Blood Pressure Reduction and Secondary Prevention of Stroke and Other Vascular Events
A Systematic Review

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Background—High blood pressure is a risk factor for stroke recurrence. We assessed the effectiveness of lowering blood pressure in preventing recurrent vascular events in patients with previous stroke or transient ischemic attack.

Summary of Review—We performed a systematic review and meta-regression of completed randomized controlled trials that investigated the effect of lowering blood pressure on recurrent vascular events in patients with prior ischemic or hemorrhagic stroke or transient ischemic attack. Trials were identified from searches of 3 electronic databases (Cochrane Library, EMBASE, MEDLINE). Seven randomized controlled trials, with 8 comparison groups, were included. Lowering blood pressure or treating hypertension with a variety of antihypertensive agents reduced stroke (odds ratio [OR], 0.76; 95% CI, 0.63 to 0.92), nonfatal stroke (OR, 0.79; 95% CI, 0.65 to 0.95), myocardial infarction (OR, 0.79; 95% CI, 0.63 to 0.98), and total vascular events (OR, 0.79; 95% CI, 0.66 to 0.95). No effect was seen on vascular or all-cause mortality. Heterogeneity was present for several outcomes and was partly related to the class of antihypertensive drugs used; angiotensin-converting enzyme inhibitors and diuretics separately, and especially together, reduced vascular events, while β-receptor antagonists had no discernable effect. The reduction in stroke was related to the difference in systolic blood pressure between treatment and control groups ($P=0.002$).

Conclusions—Evidence from randomized controlled trials supports the use of antihypertensive agents in lowering blood pressure for the prevention of vascular events in patients with previous stroke or transient ischemic attack. Vascular prevention is associated positively with the magnitude by which blood pressure is reduced. (Stroke. 2003;34:2741-2749.)

Key Words: adrenergic beta-antagonists □ angiotensin-converting enzyme inhibitors □ blood pressure □ cardiovascular diseases, prevention and control □ diuretics □ myocardial infarction □ stroke
words: blood pressure lowering, blood pressure reduction, stroke, transient ischemic attack, antihypertensive, hypertension, randomized controlled trial, and controlled clinical trial. The reference lists of earlier relevant systematic reviews, a–k a nonsystematic review, l and identified trial publications were also searched. Information from pharmaceutical companies was sought as well.

We included nonconfounded RCTs that determined the effect of lowering BP or treatment of hypertension in patients with prior stroke (>14 days after ictus) or TIA on the development of further vascular events. Studies assessing the effect of lowering BP during the acute phase of stroke (which we have assessed in a separate meta-analysis l) and those involving <10% of patients with previous stroke or TIA were excluded. Confounded trials (in which ≥2 active treatments were compared in the absence of a control arm) were also excluded.

BP and Vascular Outcomes

The 3 authors extracted data independently from identified publications with respect to patient numbers, stroke subtype, time from stroke to enrollment, history of previous hypertension, type of antihypertensive treatment, baseline BP, difference in BP between treatment and control groups, and follow-up period. Outcome events included stroke (all, fatal, nonfatal), myocardial infarction (MI) (all), total vascular events (combined stroke, MI, and vascular death), and mortality (all-cause, vascular). We contacted trialists to obtain results for patients with prior stroke or TIA in which studies also included patients with nonstroke vascular disease (eg, ischemic heart disease [IHD] or peripheral vascular disease).

Statistical Analysis

Data were double entered (P.R., J.L.-B.) into the Cochrane Collaboration Review Manager package (RevMan, version 4.1) and cross-checked. Odds ratios (ORs) and 95% CIs were calculated with random effects models since we expected heterogeneity to exist because of differences between the trials, eg, type of included patients (hypertensive versus normotensive), drug class, and length of follow-up. Heterogeneity was assessed with a $\chi^2$ test. We explored the causes of heterogeneity using sensitivity analyses based on trial quality (judged on multiple criteria: status of blinding, randomization, completeness of follow-up, and whether placebo-controlled) and subgroup analyses based on drug class, history of hypertension, and stroke type.

Meta-regression was performed with the “metareg” function in the Stata (STATA Corp) statistical package. Publication bias was assessed with Begg’s funnel plot and Egger’s test l1 (Stata function “metabias”) on outcome data for stroke and all vascular events. Significance was set at $P<0.05$.

Results

Trials

Seven RCTs fulfilled the inclusion criteria (Table 1, Figure 1), 12–18 each of which had been published. Seventeen studies were excluded on the grounds that they were either not randomized, were largely trials of primary prevention, only included a small number of patients with prior cerebrovascular disease, or were bloodstream infections.

