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Haifeng Zhang, Lutgarde Thijs and Jan A. Staessen

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## 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.<sup>1,2</sup> Blood pressure is the most consistent and powerful predictor of stroke. Population mortality trends for stroke parallel those in hypertension.<sup>3,4</sup> A systolic blood pressure >115 mm Hg explains 60% of the population-attributable risk of stroke.<sup>5</sup> In the Framingham cohort,<sup>6</sup> 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,<sup>7</sup> stroke is the third cause of death only preceded by heart disease and total cancer. Two thirds of stroke deaths occur in developing nations.<sup>8</sup> 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.<sup>1</sup> 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.<sup>9,10</sup> Monogenic stroke disorders,<sup>11</sup> such as, for instance, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy,<sup>12</sup> 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,<sup>13</sup> inflammation, oxidative stress, dyslipidemia, or the generation of angiotensin II.<sup>14,15</sup> Small vessel disease of the brain underlies 20% to 30% of ischemic strokes and a larger proportion of intracerebral hemorrhages.<sup>13</sup>

#### Modifiable Risk Factors

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

However, among the modifiable risk indicators, high blood pressure has by far the largest impact.<sup>1,9</sup> 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).<sup>18</sup> 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.<sup>18</sup> 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.<sup>19,20</sup>

### Stroke Prediction From Automated Blood Pressure Measurements

Prospective observational<sup>21,22</sup> and intervention<sup>23</sup> studies consistently noticed that blood pressure recorded either by ambulatory monitoring<sup>21,23</sup> or by self-measurement<sup>22</sup> predicted cardiovascular complications, in particular, stroke, over and beyond the office blood pressure. In the Ohasama study,<sup>22</sup> 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 al<sup>24</sup> 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<sup>25,26</sup> not only substantiated these initial observations<sup>24</sup> but investigated other characteristics of the diurnal blood pressure profile as well. Kario et al<sup>25</sup> 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

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

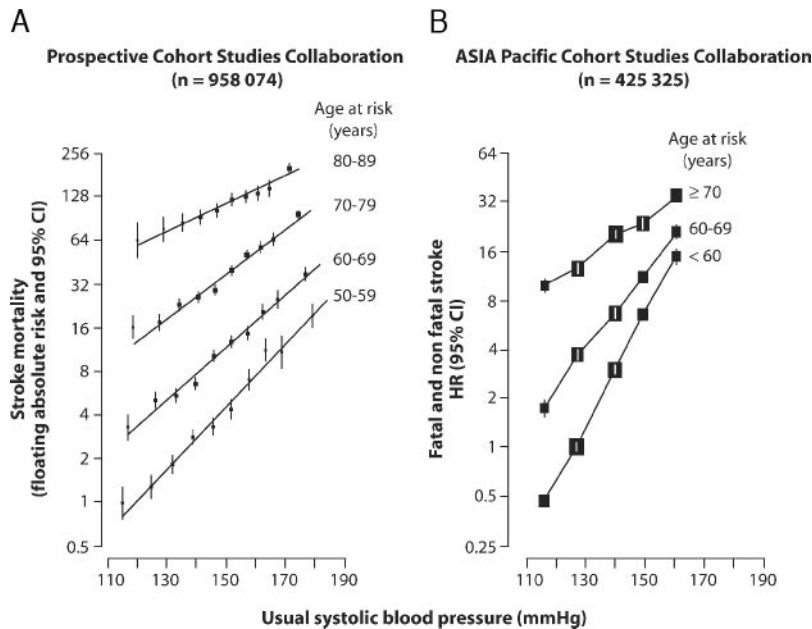
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**Figure 1.** Age-specific relations of systolic blood pressure with stroke mortality (A) in 61 cohorts (n=958 074; 70% of participants from Europe, 20% from North America or Australia, and 10% from Japan and China) and with fatal and nonfatal stroke (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.<sup>25</sup>

