Calcium-Channel Blockade and Cardiovascular Prognosis: Recent Evidence From Clinical Outcome Trials

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This article has three purposes: 1) to summarize recent findings of the Syst-Eur Trial; 2) to provide a short overview of the large trials in hypertension that have compared older with newer drug classes; and 3) to update the results of a meta-regression analysis that addressed the question of: to what extent blood pressure (BP) lowering can explain the findings of recent outcome trials in hypertensive patients or high-risk patients with normotension or hypertension. The Syst-Eur trial showed that in older patients with isolated systolic hypertension, drug treatment starting with a dihydropyridine calcium channel blocker reduced the risk of stroke and of all cardiovascular complications. Furthermore, this treatment regimen improved the prognosis of diabetic patients; reduced the incidence of proteinuria; and prevented dementia, in particular Alzheimer’s disease. The pooled evidence from nine recently published actively controlled outcome trials involving 62,605 hypertensive patients proved that calcium channel blockers have the same long-term efficacy and safety as the older drug classes. Compared with diuretics and β-blockers, calcium channel blockers may offer greater protection against stroke and less protection against myocardial infarction, resulting in similar overall cardiovascular benefit. A meta-regression analysis including 30 trials and 149,407 hypertensive or high-risk patients showed that BP gradients largely accounted for most—if not all—of the differences in outcome. These findings emphasize the desirability of tight BP control. The hypothesis that angiotensin converting enzyme inhibitors or α-blockers might influence outcome beyond their BP lowering-effects was not confirmed. Am J Hypertens 2002;15:85S–93S © 2002 American Journal of Hypertension, Ltd.

Key Words: Calcium channel blocker, dementia, diabetes mellitus, isolated systolic hypertension, outcome.

The Syst-Eur* trial was conducted in older (≥60 years) patients with isolated systolic hypertension (systolic pressure 160 to 219 mm Hg with diastolic pressure <95 mm Hg).1,2 Syst-Eur was the first double-blind, randomized controlled outcome trial that demonstrated antihypertensive treatment starting with a dihydropyridine calcium channel blocker significantly reduced the incidence of stroke and that of major cardiovascular end points by 42% and 31%, respectively.1 In general, treatment was equally effective irrespective of the patients’ entry characteristics, including sex, age, presence or absence of previous cardiovascular complications, and level of systolic pressure.3 After the publication of the main Syst-Eur results,1,3 further analyses focused on the effects of active treatment on outcome in diabetic and nondiabetic patients,4 on renal function,5 and on the prevention of dementia.6–8

Recent outcome trials investigated the benefits associated with different levels of blood pressure (BP) control9,10 or compared older classes of antihypertensive drugs such as diuretics or β-blockers, with newer classes of agents such as calcium channel blockers,11–14 angiotensin converting enzyme (ACE) inhibitors,14,15 or the α-blocker doxazosin.16 Furthermore, placebo-controlled studies explored whether calcium channel blockers17,18 or ACE inhibitors17,19,20 may confer additional benefit over and beyond BP lowering.

The aim of this short review is to summarize the more recent Syst-Eur findings,4,5,8 to provide an overview of the large trials in hypertension that have compared older with newer drug classes,21,22 and to briefly present the results of a meta-regression analysis that addressed the question of to what extent BP lowering could explain the findings of recent outcome trials in hypertensive patients or high-risk patients with normotension or hypertension.21,22
Recent Syst-Eur Reports
Outcome in Diabetic and Nondiabetic Patients

At randomization, 492 Syst-Eur patients (10.5%) had diabetes mellitus. At median follow-up, the net differences in BP between the placebo and active treatment groups were 8.6 mm Hg systolic and 3.9 mm Hg diastolic in the diabetic patients and 10.3 mm Hg systolic and 4.5 mm Hg diastolic in the 4203 nondiabetic Syst-Eur patients.

In diabetic patients, with adjustments for possible confounders applied, active treatment reduced all-cause mortality by 55%, cardiovascular mortality by 76%, all cardiovascular end points by 69%, fatal and nonfatal stroke by 73%, and all cardiac end points by 63% (Fig. 1). In the nondiabetic patients, active treatment decreased all cardiovascular end points by 26% and fatal and nonfatal stroke by 38%. Active treatment reduced total mortality (P = .04), cardiovascular mortality (P = .02), and all cardiovascular end points (P = .01) significantly more in the diabetic than in the nondiabetic patients.

