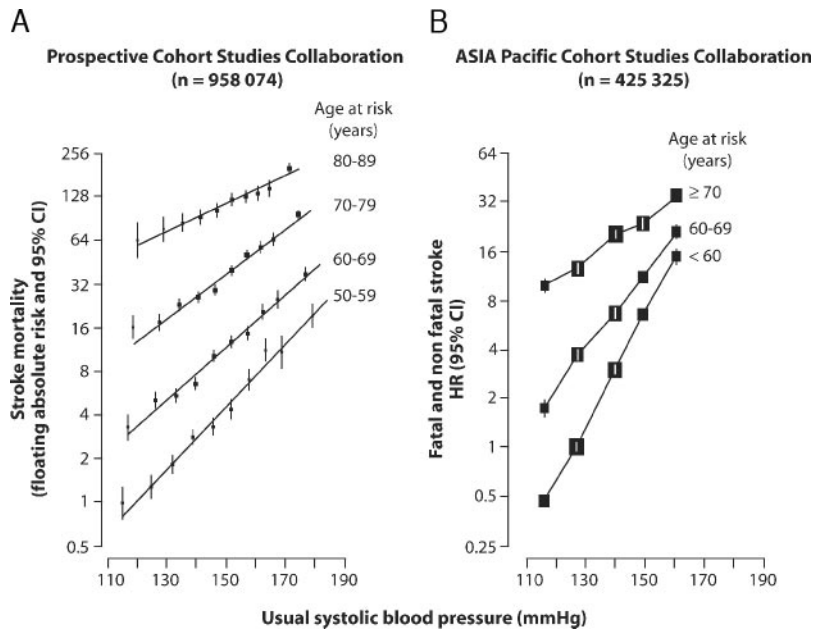


Figure 1. Age-specific relations of systolic blood pressure with stroke mortality (A) in 61 cohorts (n=958 074; 70% of participants from Europe, 20% from North America or Australia, and 10% from Japan and China) and with fatal and nonfatal stroke (B) in 37 cohorts (n=425 325; 17% of participants from Australia and New Zealand and 73% from Asian countries). This figure illustrates the universal dependence of the stroke risk on blood pressure. Reproduced with permission from references 18 and 19, respectively.

silent brain infarcts (57% versus 33%) and a higher stroke incidence (19% versus 7%) during an average of 41 months of follow-up, even after accounting for the 24-hour blood pressure level, dipping status, and the prevalence of silent cerebral infarcts at enrollment.²⁵

White-coat hypertension is a normal daytime ambulatory blood pressure in the presence of an elevated clinic blood pressure.² Masked hypertension is a raised daytime ambulatory blood pressure in subjects with normotensive values on conventional measurement at the clinic.² In a meta-analysis based on individual data from 5955 subjects,²⁷ the risk of stroke over the whole follow-up was similar in subjects with normotension and white-coat hypertension at baseline and was 2-fold raised in those with ambulatory hypertension. The cumulative hazard for stroke was comparable in the white-coat hypertension and normotensive group up to year 6 of follow-up.²⁷ However, there was an increase in the hazard of stroke in the white-coat hypertension group, with the Kaplan-Meier curve diverging from that of the normotensive group and crossing that of the ambulatory hypertension group by year 9 of follow-up, suggesting that in the long run, white-coat hypertension might also be a predictor of stroke.²⁷ The ambulatory arterial stiffness index, which can be readily computed from 24-hour ambulatory blood pressure recordings, reflects arterial stiffness.²⁸ In Irish hypertensive patients,²⁹ this novel index was a better predictor of fatal stroke than the 24-hour pulse pressure.

Prevention of Stroke

Many stroke survivors are left with cognitive, affective, and physical impairments, become dependent, and require life-long assistance with activities of daily living.¹ Prevention is the only possible way to curb the stroke pandemic.¹ This goal cannot be achieved without better control of hypertension.^{3,4}

Primary Prevention of Stroke

In placebo-controlled trials, antihypertensive treatment of middle-aged or older hypertensive patients with predomi-

nantly diastolic hypertension proved that a 5- to 6-mm Hg decline in diastolic blood pressure maintained over 5 years reduced the incidence of stroke by $\approx 40\%$.³⁰ In older patients with isolated systolic hypertension, antihypertensive treatment over 4 years lowered systolic blood pressure on average by 10 mm Hg and decreased fatal and nonfatal stroke by 30% in Western^{31,32} and Asian³³ patients alike.

Consecutive overviews³³⁻³⁷ of actively controlled trials compared the incidence of stroke between patients randomly assigned to initial treatment with old drugs (diuretics and/or β -blockers) and those started on newer agents (calcium channel blockers [CCBs], angiotensin-converting enzyme inhibitors [ACEIs], α -blockers, or angiotensin II type-1 receptor blockers [ARBs]). Because of the recent publication of 2^{38,39} large-scale trials, we updated⁴⁰ our analysis.³⁵ In the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT-BPLA),³⁸ patients randomized to amlodipine with or without perindopril compared with those allocated atenolol with or without bendroflumethiazide had 2.7-mm Hg lower systolic blood pressure and a hazard ratio for stroke of 0.77 (95% CI, 0.66 to 0.89; $P=0.0003$). The Felodipine Event Reduction Trial (FEVER)³⁹ compared the incidence of stroke and other cardiovascular events over a mean follow-up of 40 months among 9711 Chinese hypertensive patients randomly assigned either to a low-dose combination of hydrochlorothiazide and felodipine or to monotherapy with low-dose hydrochlorothiazide. The 4-mm Hg lower systolic blood pressure in the felodipine group resulted in a reduction by 27% (95% CI, 11% to 40%) in the incidence of fatal and nonfatal stroke.³⁹ As shown in Figure 2, compared with older drugs, CCBs provided significantly better protection against stroke (pooled odds ratios, 0.86; 95% CI, 0.81 to 0.92), whereas the opposite was the case for ACEIs (1.10; 95% CI, 1.01 to 1.20). Compared with control, treatment initiated with ARBs lessened the incidence of stroke by 26% (95% CI, 14% to 36%). Overall, newer compared with older agents provided 7% (95% CI, 2% to 11%) better protection against stroke (Figure