Table 1. Characteristics of Included Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Quality</th>
<th>Drug (daily dose); Control</th>
<th>Other Antihypertensive Therapy, %</th>
<th>Stroke Type, %</th>
<th>Subjects (Centers)</th>
<th>Age (y/Male, %)</th>
<th>Time From Stroke to Trial, mo</th>
<th>Follow-Up Interval, years</th>
<th>Prior Hypertension, %</th>
<th>Baseline BP, mm Hg</th>
<th>Change in BP, mm Hg (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carter 1970 b, B</td>
<td></td>
<td>Thiazide diuretic mg: methyldopa (750 mg); control</td>
<td>?</td>
<td>“IS” 100</td>
<td>99 (1)</td>
<td>7/58</td>
<td>&gt;0.5</td>
<td>2–5</td>
<td>100</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>HSCSG 1974 a, A</td>
<td></td>
<td>Deserpidine 1 mg and methylclohiazide 10 mg; placebo</td>
<td>0</td>
<td>IS/ICH 96 TIA 4</td>
<td>452 (10)</td>
<td>59/60</td>
<td>&lt;12</td>
<td>2.8</td>
<td>100</td>
<td>167/100</td>
<td>25.0/12.3 (15/12%)</td>
</tr>
<tr>
<td>Dutch TIA 1993 a, A</td>
<td></td>
<td>Atenolol (50 mg); placebo</td>
<td>?</td>
<td>IS 66 TIA 34</td>
<td>1473 (56)</td>
<td>~66/64</td>
<td>&lt;3*</td>
<td>2.6</td>
<td>29</td>
<td>157/91</td>
<td>5.8/2.9 (4/3%)</td>
</tr>
<tr>
<td>PATS 1995 a, A</td>
<td></td>
<td>Indapamide (2.5 mg); placebo</td>
<td>0</td>
<td>IS 71 ICH 14 TIA 12 SARI 2</td>
<td>5665 (44)</td>
<td>60/72</td>
<td>14</td>
<td>2</td>
<td>84</td>
<td>154/83</td>
<td>6.2/2.9 (4/3%)</td>
</tr>
<tr>
<td>TEST 1995 a, A</td>
<td></td>
<td>Atenolol ? mg; placebo</td>
<td>?</td>
<td>IS/ICH 67 TIA 20</td>
<td>720 (21)</td>
<td>70/60</td>
<td>&lt;0.75</td>
<td>2.5</td>
<td>100</td>
<td>161/88</td>
<td>4/3 (2/3%)</td>
</tr>
<tr>
<td>HOPE 2000 a, A</td>
<td></td>
<td>Ramipril; placebo</td>
<td>64†</td>
<td>“Stroke” &amp; TIA 100</td>
<td>1013 (267†)</td>
<td>66/73†</td>
<td>&gt;1</td>
<td>5†</td>
<td>47†</td>
<td>139/79†</td>
<td>3.3/1.4† (2/2%)</td>
</tr>
<tr>
<td>PROGRESS 2001 a, A</td>
<td></td>
<td>Perindopril 4 mg; placebo</td>
<td>51</td>
<td>IS 70 ICH 11 TIA 23</td>
<td>2561 (172)</td>
<td>65/68</td>
<td>0.5–60</td>
<td>4.1</td>
<td>40</td>
<td>144/84</td>
<td>4.9/2.5 (3/3%)</td>
</tr>
<tr>
<td>PROGRESS 2001 a, A</td>
<td></td>
<td>Perindopril 4 mg + indapamide 2.5 mg; double-placebo</td>
<td>50</td>
<td>IS 71 ICH 11 TIA 22</td>
<td>3544 (172)</td>
<td>63/71</td>
<td>0.5–60</td>
<td>4.1</td>
<td>54</td>
<td>149/87</td>
<td>12.3/5.0 (8/6%)</td>
</tr>
</tbody>
</table>

Trial quality judged as A, true randomization and allocation concealed; B, process of randomization not given, concealment of allocation unclear. Blood pressure: given as systolic/diastolic; ICH indicates intracerebral hemorrhage; IS, ischemic stroke; TIA, transient ischemic attack.

*22% of patients recruited within 1 week of stroke onset.
†Data relate to whole trial and not just subgroup of patients with prior cerebrovascular disease.
‡Data reported in a substudy.

Figure 1. Flow diagram of RCTs selected for inclusion in the systematic review of BP reduction and the secondary prevention of stroke.
lar disease, were ongoing or planned, and/or were confounded (ie, there was no control inactive group) (Table 2).