Prevention of Dementia

The Vascular Dementia Project investigated whether antihypertensive drug treatment could reduce the incidence of dementia. At baseline and follow-up, cognitive function was assessed by the Mini-Mental State Examination. If the score was 23 or less, the diagnosis of dementia was established based on the Diagnostic and Statistical Manual of Mental Disorders, third edition, revised (DSM-III-R).

In total, 2418 patients were enrolled in the dementia study. Median follow-up by intent-to-treat analysis was 2.0 years. Of the 32 incident cases of dementia, 23 were Alzheimer’s disease, 7 had a mixed etiology, and only 2 were vascular. Compared with placebo (n = 1180), active treatment (n = 1238) reduced the incidence of dementia by 50% (P = .05), from 7.7 to 3.8 cases per 1000 patient-years (Fig. 2). In the per-protocol analysis, active treatment decreased the rate by 60% (P = .03). Active treatment prevented mainly degenerative dementia.

After termination of the placebo-controlled phase of the Syst-Eur trial in February 1997, all patients were offered active trial medication for a further period of observation (Syst-Eur 2). Median follow-up increased from 2.0 to 3.9 years and the number of incident cases of dementia from 32 to 64. Systolic/diastolic pressure in the former placebo group drifted gradually toward but at 8 years of follow-up remained 3.3/3.9 mm Hg above the level in the former active treatment group (P < .001). Long-term active treatment (n = 1485), compared with control (n = 1417), reduced the incidence of dementia by 55%, from 7.4 to 3.3 cases per 1000 patient-years (43 vs 21 patients; P = .0008). By inference, treatment of 1000 patients for 5 years could prevent 20 cases of dementia (95% confidence interval [CI] 7–33 cases).

Renal Function

The long-term changes in renal function were studied in 2258 treated and 2148 untreated patients, of whom 455 had diabetes mellitus and 390 had proteinuria. Serum creatinine concentration at randomization was less than 176.8 μmol/L (2.0 mg/dL), averaging 88 μmol/L.

At the time of the last serum creatinine measurement, the BP difference (P < .001) between the two groups was 11.6/4.1 mm Hg. In the intent-to-treat analysis (11,427 patient-years), serum creatinine levels and the calculated creatinine clearance were not influenced by active treatment. However, in the patients randomized to active treatment, the incidence of mild renal dysfunction (serum creatinine ≥176.8 μmol/L) decreased by 64% (P = .04) and that of proteinuria by 33% (P = .03). Active treatment reduced the risk of proteinuria more (P = .04) in diabetic than in nondiabetic patients: 71% vs 20%. In nonproteinuric patients, active treatment did not influence serum creatinine (+0.84 μmol/L; P = .13), whereas in patients with proteinuria at entry, serum creatinine decreased on active treatment (−6.52 μmol/L; P = .02). The P value for interaction was .001.

Older Versus Newer Drug Classes

We recently performed an overview of the actively controlled trials in hypertensive patients. Our statistical methods, inclusion and exclusion criteria for trials, and
definitions of events have been published in detail. In short, we selected the outcome trials in hypertensive patients that compared older classes of antihypertensive agents, such as diuretics or β-blockers, with newer agents, such as calcium channel blockers, ACE inhibitors, or the α-blocker doxazosin. We identified 11 such studies. However, we excluded one trial because randomization was not between older and newer drugs but between special intervention and usual care, and a second study because the cardiovascular outcome data had been published only in aggregate form. For analysis we combined three smaller trials that tested a calcium channel blocker against a thiazide and in which the rate of cardiovascular complications was less than 40 events in 414 Japanese patients followed up for 5 years or below 1 event per 1000 patient-years. Thus, in our meta-analysis, we combined evidence from nine trials involving 62,605 hypertensive patients.