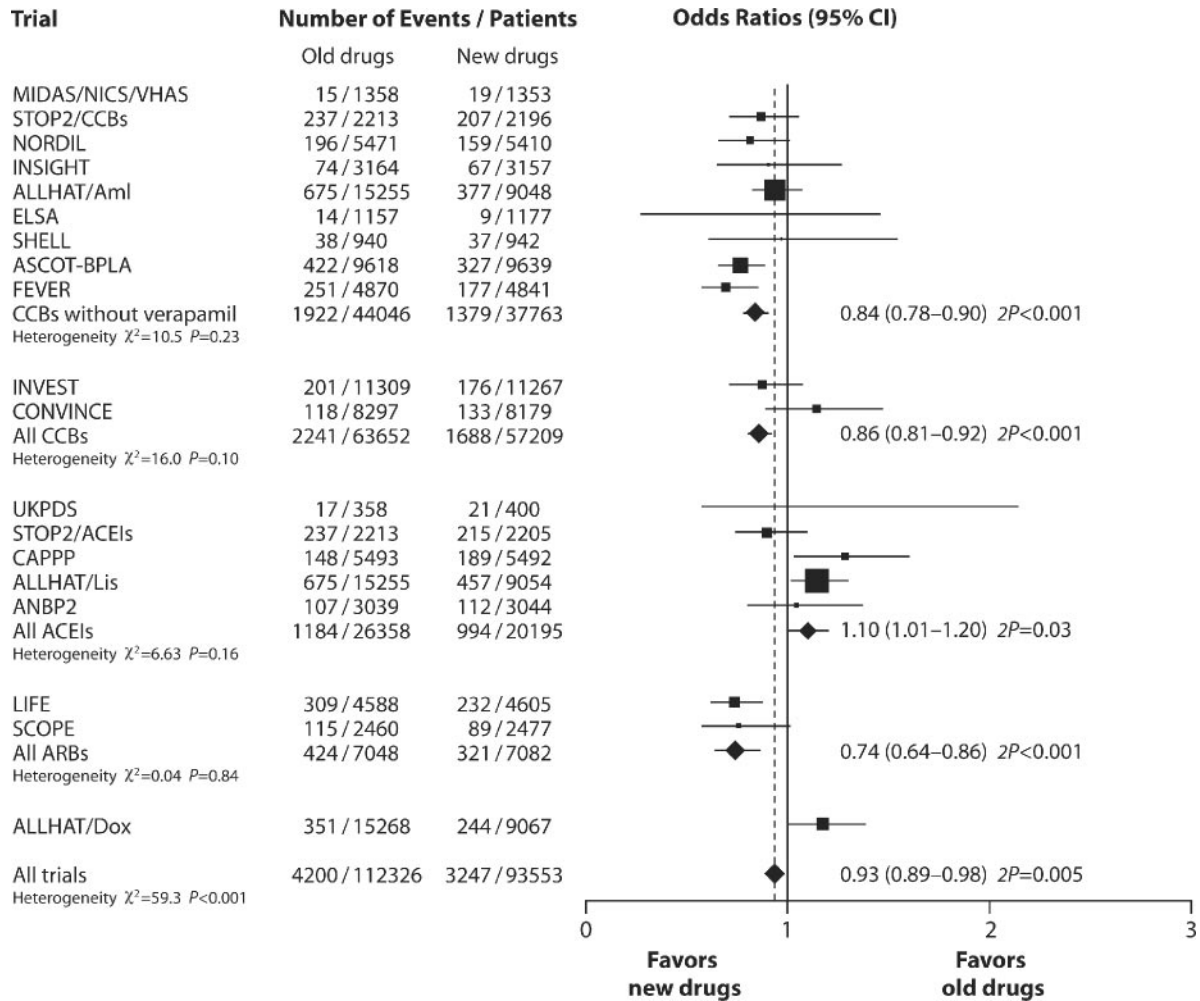


Figure 2. Effects of blood pressure lowering treatment on fatal and nonfatal stroke in actively controlled trials comparing new with old (diuretics and or β -blockers) antihypertensive drugs. Dox indicates the α -blocker doxazosin. ■, odds ratios in individual trials with a size proportional to the inverse of the variance of the odds ratios. — and ♦, 95% CIs for individual trials and summary statistics, respectively. Pooled estimates were computed from a random-effect model in case of significant heterogeneity and otherwise from fixed-effect models. |, position of the point estimate of the pooled effect size for all trials combined. ASCOT-BPLA and FEVER indicate the blood-pressure lowering arm of the Anglo-Scandinavian Cardiac Outcomes Trial³⁸ and the Felodipine Event Reduction Trial,³⁹ respectively. The other trial acronyms are given in references 34 and 35.

2). However, for the interpretation of these results, one should account for the blood pressure gradients between the groups randomly assigned in trials.

Secondary Prevention

Seven randomized, controlled trials^{41–47} investigated the effects of antihypertensive drug treatment versus no treatment or placebo on recurrent stroke and cardiovascular complications in hypertensive or normotensive patients with a previous history of cerebrovascular disease (Figure 3). In 3 trials,^{41–43} in which either methyldiazinide combined with deserpidine⁴¹ or atenolol^{42,43} were compared with placebo, the average reductions in blood pressure ranged from 4⁴³ to 25⁴¹ mm Hg systolic and from 3^{42,43} to 13⁴¹ mm Hg diastolic. These 3 studies^{41–43} could not confirm the significant 67% benefit on stroke recurrence ($P=0.02$), as initially reported by Carter⁴⁷ in a much smaller trial.

In the Chinese Post-stroke Antihypertensive Treatment Study (PATS),⁴⁴ 5665 patients with a history of cerebrovascular

disease were randomly assigned to indapamide 2.5 mg per day or placebo. Follow-up averaged 2 years. Indapamide decreased blood pressure by 5 mm Hg systolic and 2 mm Hg diastolic and reduced stroke recurrence by 29% ($P=0.0009$).⁴⁴ The perindopril PROtection aGainst REcurrent Stroke Study (PROGRESS) included 6105 patients of predominantly white extraction but also 39% Asians.⁴⁵ Patients in the active treatment group received perindopril (4 mg per day) either alone or together with indapamide (2.5 mg per day).⁴⁵ Combination therapy lowered systolic and diastolic blood pressure by 12.3 and 5.0 mm Hg, respectively and reduced stroke recurrence by 43% ($P<0.001$). Monotherapy with perindopril lowered blood pressure by 5.0 mm Hg systolic and 2.0 mm Hg diastolic, but the relative risk reduction was only 4% (95% CI, –19% to 23%).⁴⁵ In the Heart Outcomes Prevention Evaluation (HOPE) trial,^{46,48} 1013 patients with a previous history of cerebrovascular disease were randomly assigned to ramipril (up to 10 mg per day) or matching placebo given on top of unspecified background therapy. Compared with placebo, the ACEI reduced blood pressure by