The combined sample size was 15 527 (Table 1), with two thirds of the data coming from 2 studies, Post-Stroke Antihypertensive Treatment Study (PATS) and Perindopril Protection Against Recurrent Stroke Study (PROGRESS).14,17 The 7 trials had recruited patients with ischemic stroke, primary intracerebral hemorrhage, and TIA. The average time from stroke onset to randomization ranged from 3 weeks to 14 months, and patients were followed for a period of 2 to 5 years (Table 1). Three RCTs limited recruitment to patients with high BP12,15,18; the remaining trials entered patients irrespective of their baseline BP. Antihypertensive medications were discontinued before randomization for 2 RCTs.12,14 Mean baseline BPs varied from 139 to 167/79 to 100 mm Hg. Three classes of pharmacological agents were used to lower BP: β-receptor antagonists (atenolol), diuretics (indapamide, methyclothiazide), and angiotensin-converting enzyme (ACE) inhibitors (perindopril, ramipril); 2 older trials used mixed treatment and included a centrally acting drug (methylodopa) or Rauwolfia alkaloid (deserpidine).12,18 No relevant trials involving nonpharmacological interventions (eg, salt restriction), α-receptor antagonists, angiotensin receptor antagonists, or calcium channel blockers were identified.

Blood Pressure

Treatment generally caused small end-of-trial reductions of systolic and diastolic BP (<10/<5 mm Hg) compared with control, although the Hypertension-Stroke Cooperative Study Group (HSCSG)12 was an exception in which the difference in BP between treated and control groups was 25/12 mm Hg (Table 1). The reported fall in BP was small across the Heart Outcome Prevention Evaluation (HOPE) trial (3/1 mm Hg)16,19 and is likely to be an underestimate since treatment was given in the evening and BP was measured the next day. Furthermore, a small substudy of HOPE involving patients with peripheral arterial disease reported much larger falls of ambulatory BP (10/4 mm Hg over 24 hours, 17/8 mm Hg overnight) in the ramipril-treated group.20

### Vascular Outcomes

Stroke events were almost 3-fold more frequent than MI (control group rates: 11.5% versus 4%) over the follow-up period of the studies (up to 5 years). Treatment with antihypertensive therapy was associated with significant reductions of between one fifth and one quarter in stroke, nonfatal stroke, MI, and combined vascular events (Table 3, Figure 2). A nonsignificant reduction in fatal stroke was also seen, similarly of 24%; the low number of events probably explains the lack of statistical significance in this latter analysis. Sensitivity analyses based on inclusion of studies of A quality (Table 1) alone did not suggest any substantial effect of this factor on the results. No publication bias was apparent on visual inspection of funnel plots or Egger’s test for the outcomes of stroke and vascular events.

Heterogeneity in results was present statistically for stroke and combined vascular events and was graphically visible for all outcomes (Table 3, Figure 2); this heterogeneity appeared to be related to varying effectiveness of the different drug classes (Table 4). While β-receptor antagonists did not significantly influence any outcome, diuretics reduced stroke

