Published in final edited form as:

Curr Cardiovasc Risk Rep. 2012 August ; 6(4): 281–290. doi:10.1007/s12170-012-0246-0.

J Curve in Hypertension

Tanja Dudenbostel and

Vascular Biology and Hypertension Program, Division of Cardiovascular Disease, Department of Medicine, University of Alabama at Birmingham, Birmingham, AL 35294-2041, USA, 933 19th Street S, Community Health Services Building (CHSB), Room 115, Birmingham, AL 35294-2041, USA

Suzanne Oparil

Vascular Biology and Hypertension Program, Division of Cardiovascular Disease, Department of Medicine, University of Alabama at Birmingham, Birmingham, AL 35294-2041, USA

Abstract

The relationship between blood pressure and cardiovascular disease risk among treated hypertensives is J-shaped: risk is increased at high levels of blood pressure, falls in parallel with blood pressure reduction and increases again when blood pressure falls below a nadir (the point at which blood pressure is too low to maintain perfusion of vital organs). Randomized controlled trials of antihypertensive treatment have identified J-shaped relationships between achieved systolic and diastolic blood pressures and all-cause mortality, as well as fatal and nonfatal cardiovascular events, but not stroke or renal outcomes, in the general population of hypertensives and high-risk prehypertensives, particularly in subgroups such as the elderly and those with coronary artery disease, chronic kidney disease, diabetes, left ventricular hypertrophy, and high cardiovascular risk because of multiple comorbidities and concomitant risk factors. Blood pressure targets <130–140/70–85 mm Hg were not beneficial for any outcome except stroke and chronic kidney disease.

Keywords

Morbidity; Mortality; Systolic; Diastolic; Comorbidities; Chronic kidney disease; Coronary artery disease; Elderly

Introduction

Data from observational studies in the general population have revealed that naturally occurring lower blood pressure (BP) is associated with reduced risk for overall and cardiovascular mortality. Early data from life insurance examinations indicated that optimal BP appeared to be ~110/70 mm Hg [1, 2]. A meta-analysis of 61 prospective studies of one

Correspondence to: Tanja Dudenbostel.

Disclosure: T. Dudenbostel: none; S. Oparil: Data Safety Monitoring Board membership for Eli Lilly, consultancy for Bayer, Daiichi Sankyo Inc., Medtronic, Novartis and Pfizer.

Conflicts related to this article: None

million apparently healthy adults with no previous cardiovascular disease (CVD) followed for an average of 13 years found that usual BP was directly related to fatal coronary artery disease (CAD), fatal stroke, and overall mortality over the entire range without any evidence of a threshold down to a BP of 115/75 mm Hg [3]. Further, interventional studies of antihypertensive treatment showed that reducing BP reduced mortality, CVD events, and progression of vascular disease, and that the effect size appeared to be proportional to the magnitude of the reduction in BP, independent of specific choices of medications and specific thresholds and goals for treatment [4]. Together, these findings led to the general perception in the medical community that “lower BP is better” without any limit and aggressive antihypertensive therapy was espoused with enthusiasm.

The first challenge to the “lower is better” approach to BP management arose from a retrospective study of 169 hypertensive patients followed for a mean of 6 years that demonstrated a 5-fold greater risk of myocardial infarction (MI) in those with a diastolic BP (DBP) <90 mm Hg compared with those with a DBP of 100–109 mm Hg [5]. The author concluded that “normalization” of BP may precipitate as many MIs as it prevents. In his landmark study, Cruickshank et al reported on 902 patients with moderate-to-severe hypertension who were treated with atenolol alone or in combination with other antihypertensive agents and were followed for a mean of 6.1 years [6•]. The rate of death from MI was lowest when DBP was reduced to ~85 mm Hg and was higher when DBP was greater or less than 85–90 mm Hg. Importantly, there was a J-shaped relation between rate of death from MI and treated DBP only in the 342 patients with evidence of preexisting CAD defined as previous MI, angina, intermittent claudication, or ECG evidence of ischemia. The authors concluded that the J-shaped relation of DBP and MI could offset the beneficial effects of BP lowering in patients with antecedent CAD.

Since the original Cruickshank report, the J-curve concept has been the subject of constant reevaluation in the debate about how low the systolic BP (SBP) and DBP treatment goals should be in order to optimize CVD risk reduction without introducing harm. An early meta-analysis of cohort studies and randomized trials (13 studies, >48,000 participants) of treated hypertensive patients that stratified CVD outcomes by level of achieved BP revealed J-shaped relationships between treated BP and some, but not all, CVD outcomes [7•].