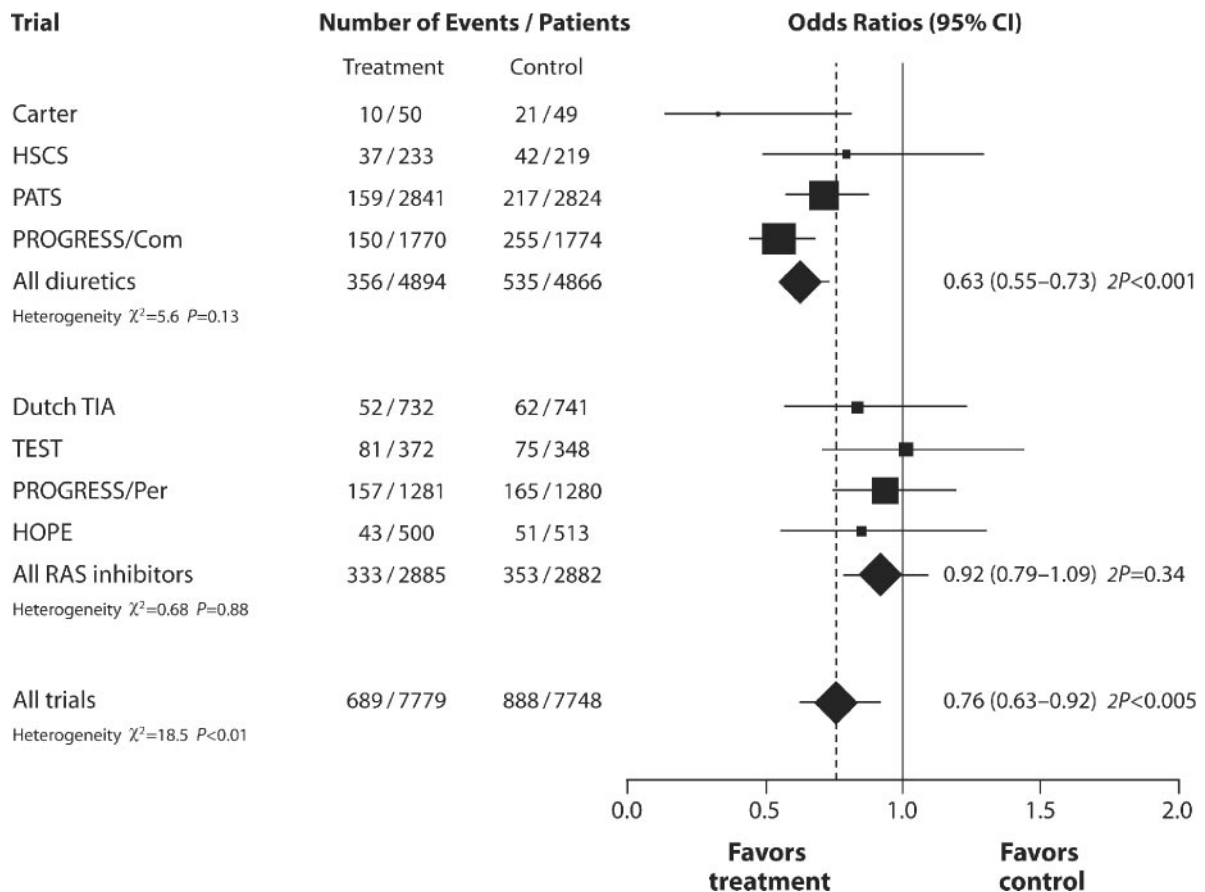


Figure 3. Effects of blood pressure lowering on fatal and nonfatal recurrent stroke. ■, odds ratios in individual trials with a size proportional to the inverse of the variance of the odds ratios. — and ◆, 95% CIs for individual trials and summary statistics, respectively. Pooled estimates were computed from a random-effect model in case of significant heterogeneity and otherwise from fixed-effect models. |, position of the point estimate of the pooled effect size for all trials combined. The individual studies were: Carter’s trial⁴⁷; the Hypertension-Stroke Cooperative Study (HSCG)⁴¹; the Dutch TIA Trial⁴²; the Tenormin after Stroke and TIA Trial (TEST)⁴³; PATS; PROGRESS – monotherapy (PROGRESS/Per) and combined therapy (PROGRESS/Com) arms⁴⁵; and HOPE.⁴⁶

3.1 mm Hg systolic and 1.7 mm Hg diastolic, but the relative risk reduction of 15% was not significant (95% CI, -42% to 30%).⁴⁶

We computed pooled results (Figure 3) across the 7 secondary prevention trials on stroke recurrence,^{41–47} updating⁴⁰ previous estimates.^{33–35,49} Our analysis included 15 527 patients. For stroke, we noticed significant heterogeneity across the trials ($P=0.01$), which was mainly because of the contrasting results between the 2 subgroups of the PROGRESS trial and the inconsistency between treatments including or not including diuretics. Based on a random effect model (Figure 3), the pooled odds ratio for the 7 trials^{41–47} combined was 0.76 (95% CI, 0.63 to 0.92). Sensitivity analyses showed that the pooled odds ratio was 0.63 (95% CI, 0.55 to 0.73) in trials involving diuretics as a major component of therapy,^{41,44,45,47} and 0.92 (95% CI, 0.79 to 1.09) in the trials in which the mainstay of treatment involved inhibition of the renin system by atenolol^{42,43} or monotherapy with perindopril⁴⁵ or ramipril.^{46,48}

In addition to these trials,^{41–47} the Morbidity and Mortality After Stroke, Eprosartan Compared With Nitrendipine for Secondary Prevention Study (MOSES)⁵⁰ included 1405 hypertensive patients with a cerebrovascular event within 2 years of randomization. According to an open design with blinded end point validation, they were randomly assigned to

nitrendipine or eprosartan, rolled over from previous treatment to the study medication, and followed up for a mean of 2.5 years. A number of methodologic problems should be noted. So-called flexibility with regard to the use of the study medications and combination therapy to reach a target blood pressure of <140 mm Hg systolic and <90 diastolic mm Hg substantially weakened the validity of the outcome results. Indeed, more patients in the eprosartan than nitrendipine group crossed over (14.4% versus 4.8%). Furthermore, MOSES actually compared the only registered daily dose of eprosartan (600 mg per day) with a suboptimal dose of nitrendipine. Mean daily doses at the end of the trial were 623 mg for eprosartan and 16.2 mg for nitrendipine.⁵⁰ In comparison, in the Systolic Hypertension in Europe Trial,⁵¹ mean daily doses of nitrendipine throughout follow-up were ≈30 mg in all of the patients and ≈35 mg in those progressing to combination therapy. MOSES reported similar blood pressure levels in both treatment groups confirmed by 24-hour ambulatory monitoring at 12, 24, and 48 months, but the article mentioned only the ambulatory blood pressure levels at baseline.⁵⁰ The primary outcome was the composite of total mortality and all cardiovascular and cerebrovascular events, including recurrent events. The main outcome analysis, therefore, included patients with multiple events during follow-up