### Table 2. Characteristics of Excluded Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Antihypertensive Agent</th>
<th>Stroke Subjects, n (% of total)</th>
<th>Reason for Exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marshall15</td>
<td>1964</td>
<td>Not specified</td>
<td>42 (100)</td>
<td>Nonrandomized secondary prevention study</td>
</tr>
<tr>
<td>HDFP16</td>
<td>1979</td>
<td>Not specified</td>
<td>274 (2.2)</td>
<td>Nonrandomized primary prevention study</td>
</tr>
<tr>
<td>MRFIT37</td>
<td>1982</td>
<td>Not specified</td>
<td>17 (0.2)</td>
<td>Nonrandomized primary prevention study</td>
</tr>
<tr>
<td>EWPHE38</td>
<td>1985</td>
<td>Triamterene + hydrochlorothiazide (diuretic) ± methylodopa (centrally acting)</td>
<td>63 (5.0)</td>
<td>Primary prevention RCT</td>
</tr>
<tr>
<td>Coope39</td>
<td>1986</td>
<td>Atenolol (β-RA) or bendrofluazide (diuretic)</td>
<td>17 (2.2)</td>
<td>Primary prevention RCT</td>
</tr>
<tr>
<td>Kinnander40</td>
<td>1987</td>
<td>β-RA</td>
<td>120 (100)</td>
<td>Nonrandomized secondary prevention study</td>
</tr>
<tr>
<td>SHEP41</td>
<td>1991</td>
<td>Chlorthalidone (diuretic) ± atenolol (β-RA)</td>
<td>99 (2.1)</td>
<td>Primary prevention RCT</td>
</tr>
<tr>
<td>STOP42</td>
<td>1996</td>
<td>ACE-I or CCB vs β-RA or diuretic</td>
<td>66 (4.2)</td>
<td>Primary prevention RCT (confounded/no control group)</td>
</tr>
<tr>
<td>Azuma43</td>
<td>1997</td>
<td>Acebutolol (β-RA) vs captopril (ACE-I) vs nifedipine (CCB)</td>
<td>44 (100)</td>
<td>Nonrandomized secondary prevention study</td>
</tr>
<tr>
<td>CAPPP44</td>
<td>1999</td>
<td>Captopril (ACE-I) vs diuretic or β-RA</td>
<td>167 (1.5)</td>
<td>Primary prevention RCT (confounded/no control group)</td>
</tr>
<tr>
<td>STOP 246</td>
<td>1999</td>
<td>β-RA or diuretic vs ACE-I vs CCB</td>
<td>258 (3.9)</td>
<td>Primary prevention RCT (confounded/no control group)</td>
</tr>
<tr>
<td>NORDIL46</td>
<td>2000</td>
<td>Diltiazem (CCB) vs β-RA or diuretic</td>
<td>162 (1.5)</td>
<td>Primary prevention RCT (confounded/no control group)</td>
</tr>
<tr>
<td>LIFE47</td>
<td>2002</td>
<td>Losartan (ARA) vs atenolol (β-RA)</td>
<td>728 (7.9)</td>
<td>Primary prevention RCT (confounded/no control group)</td>
</tr>
<tr>
<td>MOSES44</td>
<td>2002</td>
<td>Eprosartan (ARA) vs nifedipine (CCB)</td>
<td>?</td>
<td>Ongoing secondary prevention RCT (confounded/no control group)</td>
</tr>
<tr>
<td>ONTARGET</td>
<td>2002</td>
<td>Telmisartan vs telmisartan + ramipril vs telmisartan</td>
<td>23 400 (7)</td>
<td>Ongoing secondary prevention RCT</td>
</tr>
<tr>
<td>TRANSEND</td>
<td>2002</td>
<td>Telmisartan vs placebo</td>
<td>5 000 (7)</td>
<td>Ongoing secondary prevention RCT</td>
</tr>
<tr>
<td>ProFESS</td>
<td>2003</td>
<td>Telmisartan vs placebo</td>
<td>15 500 (100)</td>
<td>Planned secondary prevention RCT, starts late 2003</td>
</tr>
</tbody>
</table>

ACE-I indicates angiotensin converting enzyme inhibitor; ARA, angiotensin receptor antagonist; β-RA, β-receptor antagonist; CCB, calcium channel blocker; RCT, randomized controlled trial.
ACE inhibitors did not alter stroke rates but reduced MI and all vascular events by 26% (significant) and 17% (nonsignificant), respectively (Table 4). However, the most potent effects were seen with the combination of diuretic and ACE inhibitors in which stroke, MI, and all vascular events were each reduced by 40% to 45%; nonsignificant reductions in fatal stroke and total death were also observed.

The 2 trials involving a β-receptor antagonist recruited some patients during the acute phase of stroke (Table 1). Since early treatment with β-receptor antagonists may be
associated with a poor outcome,\textsuperscript{21} we assessed the effect of lowering BP with agents other than \(\beta\)-receptor antagonists (ie, diuretics, ACE inhibitors, or their combination) in a post hoc analysis (Table 4). The positive effects of lowering BP on subsequent stroke, MI, and vascular events were each enhanced by removal of the \(\beta\)-receptor antagonist trials.

Trials including patients irrespective of their BP status found significant reductions in stroke and all vascular events (Table 4). Nonsignificant reductions in these outcomes (with comparable ORs) were also apparent for trials that limited recruitment to patients with prior hypertension, although the numbers of patients and events in these studies were relatively small. Most trials included patients with either ischemic or hemorrhagic stroke or TIA, and these also found significant reductions in stroke and all vascular events. Only 2 trials limited recruitment to ischemic stroke, and these were small; a nonsignificant reduction in stroke, but not all vascular events, was apparent (Table 4).

**Outcome and BP**

The relationship between outcomes (using OR) and difference in systolic BP was assessed by meta-regression. Reduction in stroke was related nonlinearly (second-order quadratic function) to the difference in systolic BP between the active and control groups whether the HOPE ambulatory systolic BP data (\(P=0.004\)) or office systolic BP data (\(P=0.002\)) were used; the relationship between vascular events and difference in systolic BP was significant with the HOPE ambulatory systolic BP data (\(P=0.003\)) but not for office systolic BP (\(P=0.24\)).

