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 lower 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, target 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). 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 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 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                         |

CAPP, 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.

Target blood pressure

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.

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