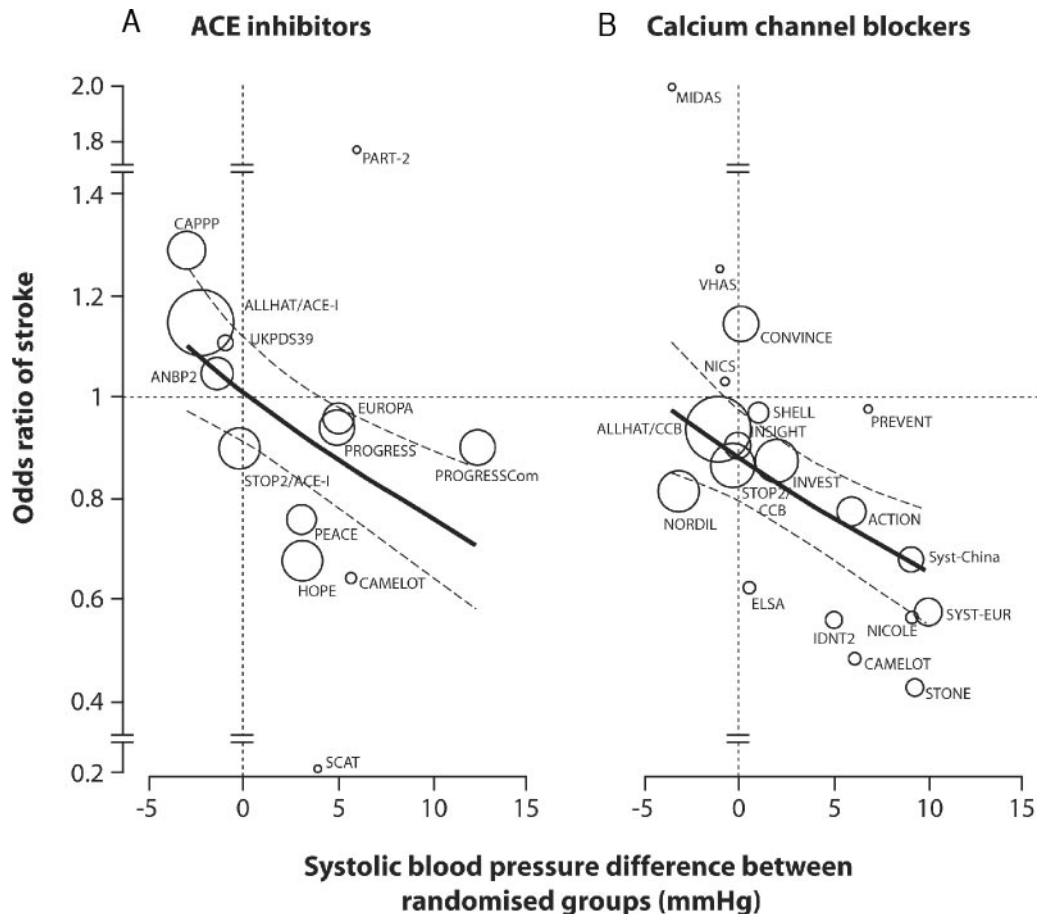


Figure 4. Relation between odds ratios for stroke and differences in achieved systolic blood pressure between randomized groups in trials with experimental treatment based on ACEIs (A) or CCBs (B). \circ , individual trials and have a diameter proportional to the inverse of the variance of the odds ratios in individual trials. The metaregression lines are represented with 95% CIs. Reproduced with permission from reference 37.

more than once. Cerebrovascular events also encompassed the weaker end point of transient ischemic attack. The incidence density ratio comparing eprosartan to nitrendipine was 0.79 (95% CI, 0.66 to 0.96; $P=0.014$) for the composite end point and 0.75 (95% CI, 0.58 to 0.97; $P=0.026$) for stroke recurrence.⁵⁰ In state-of-the-art actuarial analyses, only considering time to the first event within each category (with censoring), the hazard ratios were 0.69 (95% CI, 0.50 to 0.97; $P=0.031$) for cardiovascular events and 0.88 (95% 0.65 to 1.20; $P=0.42$) for the first recurrent cerebrovascular complication.⁵⁰

Blood Pressure Lowering Versus Ancillary Drug Properties

Until the turn of the millennium,^{48,52} the consensus interpretation of the evidence produced by the outcome trials in hypertensive patients was that blood pressure is a risk factor amenable to intervention, lower levels entailing lower risk. Stroke is the complication of hypertension, which is most directly linked to the blood pressure level.¹ Not surprisingly, metaregression analyses published by us^{34–37} and other research consortia⁵³ demonstrated that, in keeping with large-scale prospective observational studies (Figure 1)^{18,20} also in randomized clinical trials, small gradients in the achieved

systolic blood pressure explained most of the differences in the cardiovascular outcomes. This association was particularly strong for the prevention of stroke.^{34–37}

In an update of our metaregression analysis (Figure 4),³⁷ we accounted not only for the differences in the achieved systolic blood pressure between groups randomly assigned in clinical trials, but also for drug class, the interaction between on-treatment systolic pressure and drug class, age at randomization, year of publication, and duration of follow-up. We included trials that compared either CCBs or ACEIs with placebo or older drugs.³⁷ We corroborated that blood pressure reduction was by far the most important determinant of cardiovascular outcome.^{34–36,53} In addition, in keeping with previous analyses,^{34–36,53} we found that CCBs compared with ACEIs, over and beyond blood pressure, provided a benefit ($\approx 14\%$; $P=0.042$) in the prevention of stroke and that the same was true for ACEIs compared with CCBs in relation to coronary heart disease ($\approx 10\%$; $P=0.028$).³⁷ These findings suggested that CCBs might be especially indicated for the prevention of stroke in populations at high risk, such as Asians³⁹ or older patients with isolated systolic hypertension.⁵¹

Predictions based on our metaregression model published in 2001³⁶ revealed few exceptions to the rule that the

Observed Versus Predicted Odds Ratios for Stroke by Between-Group Differences in Systolic Blood Pressure in Randomized Clinical Trials