White-coat hypertension is a normal daytime ambulatory blood pressure in the presence of an elevated clinic blood pressure.<sup>2</sup> Masked hypertension is a raised daytime ambulatory blood pressure in subjects with normotensive values on conventional measurement at the clinic.<sup>2</sup> In a meta-analysis based on individual data from 5955 subjects,<sup>27</sup> 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.<sup>27</sup> 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.<sup>27</sup> The ambulatory arterial stiffness index, which can be readily computed from 24-hour ambulatory blood pressure recordings, reflects arterial stiffness.<sup>28</sup> In Irish hypertensive patients,<sup>29</sup> this novel index was a better predictor of fatal stroke than the 24-hour pulse pressure.

### Prevention of Stroke

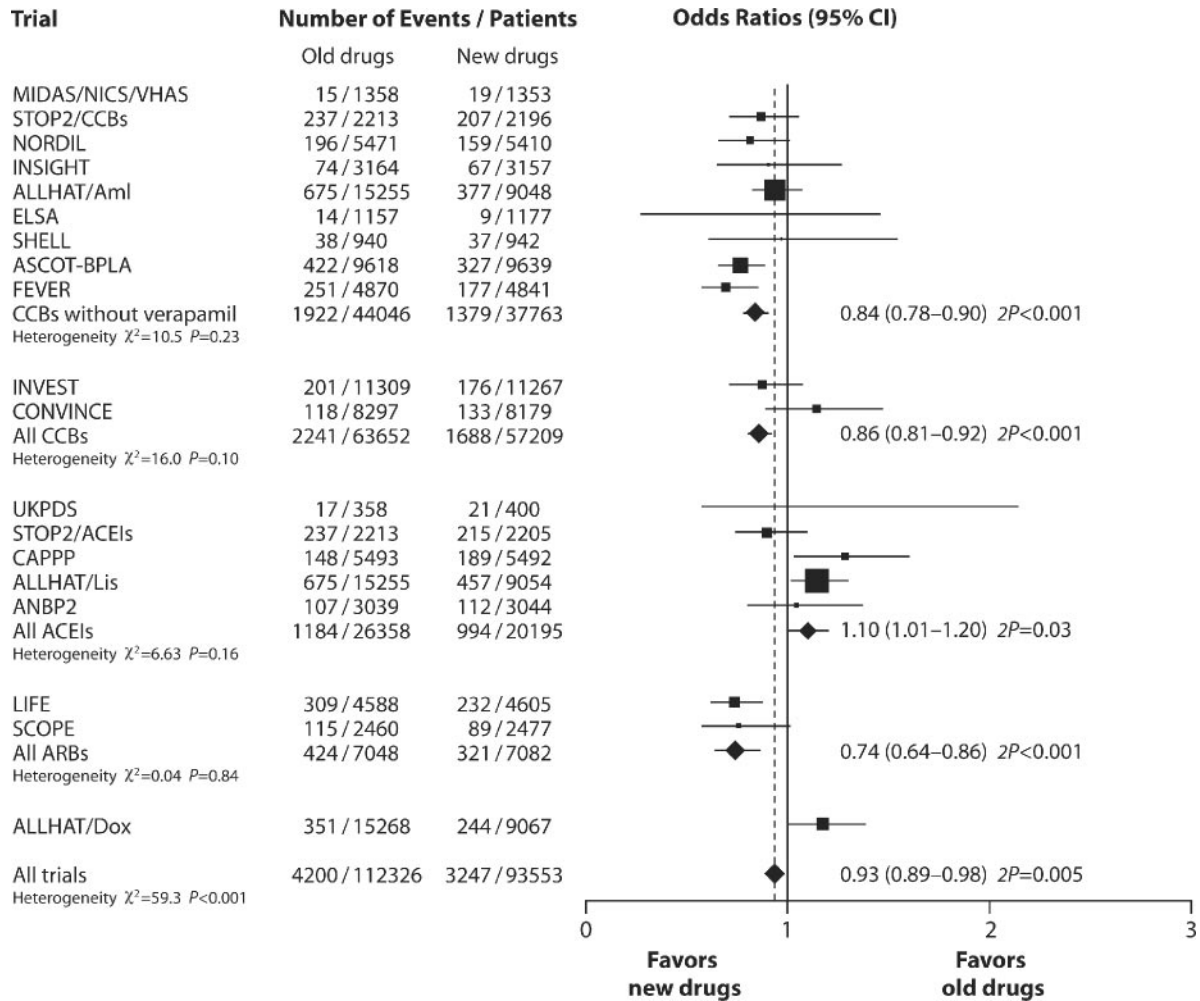
Many stroke survivors are left with cognitive, affective, and physical impairments, become dependent, and require life-long assistance with activities of daily living.<sup>1</sup> Prevention is the only possible way to curb the stroke pandemic.<sup>1</sup> This goal cannot be achieved without better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