With regard to fatal combined with nonfatal outcomes, there was significant heterogeneity among the trials, which was largely driven by the higher risk of cardiovascular complications, stroke, and congestive heart failure in patients on treatment with doxazosin compared with chlorthalidone in the ALLHAT trial. (Significant heterogeneity indicates that differences in the results of the trials included in the meta-analysis cannot be attributed to chance.) For these events, the odds ratios were 1.25 (CI 1.17–1.33, P < .001), 1.19 (CI 1.01–1.40, P = .04), and 2.04 (CI 1.79–2.32, P < .001), respectively. After exclusion of the ALLHAT trial, there was still slight heterogeneity in the overall risk of cardiovascular complications on treatment with ACE inhibitors compared with older drugs (P = .03). This was due to the higher risk of stroke in the CAPPP patients randomized to captopril (Fig. 3). The odds ratio was 1.25 (CI 1.01–1.55, P = .04). Among the individual trials, NORDIL study patients allocated diltiazem had a lower risk of stroke than their counterparts randomized to the drugs of the older classes. The odds ratio was 0.80 (CI 0.65–0.99; P = .04), but this did not lead to significant heterogeneity among the trials involving calcium channel blockers.

After exclusion of ALLHAT, there were no differences in overall cardiovascular risk between the patients randomized to diuretics or β-blockers and those allocated initial treatment with calcium channel blockers or ACE inhibitors. However, in the patients randomized to calcium channel blockers, compared with those in whom treatment was started with older drugs, there was a greater reduction in the risk of stroke (13.5%, CI 1.3–24.2, P = .03; Fig. 3) and a lesser reduction in the risk of myocardial infarction (19.2%, CI 3.5–37.3, P = .01; Fig. 3). In patients randomized to ACE inhibitors, the risk reductions were similar for stroke and myocardial infarction (Fig. 3).

**Meta-Regression Update**

We based our analysis on summary statistics reported in the literature. In comparison with our original report, we extended our meta-regression analysis by adding PATS trial; the recently published RENAL trial; the PROGRESS/Com trial; and the PROGRESS/Per trial. We excluded the IDNT and...
the IRMA 2 study because in these two trials the number of cardiovascular events was not reported. Within each trial, the reference group consisted of patients left untreated, allocated placebo, or placebo, randomized to older drug classes, or to a treatment strategy leading to less tight BP control. Net treatment effects on BP were determined by subtracting the mean change in the reference group (follow-up minus baseline) from the corresponding mean change in the experimental group (experimental minus baseline) for all cardiovascular events or of stroke recurrence. Fig. 4 illustrates the correlated odds ratios of experimental versus reference treatment with the corresponding BP differences. For these calculations, odds ratios were logarithmically transformed. For all outcomes considered in the analysis, the regression lines were weighted by the inverse of the variance of the individual odds ratios. These regression lines and their 95% CI allowed to predict for each end point in each trial the odds ratio that one can expect to be associated with the observed difference in systolic pressure between the randomized groups.

<table>
<thead>
<tr>
<th>Trials</th>
<th>Number of events</th>
<th>Odds ratios and CIs</th>
<th>Difference (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatal and non-fatal stroke</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MIDAS1/2</td>
<td>19:19</td>
<td>-19.5 (7.0%) 2p=0.03</td>
<td>-1.8/5 mm Hg</td>
</tr>
<tr>
<td>UKPDS</td>
<td>17:21</td>
<td>+5.8 (7.8%) 2p=0.45</td>
<td>+5.5/4 mm Hg</td>
</tr>
<tr>
<td>STOP2</td>
<td>237:422</td>
<td>-3.9 (5.6%) 2p=0.47</td>
<td>-3.0/4 mm Hg</td>
</tr>
<tr>
<td>STOP2/CCB</td>
<td>237:207</td>
<td>+1.7 (4.7%) 2p=0.72</td>
<td>+1.2/3 mm Hg</td>
</tr>
<tr>
<td>STOS2/ACE</td>
<td>237:215</td>
<td></td>
<td></td>
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<tr>
<td>CAPPP</td>
<td>148:189</td>
<td></td>
<td></td>
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<tr>
<td>NORDIL</td>
<td>196:159</td>
<td></td>
<td></td>
</tr>
<tr>
<td>INSIGHT</td>
<td>74:67</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALLHAT</td>
<td>391:344</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All trials</td>
<td>502:452</td>
<td>-19.5 (7.0%) 2p=0.03</td>
<td>-1.8/5 mm Hg</td>
</tr>
<tr>
<td>Heterogeneity</td>
<td>0.82</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Fatal and non-fatal myocardial infarction |
| MIDAS1/2 | 16:16 | +19.2 (7.5%) 2p=0.01 | +5.6/4 mm Hg |
| UKPDS | 46:61 | -1.3 (8.1%) 2p=0.90 | -1.2/3 mm Hg |
| STOP2 | 154:179 | +10.1 (5.8%) 2p=0.09 | +4.6/3 mm Hg |
| STOP2/CCB | 154:139 | +6.4 (4.4%) 2p=0.16 | +3.1/2 mm Hg |
| STOS2/ACE | 161:162 |  |  |
| CAPPP | 157:183 |  |  |
| NORDIL | 61:77 |  |  |
| INSIGHT | 808:605 |  |  |
| ALLHAT | 389:455 | +19.2 (7.5%) 2p=0.01 | +5.6/4 mm Hg |
| Heterogeneity | 0.95 |  |  |
| CCIs and ACCs Heterogeneity | 0.45 |  |  |
| CCBs and ACCs Heterogeneity | 0.40 |  |  |
| All trials Heterogeneity | 0.79 |  |  |