Design	Trial/Subgroup	Patients, n	Events, %	DSBP, mm Hg	Observed Odds Ratio*	Predicted Odds Ratio†	P‡
DB/P	ACTION	7665	2.6	+6.0	0.78 (0.58 to 1.05)	0.68 (0.62 to 0.74)	0.38
DB/A	ALLHAT/Dox	24 335	2.3	-2.3	1.18 (0.99 to 1.39)	1.06 (0.92 to 1.22)	0.33
DB/A	ALLHAT/Aml	24 303	4.4	-1.1	0.94 (0.82 to 1.07)	1.00 (0.89 to 1.12)	0.43
DB/A	ALLHAT/Lis	24 309	4.4	-2.3	1.15 (1.01 to 1.30)	1.08 (0.94 to 1.24)	0.51
O/A	ANBP2	6083	3.5	-1.4	1.05 (0.79 to 1.38)	1.02 (0.90 to 1.15)	0.83
O/A	ASCOT-BPLA	19 257	4.4	+2.7	0.77 (0.66 to 0.89)	0.78 (0.67 to 0.92)	0.91
O/A	CAPP	10 985	2.7	-3.0	1.29 (1.03 to 1.61)	1.14 (0.96 to 1.34)	0.37
DB/P	DIABHYCAR	4912	4.7	+1.5	1.03 (0.80 to 1.32)	0.87 (0.79 to 0.95)	0.21
DB/P	EUROPA	12 218	1.7	+5.0	0.96 (0.68 to 1.24)	0.71 (0.65 to 0.77)	0.06
DB/P	FEVER	9711	5.2	+4.2	0.73 (0.60 to 0.89)	0.74 (0.63 to 0.87)	0.92
DB/P	HOPE	9297	4.9	+3.3	0.68 (0.52 to 0.86)	0.77 (0.69 to 0.85)	0.32
DB/A	LIFE—all patients	9193	6.7	+1.1	0.75 (0.63 to 0.90)	0.87 (0.76 to 0.95)	0.15
DB/A	LIFE—diabetic patients	1195	10.7	+3.0	0.80 (0.63 to 1.19)	0.78 (0.71 to 0.85)	0.99
O/A	NORDIL	10 881	3.6	-3.2	0.81 (0.65 to 1.01)	1.14 (0.97 to 1.35)	0.01
DB/P	PEACE	8290	2.2	+2.2	0.76 (0.56 to 1.04)	0.82 (0.75 to 0.89)	0.64
DB/P	PROGRESS/Comb	3544	14.4	+12.3	0.57 (0.46 to 0.70)	0.57 (0.51 to 0.64)	0.83
DB/P	PROGRESS/Per	2561	12.9	+5.0	0.95 (0.77 to 1.19)	0.71 (0.64 to 0.85)	0.02
DB/P	SCOPE	4937	4.7	+3.2	0.76 (0.57 to 1.02)	0.77 (0.71 to 0.84)	0.92
DB/A	VALUE	15 245	3.7	-2.2	1.15 (0.98 to 1.35)	1.15 (1.01 to 1.30)	0.99

The table includes trials with a significant difference in systolic blood pressure between randomized groups (Δ SBP), negative values indicating tighter blood pressure on reference than on experimental treatment. DB and O indicate double-blind design and prospective randomized open design with blinded end point evaluation, respectively. P and A indicate reference groups allocated placebo or active antihypertensive drugs, respectively. For each trial the total number of randomly assigned patients and the stroke rate in the control group are given. Although placebo-controlled, most (SCOPE) or all (FEVER) patients of the control group were on diuretics and/or β -blockers.

*Observed odds ratios with 95% CIs were calculated from the number of events (control/experimental) and the number of patients per group randomly assigned in each trial by use of 2×2 contingency tables.

†Odds ratio (with 95% CI) predicted by metaregression. ASCOT-BPLA and FEVER indicate the blood-pressure lowering arm of the Anglo-Scandinavian Cardiac Outcomes Trial,³⁸ and FEVER, respectively. The other trial acronyms are given in references 34 and 35.

‡Significance of the difference between observed and predicted odds ratios.

achieved systolic blood pressure accurately predicted the differences between randomized groups in the occurrence of stroke. In the Nordic DILTiazem study (NORDIL),⁵⁴ patients randomly assigned to the CCB, compared with those allocated old drugs, had a 3.1 mm Hg higher systolic blood pressure but a 19% lower incidence of stroke. The predicted³⁵ and observed⁵⁴ odds ratios (1.14³⁵ versus 0.81⁵⁴) were significantly different (Table). In the PROGRESS perindopril monotherapy arm⁴⁵ and in the European Trial on Reduction of Cardiac Events With Perindopril in Stable Coronary Artery Disease (EUROPA),⁵⁵ perindopril compared with placebo did not influence the risk of stroke in spite of a 5-mm Hg lower systolic blood pressure on the ACEI. After ASCOT-BPLA was prematurely stopped because of the higher death rate in the atenolol group,³⁸ we used the relation between cardiovascular outcomes and achieved systolic pressure published in 2001³⁶ to predict the results. We assumed a 3-mm Hg lower systolic blood pressure in patients randomly assigned to amlodipine compared with those allocated atenolol,⁵⁶ which was close to the observed 2.7-mm Hg difference.³⁸ The predicted⁵⁶ and observed³⁸ relative risk reductions for stroke (0.78⁵⁶ versus 0.77³⁸) were similar (Table), again highlighting that lower blood pressure is key to prevention. This conclusion is being further tested in the stroke results of ongoing outcome trials of blood pressure lowering therapies.⁵⁷⁻⁵⁹

The Issue of β -Blockers

Recently published quantitative overviews^{60,61} initiated a debate on whether β -blockers should remain first choice in the treatment of essential hypertension, in particular for the prevention of stroke. In their first run, the Swedish group⁶⁰ identified 17 trials but only included 4 comparing atenolol with no treatment or placebo and 5 comparing atenolol with other drug classes. In their second review,⁶¹ the same investigators broadened the scope of their review beyond atenolol. When all β -blockers were compared with placebo or no treatment, the relative risk of stroke was only reduced by 19% (95% CI, 7% to 29%), about half of the effect expected from previous hypertension trials. In actively controlled trials, β -blockers reduced the risk of stroke 14% (95% CI, 4% to 23%) less than other drug classes.

One should very carefully interpret the recommendation to no longer use β -blockers as first-line treatment of essential hypertension. The Swedish investigators^{60,61} did not account for the differences in blood pressure between randomized groups or the efficacy of β -blockade based on differences in heart rate. In the trial conducted by the Medical Research Council,⁶² investigators withdrew a substantial number of patients randomly assigned to propranolol because of bradycardia, a sign indicating effective β -blockade. The Swedish

investigators^{60,61} did not consider the large body of evidence available from secondary prevention trials of myocardial infarction, published >2 decennia ago⁶³ and confirmed recently.⁶⁴ If not for stroke, β -blockers should remain within the first-line therapeutic arsenal for the prevention of myocardial infarction and sudden death in patients with a history of coronary heart disease.^{63,64} Remarkably, in the EUROPA trial,⁵⁵ perindopril only offered protection against myocardial infarction in patients already on β -blockers.

Perspectives and Conclusions

In 2005, 56 million people died, 5.6 million of them from a stroke.⁶⁵ By 2015, this figure will rise to 6.4 million stroke deaths a year, largely because of the worldwide aging populations.⁶⁵ About a similar number of people will survive a stroke and remain disabled for the remainder of their lifespan.¹ Our review underscores that reducing blood pressure is the most effective measure to prevent stroke. Unfortunately, in Europe and many other parts of the world, the rule of halves⁶⁶ still exists, and the fraction of hypertensive patients with properly controlled blood pressure ranges from $\approx 1\%$ to 40%.^{67,68} The National Health and Nutrition and Examination Survey⁶⁹ showed that the awareness of the hypertensive population in the United States improved from 50% in the 1970s to 70% in the 1990s, whereas over the same period the proportion of hypertensive patients with normalized blood pressure increased from 10% to 29%. Whether or not this trend is continuing remains a matter of debate.^{70,71} Furthermore, in China, the developing country with largest population, only 44.7% of hypertensive patients were aware of their high blood pressure, only 28.2% were taking antihypertensive medications, and only 8.1% had achieved blood pressure control.⁷²

The worldwide prevalence and total number of adults with hypertension in 2025 will be 29% and 1.56 billion, respectively.⁷³ Improving the accessibility and delivery of medical care are short-term priorities. The long-term perspective rests on the continuous nature of the relation between stroke and blood pressure and the notion that many strokes occur in individuals currently categorized as nonhypertensive.^{18,19} Population-based strategies with the goal to produce a downward shift in the blood pressure distribution along with interventions to improve diets^{74,75} and to reduce overweight⁷⁶ and smoking^{77,78} are likely to yield the greatest reduction of the global burden of stroke.