**Discussion**

While the primary prevention of stroke through the treatment of hypertension is well established, the issue of lowering BP after a cerebrovascular event has been uncertain, particularly since this might worsen cerebral perfusion if autoregulation remains chronically damaged or severe carotid artery stenosis is present. Several trials addressing this question have been completed recently, and we have systematically reviewed the available world literature. In contrast to primary prevention studies in which hypertensive patients were studied, the majority of these secondary prevention studies recruited patients irrespective of their BP. Overall, lowering BP was associated with significant reductions in stroke, nonfatal stroke, MI, and total vascular events; a nonsignificant benefit was also seen for fatal stroke, while overall mortality was not altered.

These results were obtained in patients with prior cerebrovascular disease alone, and our meta-analysis differs from some others\textsuperscript{5,6} (but not all\textsuperscript{7,8}) in which patients with other vascular disease, especially IHD, were included. Although IHD and cerebrovascular disease share many features qualitatively, they differ quantitatively in several respects, and we consider it inappropriate to mix patients with different forms of vascular disease when assessing the effects of risk factor modification on recurrent events in a single vascular condition. The differences between IHD and stroke can be summarized as follows. First, patients have different demographic profiles; those with stroke are, on average, 10 years older and are more likely to be female. Second, the pathologies differ; patients with MI tend to have a single pathology (coronary atherothrombosis), while those with cerebrovascular disease have one of a variety of pathologies (hemorrhage, large-artery atherothromboembolism, cardioembolism, small-vessel disease). Third, risk factors and their response to treatment vary: hypercholesterolemia is quantitatively more important for IHD, while hypertension is the major modifiable factor for stroke. Finally, the presence of carotid atherosclerosis could negate the potentially beneficial effects of lowering BP if cerebral perfusion were to fall, thereby causing strokes of “hemodynamic” type; confounding effects such as this would be masked in analyses involving patients with other types of vascular disease.

### Table 4. Effect of Drug Class, Prior Blood Pressure Status and Stroke Type on Stroke, Myocardial Infarction, and All Vascular Events

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Stroke, All Trials/Subjects</th>
<th>OR (95% CI)</th>
<th>MI, All Trials/Subjects</th>
<th>OR (95% CI)</th>
<th>Vascular Events, All Trials/Subjects</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All trials</td>
<td>7/15 527</td>
<td>0.76 (0.63–0.92)</td>
<td>6/15 428</td>
<td>0.79 (0.63–0.98)</td>
<td>6/15 428</td>
<td>0.79 (0.66–0.95)</td>
</tr>
<tr>
<td>Drug class</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE-I</td>
<td>2/3574</td>
<td>0.93 (0.75–1.14)</td>
<td>2/3574</td>
<td>0.74 (0.56–0.98)</td>
<td>2/3574</td>
<td>0.83 (0.61–1.13)</td>
</tr>
<tr>
<td>(\beta)-RA</td>
<td>2/2193</td>
<td>0.93 (0.72–1.20)</td>
<td>2/2193</td>
<td>0.94 (0.60–1.45)</td>
<td>2/2193</td>
<td>1.01 (0.81–1.27)</td>
</tr>
<tr>
<td>Diuretic</td>
<td>3/6216</td>
<td>0.68 (0.50–0.92)</td>
<td>3/6216</td>
<td>1.06 (0.63–1.78)</td>
<td>2/6117</td>
<td>0.75 (0.63–0.90)</td>
</tr>
<tr>
<td>Diuretic and ACE-I</td>
<td>1/3544</td>
<td>0.55 (0.44–0.68)</td>
<td>1/3544</td>
<td>0.55 (0.30–0.79)</td>
<td>1/3544</td>
<td>0.57 (0.48–0.68)</td>
</tr>
<tr>
<td>Non (\beta)-RA</td>
<td>5/13 334</td>
<td>0.71 (0.57–0.90)</td>
<td>4/13 235</td>
<td>0.72 (0.57–0.92)</td>
<td>4/13 235</td>
<td>0.73 (0.60–0.89)</td>
</tr>
<tr>
<td>Baseline BP</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High blood pressure</td>
<td>3/1271</td>
<td>0.74 (0.45–1.22)</td>
<td>...</td>
<td>...</td>
<td>2/1172</td>
<td>0.85 (0.60–1.19)</td>
</tr>
<tr>
<td>Any</td>
<td>4/14 256</td>
<td>0.75 (0.60–0.94)</td>
<td>...</td>
<td>...</td>
<td>4/14 256</td>
<td>0.78 (0.63–0.97)</td>
</tr>
<tr>
<td>Stroke type</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>2/1572</td>
<td>0.58 (0.24–1.40)</td>
<td>...</td>
<td>...</td>
<td>1/1473</td>
<td>1.04 (0.77–1.41)</td>
</tr>
<tr>
<td>All stroke</td>
<td>5/13 955</td>
<td>0.78 (0.63–0.96)</td>
<td>...</td>
<td>...</td>
<td>5/13 955</td>
<td>0.76 (0.63–0.92)</td>
</tr>
</tbody>
</table>

