Blood Pressure: The Lower, the Better

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Hypertension is one of the major modifiable risk factors for cardiovascular (CV) morbidity and mortality. It was recently shown that 7.6 million early deaths and 92 million disabled years are attributed to hypertension (1). Lowering blood pressure (BP) reduces CV morbidity and mortality. The benefit achieved in most hypertension outcomes studies was attributed to BP reduction, and the more aggressive the BP reduction, the greater the benefit (2,3). However, it is unclear what the target BP levels should be. Lewington et al. (4) showed in a large collaborative meta-analysis that included 1 million adults with no previous vascular disease that usual BP is strongly and directly related to vascular (and overall) mortality, without any evidence of a threshold down to at least 115/75 mmHg. This observation led clinicians to believe that BP should be lowered to the lowest tolerable levels. Some of the guidelines even adopted this approach and recommended lowering BP to <140/90 mmHg in all hypertensive patients, including the elderly, and to <130/80 mmHg in diabetic and high-risk patients (5,6). The present review will analyze the available data showing that the notion "the lower, the better" is not evidence based and that there is evidence that lowering BP too aggressively may even be harmful.

EVIDENCE TO SUPPORT AGGRESSIVE BP LOWERING—
One of the largest trials that addressed the question of what should be the optimal BP was the Hypertension Optimal Treatment (HOT) trial (7). This prospective study enrolled 18,790 patients who were randomly assigned to one of three diastolic BP target groups: ≤90, ≤85, or ≤80 mmHg. Mortality and CV morbidity were not different in the three different target groups, suggesting no benefit of lowering diastolic BP to <90 mmHg. However, instead of accepting the findings of the randomized trial as designed and drawing the right conclusion, the authors did a further analysis of the trial, as if it was a prospective observational study. They combined all randomized groups into one and reported outcomes based on the BP achieved during follow-up. That analysis led to the wrong conclusion that there are benefits of lowering the diastolic BP down to 82.6 mmHg. Careful analysis showed that only diabetic patients benefited from lowering diastolic BP to 80 mmHg. In this subgroup, targeting diastolic BP to ≤80 mmHg was associated with a 51% reduction in the risk of major CV events. However, in nondiabetic patients, lowering diastolic BP to ≤80 mmHg was associated with increased CV and total mortality (8). Zanchetti et al. (9) showed in a latter subanalysis of the HOT study that, in smokers, more intensive diastolic BP lowering was associated with increased risk of all types of CV events except myocardial infarction.

Another study that supports intensive BP lowering was the Felodipine Event Reduction (FEVER) trial (10). This prospective multicenter double-blind randomized placebo-controlled trial enrolled 9,800 Chinese patients, with one or two additional CV risk factors or disease, whose BP was in the range of 140–180 mmHg (systolic) or 90–100 mmHg (diastolic) after switching from previous therapy to low-dose (12.5 mg/day) hydrochlorothiazide. Patients were randomly assigned either to low-dose felodipine extended release or placebo and followed for an average of 40 months. The achieved BP was 137.3/82.5 mmHg in the felodipine-treated arm and 142.5/85 mmHg in the control group. This difference reduced the primary end point (fatal and nonfatal stroke) by 27% ($P < 0.001$) and all-cause mortality by 31%. This study provides evidence supporting lower BP targets in high-risk patients. However, this study should be interpreted with caution, since the initial BP was 154/91 mmHg, the achieved systolic BP (SBP) in the placebo group was >140 mmHg, and, for unknown reasons, the rate of cancer was also significantly increased in the placebo arm.

In a recent meta-analysis that included 464,000 people, the authors showed that for a BP reduction of 10 mmHg systolic or 5 mmHg diastolic, there was a 22% reduction in coronary heart disease events and a 41% reduction in stroke (11). The proportional reduction in CV disease events was the same or similar regardless of pretreating BP down to 110 mmHg systolic and 70 mmHg diastolic. The results of this study support a "the lower, the better" approach to BP reduction.