From the research point of view, the management of blood pressure in acute stroke remains the most urgent issue to be addressed.^{79,80} The current practice of selecting only high-risk patients for enrollment in clinical trials on the prevention of stroke is hard to justify, because the exclusion of patients with no additional risk factors undermines external validity and unnecessarily prolongs recruitment.⁸¹

Acknowledgments

We acknowledge the expert assistance of Sandra Covens and Renilde Wolfs.

Disclosures

J.A.S. consulted for pharmaceutical companies and received funding for studies, seminars, and travel from manufacturers of drugs that lower blood pressure. The remaining authors report no conflicts.

References

- Mackay J, Mensah G. *The Atlas of Heart Disease and Stroke*. Geneva, Switzerland: World Health Organization; 2004.
- Staessen JA, Wang J, Bianchi G, Birkenhager WH. Essential hypertension. *Lancet*. 2003;361:1629–1641.
- Luepker RV, Arnett DK, Jacobs DR Jr, Duval SJ, Folsom AR, Armstrong C, Blackburn H. Trends in blood pressure, hypertension control, and stroke mortality: the Minnesota Heart survey. *Am J Med*. 2006;119:42–49.
- Wolf-Maier K, Cooper RS, Banegas JR, Giampaoli S, Hense HW, Joffres MR, Kastarinen M, Poulter N, Primatesta P, Rodríguez-Artalejo F, Stegmayr B, Thamm M, Tuomilehto J, Vanuzzo D, Vescio F. Hypertension prevalence and blood pressure levels in 6 European countries, Canada, and the United States. *JAMA*. 2003;289:2363–2369.
- Lawes CM, Vander HS, Law MR, Elliott P, MacMahon S, Rodgers A. Blood pressure and the global burden of disease 2000. Part II: estimates of attributable burden. *J Hypertens*. 2006;24:423–430.
- Seshadri S, Beiser A, Kelly-Hayes M, Kase CS, Au R, Kannel WB, Wolf PA. The lifetime risk of stroke. Estimates from the Framingham study. *Stroke*. 2006;37:345–350.
- He J, Gu D, Wu X, Reynolds K, Duan X, Yao C, Wang J, Chen CS, Chen J, Wildman RP, Klag MJ, Whelton PK. Major causes of death among men and women in China. *N Engl J Med*. 2005;353:1124–1134.
- The World Health Report 2004: Changing History*. Geneva, Switzerland: World Health Organization; 2004.
- Chalmers J, Todd A, Chapman N, Beilin L, Davis S, Donnan G, Frommer M, Huxley R, Lenfant C, MacMahon S, Mancia G, Mendis S, Whitworth J, Zanchetti A. International Society of Hypertension (ISH): statement on blood pressure lowering and stroke prevention. *J Hypertens*. 2003;21:651–663.
- Straus SE, Majumdar SR, McAlister FA. New evidence for stroke prevention: scientific review. *JAMA*. 2002;288:1388–1395.
- Alberts MJ, Tournier-Lasserre E. Update on the genetics of stroke and cerebrovascular disease 2004. *Stroke*. 2005;36:179–181.
- Tournier-Lasserre E. New players in the genetics of stroke. *N Engl J Med*. 2002;347:1711–1712.
- Gould DB, Phalan FC, van Mil SE, Sundberg JP, Vahedi K, Massin P, Bousser MG, Heutink P, Miner JH, Tournier-Lasserre E, John SWM. Role of COL4A1 in small-vessel disease and hemorrhagic stroke. *N Engl J Med*. 2006;354:1489–1496.
- Morgan L, Humphries SE. The genetics of stroke. *Curr Opin Lipidol*. 2005;16:193–199.
- Meschia JF. Ischemic stroke as a complex genetic disorder. *Semin Neurol*. 2006;26:49–56.
- Reynolds K, Lewis B, Nolen JDL, Kinney GL, Sathya B, He J. Alcohol consumption and the risk of stroke. A meta-analysis. *JAMA*. 2003;289:579–588.
- Baliga BS, Weinberger J. Diabetes and stroke: part one – risk factors and pathophysiology. *Curr Cardiol Rep*. 2006;8:23–28.
- Lewington S, Clarke R, Qizilbash N, Peto R, Collins R. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet*. 2002;360:1903–1913.
- Lawes CM, Rodgers A, Bennett DA, Parag V, Suh I, Ueshima H, MacMahon S. Blood pressure and cardiovascular disease in the Asia Pacific region. *J Hypertens*. 2003;21:707–716.
- Asia Pacific Cohort Studies Collaboration. Blood pressure indices and cardiovascular disease in the Asia Pacific region. A pooled analysis. *Hypertension*. 2003;42:69–75.
- Dolan E, Stanton A, Thijs L, Hinedi K, Atkins N, McClory S, Den Hond E, McCormack P, Staessen JA, O'Brien E. Superiority of ambulatory over clinic blood pressure measurement in predicting mortality: the Dublin outcome study. *Hypertension*. 2005;46:156–161.
- Ohkubo T, Asayama K, Kikuya M, Metoki H, Obara T, Saito S, Hoshi H, Hashimoto J, Totsune K, Satoh H, Imai Y. Prediction of ischaemic and haemorrhagic stroke by self-measured blood pressure at home: the Ohasama study. *Blood Press Monit*. 2004;9:315–320.
- Staessen JA, Thijs L, Fagard R, O'Brien ET, Clement D, de Leeuw PW, Mancia G, Nachev C, Palatini P, Parati G, Tuomilehto J, Webster J, for the Systolic Hypertension in Europe Trial Investigators. Predicting cardiovascular risk using conventional vs ambulatory blood pressure in older patients with systolic hypertension. *JAMA*. 1999;282:539–546.
- O'Brien E, Sheridan J, O'Malley K. Dippers and non-dippers. *Lancet*. 1988;ii:397.
- Kario K, Pickering TG, Umeda Y, Hoshida S, Hoshida Y, Morinari M, Murata M, Kuroda T, Schwartz JE, Shimada K. Morning surge in blood