### 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  $\approx 40\%$ .<sup>30</sup> 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<sup>31,32</sup> and Asian<sup>33</sup> patients alike.

Consecutive overviews<sup>33-37</sup> of actively controlled trials compared the incidence of stroke between patients randomly assigned to initial treatment with old drugs (diuretics and/or  $\beta$ -blockers) and those started on newer agents (calcium channel blockers [CCBs], angiotensin-converting enzyme inhibitors [ACEIs],  $\alpha$ -blockers, or angiotensin II type-1 receptor blockers [ARBs]). Because of the recent publication of 2<sup>38,39</sup> large-scale trials, we updated<sup>40</sup> our analysis.<sup>35</sup> In the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT-BPLA),<sup>38</sup> 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)<sup>39</sup> 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.<sup>39</sup> 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  $\beta$ -blockers) antihypertensive drugs. Dox indicates the  $\alpha$ -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 Trial<sup>38</sup> and the Felodipine Event Reduction Trial,<sup>39</sup> respectively. The other trial acronyms are given in references 34 and 35.

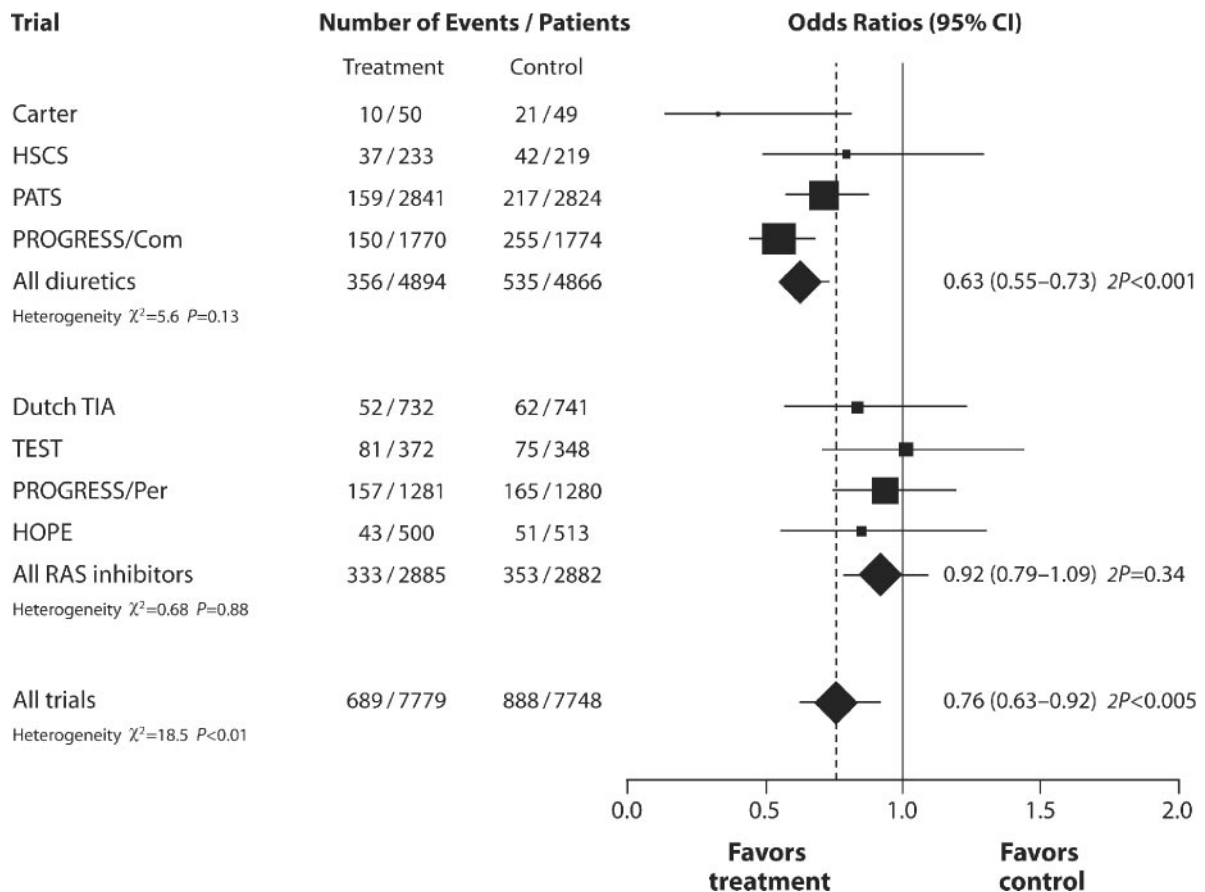
2). However, for the interpretation of these results, one should account for the blood pressure gradients between the groups randomly assigned in trials.