Another prospective study that was recently published in *The Lancet* evaluated the benefit of tight SBP control (12). In this study, 1,111 nondiabetic patients with SBP ≥150 mmHg were randomly assigned to a target SBP of <140 mmHg (usual control; $n = 553$) or <130 mmHg (tight control; $n = 558$). The primary end point was the rate of electrocardiographic left ventricular hypertrophy 2 years after randomization. Tight BP control was associated with a 37% decrease in primary end points and 50% decrease in composite CV end points ($P < 0.05$ for both). These data support the notion that lowering SBP to <130 mmHg may be beneficial. However, the results of this

study should be interpreted cautiously because it was an open study, it included a relatively small number of patients, and the primary end point was not CV morbidity and mortality.

EVIDENCE TO SUPPORT AGGRESSIVE BP LOWERING IS BASED ON A FEW STUDIES WITH DRAWBACKS

What have we learned from outcome studies?

It is clear from many clinical studies that lowering BP reduces CV morbidity and mortality (13). Several meta-analyses showed that lowering BP per se determines the benefit achieved by treatment and that an SBP decrease of 1 mmHg decreases the risk of stroke by 5%. The meta-analyses were based on old hypertension studies that included patients with very high BP levels (Table 1) (2,3,10,14–23). In most studies, the initial baseline SBP levels were >160 mmHg. The initial BP levels were even higher, since most patients were medically treated when they were recruited to the studies. In this BP range, lowering SBP by 1 mmHg decreased the rate of stroke by 5%. According to this formula, one would expect to see the same benefit when lowering SBP down from 140 mmHg. However, some recent mega-trials failed to show this benefit.

In the Ongoing Telmisartan Alone and in Combination with Ramipril Global End Point Trial (ONTARGET) study, patients with vascular disease or high-risk diabetes were randomized to receive either 10 mg ramipril per day (*n* = 8,576) or 80 mg telmisartan per day (*n* = 8,542) or both drugs (combination therapy) (*n* = 8,502) (24). The primary composite outcome was death from CV causes, myocardial infarction, stroke, or hospitalization for heart failure. The combination therapy reduced BP by 2.4/1.4 mmHg more than the ramipril, but despite the greater reduction in BP, the rate of primary end points was the same in the two treatment arms.

In the Prevention Regimen for Effectively Avoiding Second Strokes (PRoFESS) study, 20,332 patients with recent ischemic stroke were randomized to receive either 80 mg telmisartan (*n* = 10,146) or placebo (*n* = 10,186) (25). The primary outcome was recurrent stroke. During a mean follow-up of 2.5 years, the mean BP was 3.8/2.0 mmHg lower in the telmisartan group than in the placebo group. Despite the significant BP decrease with telmisartan, the rate of recurrent stroke was the same in the two treatment groups. In the Telmisartan Randomized Assessment Study in ACE-Intolerant Subjects with Cardiovascular Disease (TRANSCEND) study, 5,926 patients intolerant to ACE inhibitors with CV disease or diabetes with end-organ damage were randomized to receive either 80 mg/day telmisartan (*n* = 2,954) or placebo (*n* = 2,972) (26). The primary outcome was the composite of CV death, myocardial infarction, stroke, or hospitalization for heart failure. Mean BP was lower in the telmisartan group than in the placebo group throughout the study by 4.0/2.2 mmHg. Despite the significant difference in BP levels between the

treatment groups, the rate of primary end points was similar. There are two ways to explain the disappointing results. One possible explanation is that the angiotensin receptor blocker telmisartan is less effective than all other antihypertensive agents. This is unlikely, since it has been shown that angiotensin receptor blockers are as effective as ACE inhibitors (27). Another more likely explanation is that the initial BP in these studies was normal, and therefore we could not observe a benefit from further BP reduction. Indeed, the average initial BP levels in these studies were 142/82 mmHg in ONTARGET, 144/84 mmHg in the PRoFESS study, and 141/82 in the TRANSCEND study. These initial BP levels are in the normal range and are lower than levels in the old trials. Further support to this concept comes from analysis of the ONTARGET data according to the baseline SBP, SBP changes from baseline to event, and average in-trial SBP. This analysis showed that, in patients with baseline SBP <130 mmHg, adjusted for several covariates, CV mortality increased with further BP reduction. Furthermore, a J-curve (nadir around 130 mmHg) occurred in the relationship between in-treatment SBP and all outcomes except stroke (28). From the recent trials, it seems that the benefit of SBP lowering in high-risk patients with SBP in the range of 130–150 mmHg is doubtful. A recent meta-analysis determined if lower BP targets (≤135/85 mmHg) are associated with reduction in mortality and morbidity compared with standard BP targets (≤140–160/90–100 mmHg) (29). The authors identified seven trials (22,089 subjects) that compared different diastolic BP targets. They showed that using more drugs in the lower target groups did achieve modestly lower BP. However, this strategy did not prolong survival or reduce stroke, heart attack, heart failure, or kidney failure. This meta-analysis, in conjunction with the recent clinical trials, casts doubt on the guidelines to lower BP to below 140/90 mmHg in all hypertensive patients, including the elderly, and to levels below 130/80 in diabetic and high-risk patients.