- pressure as a predictor of silent and clinical cerebrovascular disease in elderly hypertensives: a prospective study. *Circulation*. 2003;107:1401–1406.
26. Metoki H, Ohkubo T, Kikuya M, Asayama K, Obara T, Hashimoto J, Totsune K, Hoshi H, Satoh H, Imai Y. Prognostic significance for stroke of a morning pressor surge and a nocturnal blood pressure decline: the Ohasama study. *Hypertension*. 2006;47:149–154.
 27. Verdecchia P, Reboldi GP, Angeli F, Schillaci G, Schwartz JE, Pickering TG, Imai Y, Ohkubo T, Kario K. Short- and long-term incidence of stroke in white-coat hypertension. *Hypertension*. 2005;45:203–208.
 28. Li Y, Wang JG, Dolan E, Gao PJ, Guo HF, Nawrot T, Stanton AV, Zhu DL, O'Brien E, Staessen JA. Ambulatory arterial stiffness index derived from 24-hour ambulatory blood pressure monitoring. *Hypertension*. 2006;47:359–364.
 29. Dolan E, Thijs L, Li Y, Atkins N, McCormack P, McClory S, O'Brien E, Staessen JA, Stanton AV. Ambulatory arterial stiffness index as a predictor of cardiovascular mortality in the Dublin Outcome Study. *Hypertension*. 2006;47:365–370.
 30. Collins R, MacMahon S. Blood pressure, antihypertensive drug treatment and the risks of stroke and of coronary heart disease. *Br Med Bull*. 1994;50:272–298.
 31. Staessen JA, Gasowski J, Wang JG, Thijs L, Den Hond E, Boissel JP, Coepe J, Ekblom T, Gueyffier F, Liu L, Kerlikowske K, Pocock S, Fagard RH. Risks of untreated and treated isolated systolic hypertension in the elderly: meta-analysis of outcome trials. *Lancet*. 2000;355:865–872.
 32. Perry HM Jr, Davis BR, Price TR, Applegate WB, Fields WS, Guralnik JM, Kuller L, Pressel S, Stamler J, Probstfield JL, for the Systolic Hypertension in the Elderly Program (SHEP) Cooperative Research Group. Effect of treating isolated systolic hypertension on the risk of developing various types of strokes. The Systolic Hypertension in the Elderly Program (SHEP). *JAMA*. 2000;284:465–471.
 33. Wang JG, Li Y. Primary and secondary prevention of stroke by antihypertensive drug treatment. *Expert Rev Neurother*. 2004;4:1023–1031.
 34. Staessen JA, Wang JG, Thijs L. Cardiovascular prevention and blood pressure reduction: a quantitative overview updated until 1 March 2003. *J Hypertens*. 2003;21:1055–1076.
 35. Staessen JA, Li Y, Thijs L, Wang JG. Blood pressure reduction and cardiovascular prevention: an update including the 2003–2004 secondary prevention trials. *Hypertens Res*. 2005;28:385–407.
 36. Staessen JA, Wang JG, Thijs L. Cardiovascular protection and blood pressure reduction: a meta-analysis. *Lancet*. 2001;358:1305–1315.
 37. Verdecchia P, Reboldi G, Angeli F, Gattobigio R, Bentivoglio M, Thijs L, Staessen JA, Porcellati C. Angiotensin-converting enzyme inhibitors and calcium channel blockers for coronary heart disease and stroke prevention. *Hypertension*. 2005;46:386–392.
 38. Dahlöf B, Sever PS, Poulter NR, Wedel H, Beevers DG, Caulfield M, Collins R, Kjeldsen SE, Kristinsson A, McInnes GT, Mehlsen J, Nieminen M, O'Brien E, Ostergren J. Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre randomised controlled trial. *Lancet*. 2005;366:895–906.
 39. Liu L, Zhao Y, Liu G, Li W, Zhang X, Zanchetti A, for the FEVER Study Group. The Felodipine Event Reduction (FEVER) Study: a randomized long-term placebo-controlled trial in Chinese hypertensive patients. *J Hypertens*. 2005;23:2157–2172.
 40. Moher D, Tsertsvadze A. Systematic reviews: when is an update an update? *Lancet*. 2006;367:881–883.
 41. Hypertension-Stroke Cooperative Study Group. Effect of antihypertensive treatment on stroke recurrence. *JAMA*. 1974;229:409–418.
 42. The Dutch TIA Trial Study Group. Trial of secondary prevention with atenolol after transient ischemic attack or nondisabling ischemic stroke. *Stroke*. 1993;24:543–548.
 43. Eriksson S, Olofsson BO, Wester PO, for the TEST study group. Atenolol in secondary prevention after stroke. *Cerebrovasc Dis*. 1995;5:21–25.
 44. PATS Collaborative Group. Post-stroke antihypertensive treatment study. A preliminary result. *Chin Med J*. 1995;108:710–717.
 45. PROGRESS Collaborative Group. Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6105 individuals with previous stroke or transient ischaemic attack. *Lancet*. 2001;358:1033–1041.
 46. Bosch J, Yusuf S, Pogue J, Sleight P, Lonn E, Rangonwala B, Davies R, Ostergren J, Probstfield J, HOPE Investigators. Use of ramipril in preventing stroke: double blind randomised trial. *BMJ*. 2002;324:699–702.
 47. Carter AB. Hypotensive therapy in stroke survivors. *Lancet*. 1970;1:485–489.
 48. The Heart Outcomes Prevention Evaluation Study Investigators. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. *N Engl J Med*. 2000;342:145–153.
 49. Rashid P, Leonardi-Bee J, Bath P. Blood pressure reduction and secondary prevention of stroke and other vascular events. A systematic review. *Stroke*. 2003;34:2741–2749.
 50. Schrader J, Luders S, Kulschewski A, Hammersen F, Plate K, Berger J, Zidek W, Dominiak P, Diener HC. Morbidity and mortality after stroke, eprosartan compared with nitrendipine for secondary prevention. Principal results of a prospective randomized controlled study (MOSES). *Stroke*. 2005;36:1218–1226.
 51. Staessen JA, Fagard R, Thijs L, Celis H, Arabidze GG, Birkenhäger WH, Bulpitt CJ, de Leeuw PW, Dollery CT, Fletcher AE, Forette F, Leonetti G, Nachev C, O'Brien ET, Rosenfeld J, Rodicio JL, Tuomilehto J, Zanchetti A, for the Systolic Hypertension in Europe (Syst-Eur) Trial Investigators. Randomised double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension. *Lancet*. 1997;350:757–764 (Correction 1997;350:1636).
 52. Dahlöf B, Devereux RB, Kjeldsen SE, Julius S, Beevers G, de Faire U, Fyhrrquist F, Ibsen H, Kristiansson K, Lederballe-Pedersen O, Lindholm LH, Nieminen MS, Omvik P, Oprial S, Wedel H, for The LIFE Study Group. Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. *Lancet*. 2002;359:995–1003.
 53. Blood Pressure Lowering Treatment Trialists' Collaboration. Effects of different blood-pressure-lowering regimens on major cardiovascular events: results of prospectively-designed overviews of randomised trials. *Lancet*. 2003;362:1527–1535.
 54. Hansson L, Hedner T, Lund-Johansen P, Kjeldsen SE, Lindholm LH, Syvertsen JO, Lanke J, de Faire U, Dahlöf B, Karlberg BE, for the NORDIL Study Group. Randomised trial of effects of calcium antagonists compared with diuretics and β -blockers on cardiovascular morbidity and mortality in hypertension: the Nordic Diltiazem (NORDIL) study. *Lancet*. 2000;356:359–365.
 55. The European Trial on Reduction of Cardiac Events With Perindopril in Stable Coronary Artery Disease Investigators. Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary heart disease: randomised double-blind, placebo-controlled, multicentre trial (the EUROPA study). *Lancet*. 2003;362:782–788.
 56. Staessen JA, Birkenhäger WH. Evidence that new hypertensives are superior to older drugs. *Lancet*. 2005;366:869–871.
 57. Teo K, Yusuf S, Sleight P, Anderson C, Mookadam F, Ramos B, Hilbrich L, Pogue J, Schumacher H. Rationale, design, and baseline characteristics of 2 large, simple, randomized trials evaluating telmisartan, ramipril, and their combination in high-risk patients: the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial/Telmisartan Randomized Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease (ONTARGET/TRANSCEND) trials. *Am Heart J*. 2004;148:52–61.
 58. Ogihara T, Matsuzaki M, Matsuoka H, Shimamoto K, Shimada K, Rakugi H, Umemoto S, Kamiya A, Suzuki N, Kumagai H, Ohashi Y, Takishita S, Abe K, Saruta T; COPE Trial Group. The combination therapy of hypertension to prevent cardiovascular events (COPE) trial: rationale and design. *Hypertens Res*. 2005;28:331–338.
 59. Editorial. Major ongoing stroke trials. *Stroke*. 2006;37:e18–e26.
 60. Carlberg B, Samuelsson O, Lindholm LH. Atenolol in hypertension: is it a wise choice? *Lancet*. 2004;364:1684–1689.
 61. Lindholm LH, Carlberg B, Samuelsson O. Should β blockers remain first choice in the treatment of primary hypertension? A meta-analysis. *Lancet*. 2005;366:1545–1553.
 62. Medical Research Council Working Party. MRC trial of treatment of mild hypertension: principal results. *BMJ*. 1985;291:97–104.
 63. Staessen J, Bulpitt C, Cattaert A, Fagard R, Vanhees L, Amery A. Secondary prevention with beta-adrenoceptor blockers in post-myocardial infarction patients. *Am Heart J*. 1982;104:1395–1399.
 64. COMMIT (Clopidogrel and Metoprolol in Myocardial Infarction Trial) collaborative group. Early intravenous then oral metoprolol in 45 852 patients with acute myocardial infarction: randomised placebo-controlled trial. *Lancet*. 2005;366:1622–1623.
 65. Editorial. Reducing the burden of stroke. *Lancet*. 2005;366:1752.
 66. Wilber JA, Barrow JG. Hypertension – a community problem. *Am J Med*. 1972;52:653–663.