In this analysis, a BP threshold point (J-point) was considered to be present if the relationship between BP and CVD outcomes was not linear and if the lowest stratification of achieved BP was associated with no decrease in CVD events. The studies consistently demonstrated a J-shaped relationship between treated DBP and CAD events and mortality, but not with stroke incidence or mortality. A J-shaped curve was found in patients with and without antecedent CAD, but was more pronounced in the former group. Interestingly, a J-shaped relationship or a flattened curve for DBP was also observed in untreated or placebo treated control participants in these studies, suggesting that the J-curve may not be strictly a treatment phenomenon. The best-fitting summary curve for CAD events was J-shaped and predicted a doubling of events at a treated DBP of 75 mm Hg compared with 85 mm Hg (the nadir of the J-curve). The calculated summary curve for total mortality by treated DBP was flat, with a plateau of 85–90 mm Hg. In contrast, there was no consistent relationship

between treated SBP and events, although the issue was often not addressed in these early studies.

Data from more recent randomized controlled trials have expanded the scope of the J-curve question. Some trials have addressed the question more directly by randomizing hypertensive or high risk pre-hypertensive participants to study arms with different treatment targets. Recent trials have also enrolled participants with progressively lower threshold and target BPs and have focused on SBP as well as DBP. Most importantly, recent trials have focused on particular at risk patient groups (eg, elderly, antecedent CAD, CVD, diabetes, chronic kidney disease (CKD), left ventricular hypertrophy (LVH)) and have added progression of CKD to the list of outcomes under consideration. For this review, we conducted a PubMed search of literature published from 1959 until January 2012 using the terms systolic and diastolic blood pressure and J-curve. We also checked the reference lists of reviews, original studies, and meta-analyses to find additional studies, and included the most recent analyses of major clinical trials, eg, ACCORD, ONTARGET, VALUE, and INVEST. In the following, we will define the J-curve effect, discuss its pathophysiological mechanisms, and review evidence from recent clinical trials of antihypertensive treatment that redefines the J-curve concept for the general hypertensive population and for hypertensive patients with special comorbidities.

J-Curve Definition

The J-curve describes the shape of the relationship between BP and the risk of CV morbidity and mortality [8]. This concept reflects the observations that CVD risk is increased at high levels of BP, falls in parallel with BP reduction, and increases again when BP falls below a nadir. The nadir represents a point at which BP is too low to maintain perfusion of vital organs, particularly the heart.

Cardiohemodynamic Mechanisms

The J-curve was initially described for DBP in patients with established CAD. Most coronary perfusion occurs during diastole, and a low mean DBP equals a low coronary perfusion pressure. Lowering of DBP results in dilation of coronary microvessels via autoregulation in order to decrease vascular resistance and maintain tissue perfusion (Fig.1). Once maximal vasodilation is achieved, further reduction of perfusion pressure or mean DBP results in decreased coronary blood flow. In individuals with CAD who have stenotic lesions of large coronary arteries, an upward shift of perfusion pressure is required to maintain distal flow past the stenosis, and therefore there is less tolerance of low DBPs [9, 10]. Thus, in individuals with CAD, a fall in DBP may lower coronary perfusion pressure to a critical level, thereby intensifying ischemia and potentially causing a CAD event. In contrast, autoregulation in the cerebral and renal vascular beds operates over a wider range of BP and is more effective in maintaining blood flow at low perfusion pressures [11, 12]. Therefore, the J-curve for DBP that has been described for CAD events may not apply to stroke and CKD outcomes.

Additional mechanisms have been adduced to account for the J-curve phenomenon in the setting of low coronary perfusion pressure (DBP) and reduced coronary blood flow [7•, 13]. In patients with LVH, myocardial O₂ consumption is increased, making the heart vulnerable to ischemic events if DBP and coronary blood flow are reduced below a critical level. In addition, basal myocardial O₂ extraction may be at near maximal levels, making it impossible for the heart to compensate for low coronary flow by removing more O₂ from the circulation. Low coronary flow has also been associated with increased blood viscosity and platelet adhesiveness, predisposing to intracoronary thrombosis and MI. Further, at the interface between patchy areas of ischemia due to low DBP/coronary flow and surrounding areas of well perfused myocardium, metabolic gradients may develop that are thought to be arrhythmogenic.

Randomized Controlled Trials of Antihypertensive Treatment

Randomized controlled trials (RCTs) of antihypertensive treatment have generally tested the primary hypothesis that lowering BP reduces the risk of fatal and nonfatal CVD outcomes. Secondary, frequently post hoc, analyses of these trials have evaluated harms related to BP lowering by attempting to identify values of achieved SBP or DBP below, which further BP reduction is associated with increased events (Table 1). Studies have included general hypertensive populations, high CVD risk populations with or without diagnosed hypertension, and particular subgroups of hypertensive persons, including the elderly and those with concomitant CAD or other vascular disease, diabetes, CKD, and LVH.