Target BP in the elderly

Aggressive BP lowering may be even more deleterious in elderly patients with isolated systolic hypertension. Lowering SBP will also lower diastolic BP to a level that may jeopardize coronary blood flow and increase coronary heart events. In the active treatment group of the Systolic Hypertension of

Table 1—Initial BP levels in some of the clinical studies

Study	Initial SBP (mmHg)	Initial diastolic BP (mmHg)
SHEP	170	77
EWPHE	182	101
STONE	168	98
SYST-EUR	174	85
SYST CHINA	170	86
CAPPP	161	99
STOP-Hypertension	194	98
INSIGHT	176	99
NORDIL	180	106
UKPDS	159	94
FEVER	154	91

CAPPP, Captopril Prevention Project; EWPHE, European Working Party on High Blood Pressure in the Elderly; FEVER, Felodipine Event Reduction; INSIGHT, International Nifedipine GITS Study: Intervention as a Goal in Hypertension Treatment; NORDIL, Nordic Diltiazem; SHEP, Systolic Hypertension in the Elderly Program; STONE, Shanghai Trial of Nifedipine in the Elderly; STOP-Hypertension, Swedish Trial in Old Patients with Hypertension; SYST CHINA, Systolic Hypertension in China; SYST-EUR, Systolic Hypertension in Europe; UKPDS, UK Prospective Diabetes Study Group.

the Elderly Program (SHEP) trial, a decrease of 5 mmHg in diastolic BP increased the risk for stroke by 14%, for coronary heart disease by 8%, and for CV disease by 11% (all significant) (30). A secondary analysis of data from the Investigational Vertebroplasty Efficacy and Safety Trial (INVEST), which included 22,576 patients with hypertension and coronary artery disease who were randomly assigned to a verapamil sustained-release or atenolol-based strategy, showed that the risk for the primary outcome, all-cause death, and myocardial infarction, but not stroke, progressively increased with low diastolic BP (31). In the recent Hypertension in the Very Elderly Trial (HYVET), patients with standing systolic BP <140 mmHg were excluded, and the target BP was 150/80 mmHg (32). The recent Japanese Trial to Assess Optimal Systolic Blood Pressure in Elderly Hypertensive Patients (JATOS) compared moderately intense with less intense treatment and found no difference in incidence of CV events between patients with achieved SBP <140 mmHg or >140 mmHg (33). Thus, there is no reason to lower SBP to <140 mmHg in elderly patients.

In recent critical analyses, Zanchetti et al. (34) emphasized the uncertainty of the recommendation to lower SBP levels below 140 mmHg in all hypertensive patients, including the elderly, and values below 130 mmHg in patients with diabetes and high-risk/very-high-risk patients. They point out that the evidence is scanty for the BP target recommendation. New studies that were published after the analyses of Zanchetti et al. suggest that, in diabetic patients, tight control of SBP is not associated with improved CV outcomes compared with usual control (35,36).