The 30 studies included in the meta-regression analysis represent 149,407 patients. They comprised nine actively controlled trials; the HOT study, which investigated different levels of BP control; three placebo-controlled trials in isolated systolic hypertension (SHEP, Syst-China, and Syst-Eur); six placebo-controlled trials in normotensive or hypertensive patients at high cardiovascular risk (HEP, PART2, PATS, PROGRESS, SCAT, and RENAAL); and 11 older trials testing the efficacy of antihypertensive drugs against no treatment (HEP or OSLO) or placebo (ATM1, trial conducted by the EWPHE). The differences between the observed odds ratios and those predicted by the meta-regression lines did not reach statistical significance for cardiovascular mortality, all cardiovascular events, stroke, or myocardial infarction (including sudden death), except for stroke in NORDIL and in the single-drug arm of the PROGRESS trial (Fig. 4 and Table 1). In NORDIL, the risk of stroke was lower on diltiazem than on the older drugs despite a 3.1 mm Hg higher systolic pressure.
Interpretation and Conclusions

The Syst-Eur trial\(^1\)–\(^3\) showed that long-acting dihydropyridines can be used instead of diuretics to initiate treatment in older patients with isolated systolic hypertension. Furthermore, antihypertensive treatment starting with a calcium channel blocker improved the prognosis of diabetic patients\(^4\); reduced the incidence of proteinuria\(^5\); and prevented dementia, in particular Alzheimer’s disease.\(^8\) Finally, the circumstantial evidence for the potentially dangerous side effects of calcium channel blockers\(^58\)–\(^61\) was not borne out when put to the test of a double blind, placebo-controlled clinical trial.

Compared with the older drug classes, calcium channel blockers and ACE inhibitors provide the same overall protection against cardiovascular complications, but calcium channel blockers provided more reduction in the risk of stroke (13.5\%) and less reduction in the risk of myocardial infarction (19.2\%). Using meta-regression, we found that in the NORDIL trial\(^13\), diltiazem, compared with diuretics or β-blockers, decreased the risk of stroke despite a 3.1 mm Hg higher systolic pressure. Furthermore, there was no heterogeneity in the stroke results between the NORDIL trial\(^13\) and the other actively controlled studies involving calcium channel blockers.\(^11\),\(^12\),\(^14\),\(^28\),\(^50\) Nevertheless, these cause-specific results must be interpreted with caution, because the confidence intervals are wide and because they may be driven not only by the drugs under study but also by the characteristics of the patients.\(^62\) Selective recruitment of middle-aged type 2 diabetic patients in the ABCD trial,\(^63\) older high-risk hypertensive patients in the INSIGHT trial,\(^12\) and elderly patients with isolated systolic hypertension in the SHEP\(^36\),\(^38\) and Syst-Eur\(^1\) studies probably explains why the rates of myocardial infarction varied from 6.3\(^12\) to 32.2\(^38\) cases per 1000 patient-years\(^12\) and why the results with regard to the prevention of myocardial infarction were contradictory.