Odds ratio (OR) and 95% confidence intervals (95% CI) determined using a random effects model. Heterogeneity was not present in any subgroup analysis. ACE-I indicates angiotensin converting enzyme inhibitor; \(\beta\)-RA, \(\beta\)-adrenergic receptor antagonists.
Considerable heterogeneity existed within the aforementioned results, due in part to significant differential effects between drug classes: β-receptor antagonists had no effect on any outcome; diuretics significantly reduced stroke and total vascular events; ACE inhibitors significantly reduced MI; and the combination of an ACE inhibitor and diuretic reduced stroke, MI, and combined vascular events. It must be stated that the data, although internally consistent, are limited by relative small numbers of trials, patients, and events for each drug class. This is especially true for β-receptor antagonists, for which the findings might be falsely neutral (type II error).

However, 2 arguments support the hypothesis that β-receptor antagonist are not particularly effective after stroke when given as used in the trials. First, they did not reduce BP proportionately by as much as the other drugs classes (β-receptor antagonist, 3%; ACE inhibitor, 4%; diuretic, 5%; combined ACE inhibitor/diuretic, 7%). Second, both trials of these agents (Dutch TIA, TEST [Tenormin after Stroke and TIA]) recruited patients relatively early after stroke (83% were enrolled within 1 month of stroke/TIA), which might have led to a lessening of benefit since the use of atenolol (or propranolol) in the treatment of acute stroke was found to worsen outcome in a separate trial.21 The explanation for this observation in acute stroke is unclear, but β-receptor antagonists reduce cardiac output, and this could reduce perfusion, leading to infarct extension and recurrent events. The effects of antihypertensive agents in reducing recurrent stroke, MI, and all vascular events were enhanced when data from trials of β-receptor antagonists were excluded. That diuretics did not reduce MI reflects, in part, that it was far less common than stroke (555 versus 1577 events), and therefore the trials were underpowered for this outcome. The low rate of MI is partly due to the PATS trial, which only included Chinese patients, an ethnic group in which MI is less common. These differential effects between drug classes contrast with primary prevention, in which ACE inhibitors, β-receptor antagonists, calcium channel blockers, and diuretics are all broadly comparable in their efficacy.22 They also contrast with preliminary evidence in acute stroke in which treatment with calcium channel blockers or β-receptor antagonists was associated with a neutral or detrimental effect,21 while an angiotensin receptor antagonist appeared to improve outcome.23

The mechanisms by which antihypertensive therapy reduces the risk of recurrent vascular events are hotly debated. Epidemiologically, a reduction in diastolic BP of 5 mm Hg is associated with one third lower risk of stroke.3 Overall, the 7 trials reported a reduction in diastolic BP of somewhat less than 5 mm Hg, and the reduction in stroke was also less than one third. However, we observed a significant association between the BP treatment effect and stroke recurrence or vascular events, whether BP data were taken from a small substudy of HOPE using ambulatory BP monitoring20 or the office BP data of the whole trial.16,19 (We believe that it is appropriate to test the data separately since the latter measures are probably an underestimate because they were measured approximately 12 to 18 hours after the evening dose of ramipril was taken.) Hence, it is likely that much of the reduction in stroke events was simply related to the magnitude of BP reduction, an assertion supported by the PROGRESS trial, in which dual therapy was superior to monotherapy in lowering both BP and stroke risk.17 This conclusion agrees with that made for primary prevention trials.5 Nevertheless, non–BP-related mechanisms may also be important. HOPE was undertaken in the belief that ACE inhibitors have a vascular protective effect in addition to their antihypertensive mechanism16; for example, ACE inhibitors do not alter or “paralyze” cerebral autoregulation and improve endothelial dysfunction in contrast to some other antihypertensive classes. While this may be true, most antihypertensive drug classes are multimodal in nature,23 having antiplatelet, anti–smooth muscle, and/or endothelial-protective effects; for example, α-receptor antagonists, β-receptor antagonists, and calcium channel blockers each have mild antiplatelet activity.26 In reality, it is likely that both BP-dependent and -independent effects are important and that these may be important differentially for various outcomes; for example, lowering BP is probably more important in the prevention of stroke, while vascular protection may be more relevant for MI.