BP goal in diabetes

Current guidelines recommend lowering BP to <130/80 mmHg in diabetic patients. However, these guidelines are not based on solid evidence. In the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial, 11,140 patients with type 2 diabetes were randomized to treatment with a fixed combination of perindopril and indapamide or matching placebo (37). After a mean of 4.3 years of follow-up, active treatment (BP 136/73 mmHg) reduced the relative risk of a major macrovascular or microvascular event by 9%, compared with the placebo treatment (BP 140/73 mmHg). The authors stated

that the study treatment was not affected by the initial BP levels. However, the mean initial BP of the studied population was 145/81 mmHg, and 7,655 (68.5%) patients had a history of current antihypertensive treatment. Analysis of subgroups revealed that in patients with no history of hypertension, active treatment did not reduce CV events. It is noteworthy that the achieved SBP in this trial was 136 mmHg. In other trials that showed benefit of BP lowering, the achieved SBP was >130 mmHg (38–40).

Only in one small study (the Appropriate Blood Pressure Control in Diabetes [ABCD]) were the achieved SBP levels <130 mmHg (41). In the normotensive ABCD study, 480 type 2 diabetic patients with baseline normal BP (<140/90 mmHg) were randomized to intensive (10 mmHg below the baseline diastolic BP) or moderate (80–89 mmHg) diastolic BP control. Despite a 9-mmHg difference in SBP between the intensive and the moderate groups, the primary end point (change in creatinine clearance) was the same. Intensive BP control was associated with improvement in only secondary outcomes (less progression to incipient or overt diabetic nephropathy, less progression to diabetic retinopathy and less incidence of stroke).

Two recent publications showed that, in diabetic patients, tight control of SBP was not associated with improved CV outcomes compared with usual control (35,36).

The INVEST trial included 6,400 diabetic patients who were divided into three groups according to mean achieved systolic BP; group 1 achieved tight control (SBP <130 mmHg), group 2 achieved usual control (SBP ≥ 130 < 140 mmHg), and group 3 was not controlled (SBP ≥140 mmHg) (35). The authors evaluated the time to primary and secondary outcome according to group. In addition, extended follow-up (only in the U.S. cohort) was done to evaluate the long-term effect on mortality. Further analysis was done to evaluate the effect of very low SBP. During the INVEST follow-up, the rate of primary outcome was 19.8% in the not controlled group and 12.6 and 12.7% in the usual and tight control groups, respectively (P < 0.001 for the not controlled vs. the other groups). The rate of all-cause mortality was significantly higher in the tight control than in the usual control group (11.0 vs. 10.2%, respectively; P = 0.035). The increased mortality in the tight control group persisted during

extended follow-up. During the extended follow-up, tight control was associated with increased mortality compared with usual control (adjusted hazard ratio 1.15 [95% CI 1.01–1.32]; P = 0.036). Analysis to evaluate the effect of very low BP showed that SBP <115 mmHg was associated with an increase in risk for mortality. This study has some limitations because it represents observational analysis of a randomized control study, and the division of the groups was according to the achieved BP. Moreover, in addition to diabetes, all patients had coronary artery disease, and the BP values during the extended follow-up are unknown. Nevertheless, the results suggest that rethinking is needed regarding the goal BP in diabetic patients with coronary heart disease.

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) blood pressure trial was a prospective randomized double-blind study that investigated whether therapy targeting normal SBP (i.e., <120 mmHg) reduces major CV events in participants with type 2 diabetes at high risk for CV events (36).

The study included 4,733 participants with type 2 diabetes who were randomly assigned to intensive therapy, targeting an SBP of <120 mmHg, or standard therapy, targeting an SBP of <140 mmHg. The primary composite outcome was nonfatal myocardial infarction, nonfatal stroke, or death from CV causes. After 1 year, the mean SBP was 119.3 mmHg in the intensive therapy group and 133.5 mmHg in the standard therapy group. Despite the 14.2-mmHg difference in SBP between the groups, the rate of primary end point was the same. Intensive therapy was associated with a lower rate of stroke (a prespecified secondary outcome) than in the standard therapy. Serious adverse events attributed to antihypertensive treatment occurred more frequently in the intensive therapy group (3.3%) than in the standard therapy group (1.3%) (P < 0.001). The results of the recent studies suggest that there is no benefit in intensive BP lowering, even in diabetic patients, and that too aggressive lowering of BP may be dangerous.