The results of our meta-regression suggest that for fatal and nonfatal complications combined, most of the benefit of antihypertensive treatment may be achieved with moderate differences in BP of approximately 15 mm Hg systolic or 5 mm Hg diastolic.\(^21\),\(^22\) This is in agreement with previous overviews.\(^64\),\(^65\) Indeed, in older patients with isolated systolic hypertension,\(^64\) lowering BP by 10 mm Hg systolic and 4 mm Hg diastolic decreased the risk of

### Table 1. Observed odds ratios and odds ratios predicted by the difference in systolic blood pressure in meta-regression for fatal and nonfatal stroke

<table>
<thead>
<tr>
<th></th>
<th>Observed Odds Ratio*</th>
<th>Predicted Mean Odds Ratio†</th>
<th>Difference (%)‡</th>
<th>P§</th>
</tr>
</thead>
<tbody>
<tr>
<td>Actively controlled trials</td>
<td></td>
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</tr>
<tr>
<td>ALLHAT(^16)</td>
<td>1.18 (0.99–1.39)</td>
<td>1.06 (0.93–1.21)</td>
<td>−10.8 (−36.8–10.2)</td>
<td>.34</td>
</tr>
<tr>
<td>CAPPP(^29)</td>
<td>1.29 (1.03–1.61)</td>
<td>1.14 (0.98–1.33)</td>
<td>−12.9 (−47.6–13.7)</td>
<td>.38</td>
</tr>
<tr>
<td>NORDIL(^13)</td>
<td>0.81 (0.65–1.01)</td>
<td>1.14 (0.98–1.34)</td>
<td>29.0 (7.7–45.5)</td>
<td>.01</td>
</tr>
<tr>
<td>Placebo-controlled trials</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HOPE(^48)</td>
<td>0.68 (0.62–0.86)</td>
<td>0.77 (0.70–0.83)</td>
<td>11.3 (−11.4–29.4)</td>
<td>.30</td>
</tr>
<tr>
<td>PROGRESS combination therapy(^51)</td>
<td>0.57 (0.46–0.70)</td>
<td>0.57 (0.51–0.62)</td>
<td>2.5 (−23.3–23.0)</td>
<td>.83</td>
</tr>
<tr>
<td>PROGRESS single-drug therapy(^51)</td>
<td>0.95 (0.77–1.19)</td>
<td>0.71 (0.65–0.78)</td>
<td>−33.6 (−71.3 to −4.1)</td>
<td>.02</td>
</tr>
</tbody>
</table>

Acronyms of all trials are explained in the Appendix.

* Odds ratio reported in the published articles.
† Mean odds ratio (95\% confidence interval) predicted by the meta-regression lines (see Fig. 4).
‡ Difference between predicted minus observed odds ratio (95\% confidence interval) expressed as a percentage of the predicted odds ratio.
§ Significance of the difference between observed and predicted odds ratios.

![FIG. 4. Relationship between the odds ratios for stroke and the corresponding differences in systolic blood pressure. The regression line was plotted with 95\% confidence interval, was adjusted for the mean systolic pressure at entry, and was weighted for the inverse of the variance of individual odds ratios. Filled symbols denote trials that compared new with old drugs. Acronyms of trials are explained and their references cited in the Appendix. Adapted with permission from Elsevier Science for Staessen JA, Wang JG, Thijs L. Cardiovascular protection and blood pressure reduction: a meta-analysis. Lancet 2001;358:1305–1315.](image-url)
stroke and myocardial infarction by 26% and 23%, respectively. In patients with predominantly diastolic hypertension, the corresponding benefits produced by a 5 to 6 mm Hg decline in diastolic pressure were 38% and 16.

In conclusion, in the trials in hypertensive patients or in normotensive or hypertensive patients at high cardiovascular risk, BP gradients largely accounted for most—if not all—of the differences in outcome. The hypothesis that in patients with uncomplicated hypertension ACE inhibitors or α-blockers might influence outcome over and beyond their BP-lowering effects remains unproven.

**Acknowledgments**

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A list of the investigators participating in the Syst-Eur Trial appears in references 1 and 3. Dr. Ji-Guang Wang was supported by the bilateral scientific and technical collaboration between the People’s Republic of China and Flanders (contract number BIL98/15). We gratefully acknowledge the expert secretarial and technical assistance of Lutgard De Pauw, RN, and Renilde Wolfs.