**Secondary Prevention**

Seven randomized, controlled trials<sup>41–47</sup> 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,<sup>41–43</sup> in which either methyldiazinide combined with deserpidine<sup>41</sup> or atenolol<sup>42,43</sup> were compared with placebo, the average reductions in blood pressure ranged from 4<sup>43</sup> to 25<sup>41</sup> mm Hg systolic and from 3<sup>42,43</sup> to 13<sup>41</sup> mm Hg diastolic. These 3 studies<sup>41–43</sup> could not confirm the significant 67% benefit on stroke recurrence ( $P=0.02$ ), as initially reported by Carter<sup>47</sup> in a much smaller trial.

In the Chinese Post-stroke Antihypertensive Treatment Study (PATS),<sup>44</sup> 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% ( $P=0.0009$ ).<sup>44</sup> The perindopril PROtection aGainst REcurrent Stroke Study (PROGRESS) included 6105 patients of predominantly white extraction but also 39% Asians.<sup>45</sup> Patients in the active treatment group received perindopril (4 mg per day) either alone or together with indapamide (2.5 mg per day).<sup>45</sup> 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%).<sup>45</sup> In the Heart Outcomes Prevention Evaluation (HOPE) trial,<sup>46,48</sup> 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



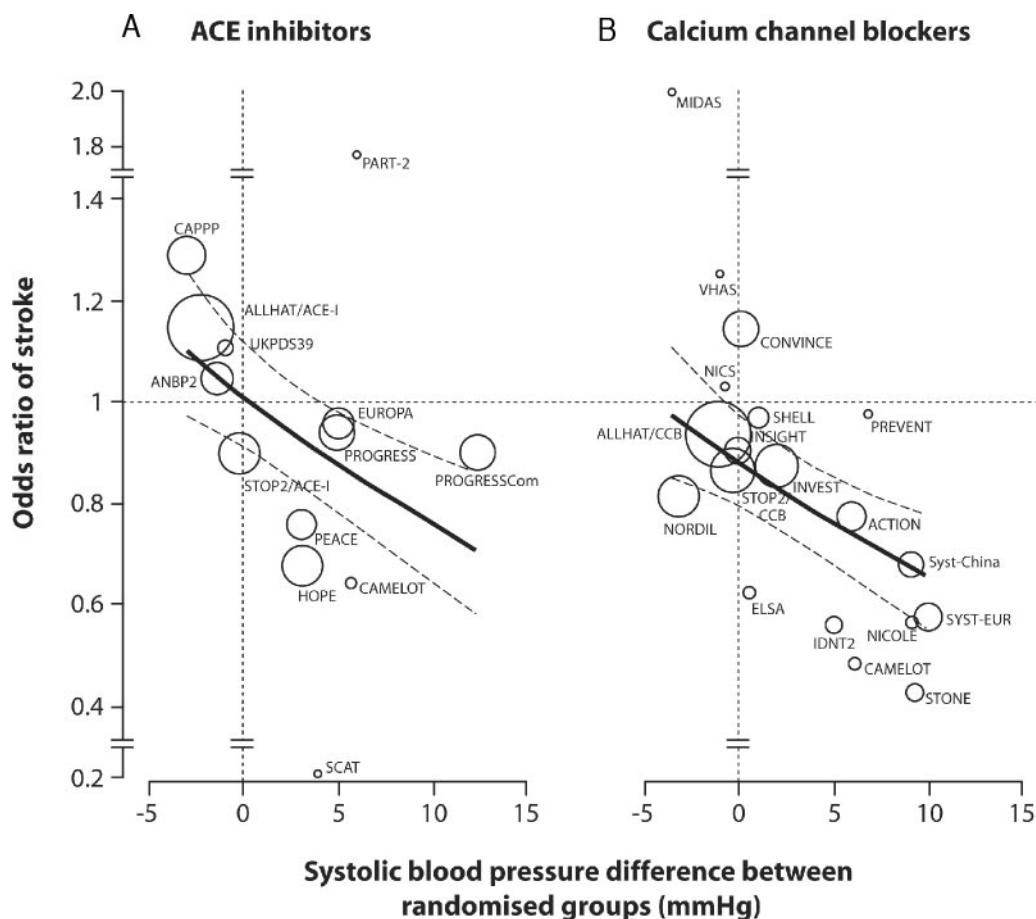
**Figure 3.** Effects of blood pressure lowering on fatal and nonfatal recurrent stroke. ■, odds ratios in individual trials with a size proportional to the inverse of the variance of the odds ratios. — and ◆, 95% CIs for individual trials and summary statistics, respectively. Pooled estimates were computed 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 trial<sup>47</sup>; the Hypertension-Stroke Cooperative Study (HSCG)<sup>41</sup>; the Dutch TIA Trial<sup>42</sup>; the Tenormin after Stroke and TIA Trial (TEST)<sup>43</sup>; PATS; PROGRESS – monotherapy (PROGRESS/Per) and combined therapy (PROGRESS/Com) arms<sup>45</sup>; and HOPE.<sup>46</sup>

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%).<sup>46</sup>

We computed pooled results (Figure 3) across the 7 secondary prevention trials on stroke recurrence,<sup>41–47</sup> updating<sup>40</sup> previous estimates.<sup>33–35,49</sup> 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<sup>41–47</sup> 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,<sup>41,44,45,47</sup> 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<sup>42,43</sup> or monotherapy with perindopril<sup>45</sup> or ramipril.<sup>46,48</sup>

In addition to these trials,<sup>41–47</sup> the Morbidity and Mortality After Stroke, Eprosartan Compared With Nitrendipine for Secondary Prevention Study (MOSES)<sup>50</sup> 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.<sup>50</sup> In comparison, in the Systolic Hypertension in Europe Trial,<sup>51</sup> 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.<sup>50</sup> 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.<sup>50</sup> 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.<sup>50</sup>

### Blood Pressure Lowering Versus Ancillary Drug Properties

Until the turn of the millennium,<sup>48,52</sup> 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.<sup>1</sup> Not surprisingly, metaregression analyses published by us<sup>34–37</sup> and other research consortia<sup>53</sup> demonstrated that, in keeping with large-scale prospective observational studies (Figure 1)<sup>18,20</sup> 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.<sup>34–37</sup>