CONCLUSIONS—Recent guideline recommendations to lower BP to <140/90 mmHg in all hypertensive patients, including the elderly, and to <130/80 mmHg in diabetic and high-risk patients is not based on solid evidence. It is clear that lowering SBP to 140 mmHg is beneficial, but there is no evidence that lowering BP

to <140 mmHg in all patients adds benefit. The blood pressure target should be determined according to the patients' global risk and accompanied diseases. Lowering SBP to <140 mmHg may be prudent in diabetic and high-risk patients. Lowering BP too much is associated with more side effects and may be dangerous. This scenario may be especially true in the elderly with isolated systolic hypertension.

References

1. Lawes CM, Vander Hoorn S, Rodgers A; International Society of Hypertension. Global burden of blood-pressure-related disease, 2001. Lancet 2008;371:1513–1518
2. Staessen JA, Wang JG, Thijs L. Cardiovascular prevention and blood pressure reduction: a quantitative overview updated until 1 March 2003. J Hypertens 2003;21:1055–1076
3. Turnbull F; Blood Pressure Lowering Treatment Trialists' Collaboration. Effects of different blood-pressure-lowering regimens on major cardiovascular events: results of prospectively-designed overviews of randomised trials. Lancet 2003;362:1527–1535
4. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R; Prospective Studies Collaboration. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet 2002;360:1903–1913
5. Chobanian AV, Bakris GL, Black HR, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. JAMA 2003;289:2560–2572
6. Mancia G, Laurent S, Agabiti-Rosei E, et al. Reappraisal of European guidelines on hypertension management: a European Society of Hypertension Task Force document. J Hypertens 2009;27:2121–2158
7. Hansson L, Zanchetti A, Carruthers SG, et al. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. Lancet 1998;351:1755–1762
8. Grossman E, Goldbourt U. Hypertension Optimal Treatment (HOT) trial. Lancet 1998;352:572
9. Zanchetti A, Hansson L, Clement D, et al. Benefits and risks of more intensive blood pressure lowering in hypertensive patients of the HOT study with different risk profiles: does a J-shaped curve exist in smokers? J Hypertens 2003;21:797–804
10. Liu L, Zhang Y, Liu G, Li W, Zhang X, Zanchetti A. The Felodipine Event Reduction (FEVER) Study: a randomized long-term placebo-controlled trial in Chinese hypertensive patients. J Hypertens 2005;23:2157–2172
11. Law MR, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. BMJ 2009;338:b1665
12. Verdecchia P, Staessen JA, Angeli F, et al. Usual versus tight control of systolic blood pressure in non-diabetic patients with hypertension (Cardio-Sis): an open-label randomised trial. Lancet 2009;374:525–533
13. Psaty BM, Lumley T, Furberg CD, et al. Health outcomes associated with various antihypertensive therapies used as first-line agents: a network meta-analysis. JAMA 2003;289:2534–2544
14. SHEP Cooperative Research Group. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. Final results of the Systolic Hypertension in the Elderly Program (SHEP). JAMA 1991;265:3255–3264
15. Brown MJ, Palmer CR, Castaigne A, et al. Morbidity and mortality in patients randomised to double-blind treatment with a long-acting calcium-channel blocker or diuretic in the International Nifedipine GITS study: Intervention as a Goal in Hypertension Treatment (INSIGHT). Lancet 2000;356:366–372
16. Hansson L, Hedner T, Lund-Johansen P, et al. Randomised trial of effects of calcium antagonists compared with diuretics and beta-blockers on cardiovascular morbidity and mortality in hypertension: the Nordic Diltiazem (NORDIL) study. Lancet 2000;356:359–365
17. Hansson L, Lindholm LH, Ekbom T, et al. Randomised trial of old and new antihypertensive drugs in elderly patients: cardiovascular mortality and morbidity the Swedish Trial in Old Patients with Hypertension-2 study. Lancet 1999;354:1751–1756
18. Hansson L, Lindholm LH, Niskanen L, et al. Effect of angiotensin-converting-enzyme inhibition compared with conventional therapy on cardiovascular morbidity and mortality in hypertension: the Captopril Prevention Project (CAPPP) randomised trial. Lancet 1999;353:611–616
19. Liu L, Wang JG, Gong L, Liu G, Staessen JA; Systolic Hypertension in China (Syst-China) Collaborative Group. Comparison of active treatment and placebo in older Chinese patients with isolated systolic hypertension. J Hypertens 1998;16:1823–1829
20. Staessen JA, Fagard R, Thijs L, et al. Randomised double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension. Lancet 1997;350:757–764
21. Amery A, Birkenhäger W, Brixko P, et al. Mortality and morbidity results from the European Working Party on High Blood Pressure in the Elderly trial. Lancet 1985;1:1349–1354
22. UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. BMJ 1998;317:703–713
23. Gong L, Zhang W, Zhu Y, et al. Shanghai Trial Of Nifedipine in the Elderly (STONE). J Hypertens 1996;14:1237–1245
24. Yusuf S, Teo KK, Pogue J, et al. Telmisartan, ramipril, or both in patients at high risk for vascular events. N Engl J Med 2008;358:1547–1559
25. Yusuf S, Diener HC, Sacco RL, et al. Telmisartan to prevent recurrent stroke and cardiovascular events. N Engl J Med 2008;359:1225–1237
26. Yusuf S, Teo K, Anderson C, et al. Effects of the angiotensin-receptor blocker telmisartan on cardiovascular events in high-risk patients intolerant to angiotensin-converting enzyme inhibitors: a randomised controlled trial. Lancet 2008;372:1174–1183
27. Parving HH, Hovind P, Rossing P. Telmisartan vs. enalapril in type 2 diabetes. N Engl J Med 2005;352:835–836
28. Sleight P, Redon J, Verdecchia P, et al. Prognostic value of blood pressure in patients with high vascular risk in the Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial study. J Hypertens 2009;27:1360–1369
29. Arguedas JA, Perez MI, Wright JM. Treatment blood pressure targets for hypertension. Cochrane Database Syst Rev 2009:CD004349
30. Somes GW, Pahor M, Shorr RI, Cushman WC, Applegate WB. The role of diastolic blood pressure when treating isolated systolic hypertension. Arch Intern Med 1999;159:2004–2009
31. Messerli FH, Mancia G, Conti CR, et al. Dogma disputed: can aggressively lowering blood pressure in hypertensive patients with coronary artery disease be dangerous? Ann Intern Med 2006;144:884–893
32. Beckett NS, Peters R, Fletcher AE, et al. Treatment of hypertension in patients 80 years of age or older. N Engl J Med 2008;358:1887–1898
33. JATOS Study Group. Principal results of the Japanese trial to assess optimal systolic blood pressure in elderly hypertensive patients (JATOS). Hypertens Res 2008;31:2115–2127