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46. Veterans Administration Cooperative Study Group on Antihypertensive Agents: Effects of treatment on morbidity in hypertension II. Results in patients with diastolic blood pressure averaging 90 through 114 mm Hg. JAMA 1970;213:1143–1152.


51. PROGRESS Collaborative Group: Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6105 individuals with previous stroke or transient ischaemic attack. Lancet 2003;360:1033–1041.


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**Appendix: Trial Acronyms**

ABCD (Appropriate Blood Pressure Control in Diabetes trial) 63;
ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial) 16, 42;
ATMH (Australian Trial in Mild Hypertension) 39;
CAPPP (CAprilopril Prevention Project) 29, 41;
EWPHE (trial conducted by the European Working Party on High Blood Pressure in the Elderly) 30, 31;
HEP (trial of Hypertension in Elderly Patients in primary care) 32;
HOPE (Heart Outcomes Prevention Evaluation Study) 48, 49;
HOT (Hypertension Optimal Treatment trial) 48, 49;
HOT M versus H (Hypertension Optimal Treatment trial 32, 33, 34 vs 90 mm Hg as target diastolic pressure);
HOT L versus H (Hypertension Optimal Treatment trial 32, 33, 34 vs 90 mm Hg as target diastolic pressure);
IDNT (Irbesartan Diabetic Nephropathy Trial); IRMA 2 (Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria study);
INSIGHT (International Nifedipine GITS Study—Intervention as a Goal for Hypertension Therapy) 15;
HSCS (Hypertension-Stroke Cooperative Study) 44;
MIDAS (Multicenter Isradipine Diuretic Atherosclerosis Study) 28;
MIDAS/NICS/VHAS (combined results of MIDAS, 28 NICS, 11 and VHAS 30); MRC1 (Medical Research Council trial of treatment of mild hypertension) 35;
MRC2 (Medical Research Council trial of treatment of hypertension in older adults) 35;
NICS (National Intervention Cooperative Study in Elderly Hypertensives) 15;
NORDIL (NORdic DIltiazem Study) 13;
OSLO (Oslo Study on the Treatment of Mild Hypertension) 35;
PART2 (Prevention of Atherosclerosis with Ramipril Trial) 19;
PART2/SCAT (combined results of PART2 19 and SCAT 20) (Simvastatin/Enalapril Coronary Atherosclerosis Trial 20);
PATS (Post-stroke Antihypertensive Treatment Study) 29;
PROGRESS (Perindopril PROtection aGainst REcurrent Stroke Study) 51, 53;
PROGRESS/Com (Perindopril PROtection aGainst REcurrent Stroke Study) 51, 53—group on combined therapy;
PROGRESS/Per (Perindopril PROtection aGainst REcurrent Stroke Study) 51, 53—group on single-drug treatment;
RCT (Randomized clinical trial) 70–80 (combined results of four smaller trials published from 1970 through 1980, including HSCS, 44 OSLO, 43 USPHS, 45 and VACS 46);
RENAAL (Reduction of Endpoint in NIDDM with the Angiotensin II Antagonist Losartan) 52;
SCAT (Systolic Hypertension in the Elderly Program) 36, 38;
STONE (Shanghai Trial of Nifedipine in the Elderly) 37;
STOP1 (Swedish Trial in Old Patients with hypertension); STOP2 (Swedish Trial in Old Patients with hypertension); STOP2/ACEIs (angiotensin converting enzyme inhibitor arm of STOP2); STOP2/CCBs (calcium channel blocker arm of STOP2); Syst-China (Systolic Hypertension in China trial); Syst-Eur (Systolic Hypertension in Europe trial); UKPDS (UKPDS Hypertension in Diabetes Study); UKPDS C versus A (UKPDS Hypertension in Diabetes Study—captopril versus atenolol); UKPDS L versus H (UKPDS Hypertension in Diabetes Study—low versus high on-treatment blood pressure); USPHS (United States Public Health Service Hospitals Cooperative Study); VACS (Veterans Administration Cooperative Study in patients with diastolic blood pressure averaging 90–114 mm Hg); VHAS (Verapamil in Hypertension and Atherosclerosis Study).