67. Kearney PM, Whelton M, Reynolds K, Whelton PK, He J. Worldwide prevalence of hypertension: a systematic review. *J Hypertens*. 2004;22:11–19.
68. Wolf-Maier K, Cooper RS, Kramer H, Banegas JR, Giampaoli S, Joffres MR, Poulter N, Primatesta P, Stegmayr B, Thamm M. Hypertension treatment and control in five European countries, Canada, and the United States. *Hypertension*. 2004;43:10–17.
69. Burt VL, Cutler JA, Higgins M, Horan MJ, Labarthe D, Whelton P, Brown C, Roccella EJ. Trends in the prevalence, awareness, treatment, and control of hypertension in the adult US population. Data from the Health Examination Surveys, 1960 to 1991. *Hypertension*. 1995;26:60–69.
70. Psaty BM, Manolio TA, Smith NL, Heckbert SR, Gottdiener JS, Burke GL, Weissfeld J, Enright P, Lumley T, Powe N, Furberg C. Time trends in high blood pressure control and the use of antihypertensive medications in older adults. *Arch Intern Med*. 2002;162:2325–2332.
71. Hajjar I, Kotchen TA. Trends in prevalence, awareness, treatment, and control of hypertension in the United States, 1988–2000. *JAMA*. 2003;290:199–206.
72. Gu D, Reynolds K, Wu X, Chen J, Duan X, Muntner P, Huang G, Reynolds RF, Su S, Whelton PK, He J. Prevalence, awareness, treatment, and control of hypertension in China. *Hypertension*. 2002;40:920–927.
73. Kearney PM, Whelton M, Reynolds K, Muntner P, Whelton PK, He J. Global burden of hypertension: analysis of worldwide data. *Lancet*. 2005;365:217–223.
74. He FJ, Nowson CA, MacGregor GA. Fruit and vegetable consumption and stroke: meta-analysis of cohort studies. *Lancet*. 2006;367:320–326.
75. EL Mozaffarian D. Optimal dietary habits for the prevention of stroke. *Semin Neurol*. 2006;26:11–23.
76. Douketis JD, Sharma AM. Obesity and cardiovascular disease: pathogenic mechanisms and potential benefits of weight reduction. *Semin Vasc Med*. 2005;5:25–33.
77. Hurley SF. Short-term impact of smoking cessation on myocardial infarction and stroke hospitalisations and costs in Australia. *Med J Aust*. 2005;183:13–17.
78. Iso H, Date C, Yamamoto A, Toyoshima H, Watanabe Y, Kikuchi S, Koizumi A, Wada Y, Kondo T, Inaba Y, Tamakoshi A, the J Am Coll Cardiol Study Group. Smoking cessation and mortality from cardiovascular disease among Japanese men and women. The J Am Coll Cardiol Study. *Am J Epidemiol*. 2005;161:170–179.
79. Adams H, Adams R, Del ZG, Goldstein LB. Guidelines for the early management of patients with ischemic stroke: 2005 guidelines update a scientific statement from the Stroke Council of the American Heart Association/American Stroke Association. *Stroke*. 2005;36:916–923.
80. Willmot M, Ghadami A, Whysall B, Clarke W, Wardlaw J, Bath PM. Transdermal glyceryl trinitrate lowers blood pressure and maintains cerebral blood flow in recent stroke. *Hypertension*. 2006;47:1209–1215.
81. Howard SC, Algra A, Warlow CP, Rothwell PM. Potential consequences for recruitment, power, and external validity of requirements for additional risk factors for eligibility in randomized controlled trials in secondary prevention of stroke. *Stroke*. 2006;37:209–215.