**Strengths and Weaknesses**

Our analyses are not ideal in several respects. First, trial-level data rather than individual patient data were assessed since the latter were not available to us. Analyses based on individual patient data are generally superior27 and also allow subgroup analyses to be performed. It is also possible to include subsets of data from trials in which nonstroke patients were enrolled, ie, from some of the trials identified in Table 2. This approach has been used previously by the Individual Data Analysis of Antihypertensive Intervention Trial (INDANA) collaboration.7 Second, we could not assess the effect of lowering BP in patients with different types of cerebrovascular disease (ischemic stroke, hemorrhagic stroke, TIA) or on particular types of recurrent stroke (ischemic or hemorrhagic stroke) since most trials did not report these data separately. In this respect, the PROGRESS trial found that perindopril-based therapy was especially effective in reducing the risk of recurrence in those with prior hemorrhagic stroke and in preventing subsequent hemorrhagic stroke.13 Third, data were not available from each trial on all the chosen outcomes.

**Implications and Future Research**

We believe that the results of this systematic review support the widespread use of antihypertensive therapy in patients with previous stroke or TIA. Nevertheless, a number of caveats are important. First, treatment should be initiated at least 1 week after the onset of stroke, a strategy that replicates the trial protocols. The management of BP immediately after stroke remains controversial because its lowering, at least in theory, could reduce cerebral perfusion and worsen outcome since autoregulation is damaged28; several ongoing trials are investigating this question.10,20,30 Second, treatment should probably start with a diuretic and/or ACE inhibitor rather than other drug classes for which data are either absent or neutral. The decision of which drugs within these classes should be used lies with the responsible physician, but positive data...
exist for indapamide (diuretic) and perindopril and ramipril (ACE inhibitors). The combination of a diuretic and ACE inhibitor might be chosen since this appears to give the largest effect on BP and vascular events, although this statement is based on the findings of a single trial.17 Drugs from other classes could then be added if BP remains high, for example, above levels such as 140/85 mm Hg (or 130/80 mm Hg in diabetics), as recommended in primary prevention.31 Third, patients may be treated irrespective of their BP, thereby benefiting normotensive subjects as well as those with overt hypertension. Fourth, treatment may be continued for several years since the trials followed patients for up to 5 years. Fifth, treatment may be started in addition to existing antihypertensive medication, as occurred in several of the trials. Last, a mega-analysis (individual patient data meta-analysis) of the existing trial data would allow the effect of lowering BP in subgroups to be studied, as has been done previously on data from the older trials.4,7

Ultimately, the decision to treat a specific patient will depend on many other factors, including the degree to which they have recovered from their stroke (the trials largely restricted recruitment to independent patients) and the presence of other diseases in which certain drug classes are specifically indicated (eg, ACE inhibitors in heart failure, β-receptor antagonists after MI) or contraindicated (eg, the avoidance of ACE inhibitors in renal artery stenosis and β-receptor antagonists in asthma). Lowering BP should also be undertaken cautiously in patients with severe bilateral carotid artery disease, at least until carotid endarterectomy has been performed. Despite the existing data, further research is required. In particular, no data are available for some of the major classes of antihypertensive agents, especially angiotensin receptor antagonists and calcium channel blockers, and these data are required since not all patients can take an ACE inhibitor and/or diuretic; ongoing trials will extend information in this direction. Such trials should be very large to provide sufficient power to analyze fatal events since the existing data largely suggest an effect on nonfatal vascular events.

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Secondary Prevention of Stroke: Beyond Meta-Analyses

Secondary prevention of stroke by blood pressure lowering drugs has been assessed in randomized controlled trials for more than 30 years, but the formal demonstration of a clinical benefit awaited the results from 2 major trials: PATS in 1995 and PROGRESS in 2001. Rashid et al have summarized the results from these and other available randomized controlled trials, to assess the effectiveness of these drugs on vascular events. In addition, they address other clinically relevant questions in exploring the heterogeneity between trials, and the relationship between blood pressure fall and risk reduction.

Overall Benefit
Overall, the use of blood pressure-lowering drugs was associated with significant reductions in stroke, myocardial infarction, and total vascular events. Beneficial trends observed for vascular or total mortality were not statistically significant. The methodology of randomized controlled trials allows affirmation that drugs per se provoked these reductions.