In an update of our metaregression analysis (Figure 4),<sup>37</sup> 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.<sup>37</sup> We corroborated that blood pressure reduction was by far the most important determinant of cardiovascular outcome.<sup>34–36,53</sup> In addition, in keeping with previous analyses,<sup>34–36,53</sup> 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 ( $\approx 10\%$ ;  $P=0.028$ ).<sup>37</sup> These findings suggested that CCBs might be especially indicated for the prevention of stroke in populations at high risk, such as Asians<sup>39</sup> or older patients with isolated systolic hypertension.<sup>51</sup>

Predictions based on our metaregression model published in 2001<sup>36</sup> 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 ( $\Delta$ 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  $\beta$ -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  $2 \times 2$  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,<sup>38</sup> 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),<sup>54</sup> 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 predicted<sup>35</sup> and observed<sup>54</sup> odds ratios (1.14<sup>35</sup> versus 0.81<sup>54</sup>) were significantly different (Table). In the PROGRESS perindopril monotherapy arm<sup>45</sup> and in the European Trial on Reduction of Cardiac Events With Perindopril in Stable Coronary Artery Disease (EUROPA),<sup>55</sup> 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,<sup>38</sup> we used the relation between cardiovascular outcomes and achieved systolic pressure published in 2001<sup>36</sup> 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,<sup>56</sup> which was close to the observed 2.7-mm Hg difference.<sup>38</sup> The predicted<sup>56</sup> and observed<sup>38</sup> relative risk reductions for stroke (0.78<sup>56</sup> versus 0.77<sup>38</sup>) 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.<sup>57-59</sup>

### The Issue of $\beta$ -Blockers

Recently published quantitative overviews<sup>60,61</sup> initiated a debate on whether  $\beta$ -blockers should remain first choice in the treatment of essential hypertension, in particular for the prevention of stroke. In their first run, the Swedish group<sup>60</sup> 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,<sup>61</sup> the same investigators broadened the scope of their review beyond atenolol. When all  $\beta$ -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,  $\beta$ -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  $\beta$ -blockers as first-line treatment of essential hypertension. The Swedish investigators<sup>60,61</sup> did not account for the differences in blood pressure between randomized groups or the efficacy of  $\beta$ -blockade based on differences in heart rate. In the trial conducted by the Medical Research Council,<sup>62</sup> investigators withdrew a substantial number of patients randomly assigned to propranolol because of bradycardia, a sign indicating effective  $\beta$ -blockade. The Swedish

investigators<sup>60,61</sup> did not consider the large body of evidence available from secondary prevention trials of myocardial infarction, published >2 decennia ago<sup>63</sup> and confirmed recently.<sup>64</sup> If not for stroke,  $\beta$ -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.<sup>63,64</sup> Remarkably, in the EUROPA trial,<sup>55</sup> perindopril only offered protection against myocardial infarction in patients already on  $\beta$ -blockers.

### Perspectives and Conclusions

In 2005, 56 million people died, 5.6 million of them from a stroke.<sup>65</sup> By 2015, this figure will rise to 6.4 million stroke deaths a year, largely because of the worldwide aging populations.<sup>65</sup> About a similar number of people will survive a stroke and remain disabled for the remainder of their lifespan.<sup>1</sup> 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 halves<sup>66</sup> still exists, and the fraction of hypertensive patients with properly controlled blood pressure ranges from  $\approx 1\%$  to 40%.<sup>67,68</sup> The National Health and Nutrition and Examination Survey<sup>69</sup> 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.<sup>70,71</sup> 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.<sup>72</sup>

The worldwide prevalence and total number of adults with hypertension in 2025 will be 29% and 1.56 billion, respectively.<sup>73</sup> 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.<sup>18,19</sup> Population-based strategies with the goal to produce a downward shift in the blood pressure distribution along with interventions to improve diets<sup>74,75</sup> and to reduce overweight<sup>76</sup> and smoking<sup>77,78</sup> 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.<sup>79,80</sup> 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.<sup>81</sup>

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