34. Zanchetti A, Grassi G, Mancia G. When should antihypertensive drug treatment be initiated and to what levels should systolic blood pressure be lowered? A critical reappraisal. J Hypertens 2009;27:923–934

35. Cooper-DeHoff RM, Gong Y, Handberg EM, et al. Tight blood pressure control and cardiovascular outcomes among hypertensive patients with diabetes and coronary artery disease. JAMA 2010;304:61–68

36. Cushman WC, Evans GW, Byington RP, et al. Effects of intensive blood-pressure control in type 2 diabetes mellitus. N Engl J Med 2010;362:1575–1585

37. Patel A, MacMahon S, Chalmers J, et al. Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): a randomised controlled trial. Lancet 2007;370:829–840

38. Heart Outcomes Prevention Evaluation Study Investigators. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. Lancet 2000;355:253–259

39. PROGRESS Collaborative Group. Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6,105 individuals with previous stroke or transient ischaemic attack. Lancet 2001;358:1033–1041

40. Estacio RO, Jeffers BW, Hiatt WR, Biggerstaff SL, Gifford N, Schrier RW. The effect of nisoldipine as compared with enalapril on cardiovascular outcomes in patients with non-insulin-dependent diabetes and hypertension. N Engl J Med 1998;338:645–652

41. Schrier RW, Estacio RO, Esler A, Mehler P. Effects of aggressive blood pressure control in normotensive type 2 diabetic patients on albuminuria, retinopathy and strokes. Kidney Int 2002;61:1086–1097