Is “Hypertension” Needed for Expecting a Benefit From Blood Pressure–Lowering Drugs?
The benefit observed in the 4 trials that included participants irrespective of their blood pressure level was of the same magnitude of that observed in the others. This reinforces the results obtained in subgroups from isolated trials, strongly advocates the prescription of the evaluated drugs in people without hypertension for the prevention of stroke recurrence, and puts into question the definition of hypertension.

Which Drug Can Be Used as a First-Line Therapy?
Exploring the heterogeneity of results suggested that it could be partially explained by the class of the first-line drug. In particular, the beta blocker atenolol was not associated with any benefit, and ACE inhibitors alone (ramipril and perindopril) reduced only the risk of myocardial infarction. On the contrary, diuretics (thiazide or indapamide) reduced the risk

Editorial Comment

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of stroke, whereas the association of indapamide with ACE inhibitor (perindopril) reduced the risk of all vascular events.

It should be emphasized that these results, from indirect comparisons, are only exploratory, with a weak level of evidence due to potential confounders: a lot of other factors may play a role in this heterogeneity, such as stroke subtype but also a variety of characteristics that will not be possibly assessed even in a meta-analysis on individual patient data. Among these factors, the choice of drug is one of the few that can be controlled: the superiority of a drug over another could be properly evaluated through direct comparisons.

What Is the Role of Blood Pressure–Lowering in This Benefit?

That the drugs from different classes did not reduce the risk similarly, whereas they reduced blood pressure in an approximately similar extent, suggests that other mechanisms than blood pressure reduction may be at play.

Of note is the fact that the majority of included trials explored the benefit associated with fixed doses of drugs, irrespective of the observed blood pressure response to drug. This demonstrates that such a simple strategy is efficient. Moreover, there is no evidence that this strategy is less efficient than others targeted toward a given level of blood pressure. We should keep in mind that, as the definition of hypertension, the definition of blood pressure target on treatment remains arbitrary, without any appropriate validation.

As others did on a larger data set, the authors explored the association between blood pressure fall and the risk reduction through a regression approach. They found this association significant from a statistical point of view. However, as others did, they obtained such a result by including in the regression equation a quadratic factor. This quadratic factor makes the results uneasy to interpret: a curvature in the regression function suggests that the association is not straight, and that intensifying blood pressure reduction does not lead to any further benefit, or even provoke adverse events that reduce the size of the benefit (J-curve phenomenon). Once again, it should be noted that association does not mean causality: it could be explained by confounders, such as other drug properties, or underlying risk of the studied population. That the provoked blood pressure fall explains at least partly the risk reduction observed on such drugs is more than likely. However, evidence accumulates to prove that the lower is not always the better.

The Future of Cardiovascular Prevention Drugs

The results from Rashid et al remind us of the limitations of the concepts at the basis of past and current guidelines on the management of blood pressure drugs:

1. The definition of hypertension is arbitrary, and people without hypertension, whatever its definition, may benefit from drugs that, among other properties, lower blood pressure.

2. The level of risk to be prevented is one of the major factors of medium-term (e.g., 5-year) benefit: in secondary stroke prevention, the level of 5-year risk is very high and concerns a category of cardiovascular events that is best prevented by blood pressure–lowering drugs.

3. It is likely that for a given level of blood pressure decrease, a given choice of drug class does not lead to the same benefit.

4. Fixed dose drug strategy may be, on average, as efficient as traditional blood pressure targeted strategy.

5. Other individual characteristics, such as the nature of the qualifying stroke (ischemic or hemorrhagic), the level of risk of subsequent vascular events (stroke, myocardial infarction), the ethnic origin (Asian, European, African), etc, in addition, or more likely in interaction with the nature of drug treatment, may explain variations of the size of benefit.

The greatest progress to expect from pharmacological cardiovascular prevention may come from the optimization of the use of available drugs, rather than the discovery of the new miraculous drug. We will not always ignore that people with a given phenotype profile, and soon a given genotype, will not have their blood pressure lowered with drug A but with drug B, even if they tolerate both as well, and if A appears more efficacious, due to a greater placebo effect. But more importantly, if A lowers blood pressure better than B, C will be the most efficient to reduce overall cardiovascular risk, even if blood pressure–lowering is between that of A and B.

To access such clinically relevant knowledge, we need to explore extensively data that accumulate from epidemiology and randomized controlled trials, but also to obtain new data from compared fixed-dose strategy in a variety of populations, looking accurately at genome, environment, and their interactions.

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