Elderly

Two of the classic placebo controlled RCTs of antihypertensive treatment in the elderly, the Systolic Hypertension in the Elderly Program (SHEP) [14, 15] and the Systolic Hypertension in Europe trial (Syst-Eur) [16, 17], provided evidence of J-shaped relationships between DBP and CVD outcomes. SHEP included 4736 elderly patients ≥ 60 years with isolated systolic hypertension (ISH) who were randomized to active antihypertensive treatment or placebo and followed for a mean of 4.5 years. Mean BP of the SHEP population at entry was ~170/77 mm Hg; after 5 years of follow-up, the mean BP in the active treatment group was 143/68 vs 155/72 mm Hg in the placebo group. There were significantly fewer strokes and CVD events in the active treatment group, indicating benefit of reducing SBP in this elderly cohort. A post hoc analysis of SHEP revealed a strongly positive relationship between declining DBP and increasing CVD events (stroke, CAD, and CVD) in the active treatment group but not in the placebo group [17]. A treatment-induced decrease of 5 mm Hg was associated with increased CVD events; the increase in relative risk became significant for DBP <70 mm Hg and approached a 2-fold excess risk for DBP <55 mm Hg. The authors concluded that it could be harmful to intensify antihypertensive treatment in individuals with DBP <70 mm Hg. However, this analysis did not subdivide the SHEP population by baseline CAD status.

Similarly, a post hoc analysis of the Syst-Eur trial evaluated the relationship between on-treatment DBP and CVD events and mortality (non-CVD and CVD) in 4583 elderly (≥ 60 years) patients with ISH randomized to placebo or active treatment [17]. In the Syst-Eur

population as a whole, lowering DBP to ~55 mm Hg with active treatment was associated with increased non-CVD mortality but did not affect CVD mortality. In contrast, there was a J-shaped relationship between DBP and CVD events with a nadir of 70 mm Hg in both active treatment and placebo groups, but only in participants with a history of CAD at baseline.

Both SHEP and Syst-Eur analyzed the relationship between on-treatment SBP and outcomes, but no J-shaped relationship was reported in either trial, likely because achieved SBPs were in excess of 140 mm Hg in both.

The Hypertension in the Very Elderly Trial (HYVET) was designed to resolve clinical uncertainty about the relative benefits and risks of antihypertensive treatment in this growing patient population. HYVET randomized 3845 patients age ≥ 80 years (baseline BP 173.0/90.8 mm Hg) to active treatment or placebo and followed them for a median of 1.8 years [18]. There were decreases in the primary endpoint (fatal or nonfatal stroke), as well as major secondary endpoints (total mortality, CVD mortality, heart failure (HF), and fatal stroke) in the active-treatment group at an achieved BP of 143.5/77.9 mm Hg compared with the placebo group at a BP of 158.5/83.2 mm Hg. Fewer serious adverse events were reported in the active-treatment group, and there was no J-shaped relationship for either SBP or DBP with any outcome in either group. This landmark study was the first to report mortality benefits of antihypertensive treatment in the very elderly. A limitation of HYVET that reduces its generalizability to the entire population of very elderly hypertensives was inclusion of very healthy elderly persons (only 12 % had a history of CVD), who would likely be insensitive to a J-curve effect of BP reduction.

The Japanese Trial to Assess Optimal Systolic Blood Pressure in Elderly Hypertensive Patients (JATOS) compared the effect of strict SBP control (<140 mm Hg) with that of mild SBP control (140–160 mm Hg) in 4418 elderly (age 65–85 years) patients with hypertension [19]. Achieved SBPs differed by ~10 mm Hg (135.9/74.8 vs 145.6/78.1 mm Hg) between treatment groups after 2 years of follow-up, but there was no significant difference in the primary endpoint (a composite of CVD, cardiac and vascular disease and renal failure) or secondary endpoints (total deaths and safety issues). Further, there was neither a J-shaped relationship between achieved SBP and outcomes nor added benefit from more aggressive BP reduction.

The Valsartan Isolated Systolic Hypertension in the Elderly (VALISH) trial evaluated whether strict SBP control (<140 mm Hg) is superior to moderate (140 to <150 mm Hg) SBP control in reducing CV morbidity and mortality in elderly patients (≥ 70 years) [20]. After a follow-up of 2.85 years there was no difference in the primary outcome (a composite of CVD events) between the strict and moderate treatment groups. The investigators concluded that moderate control of SBP (<150 mm Hg) may be sufficient to reduce CVD events in elderly hypertensive patients. However, similar to JATOS, the trial was underpowered to evaluate whether SBP control <140 mm Hg was superior to SBP control 140 to <150 mm Hg.

A subanalysis of INVEST (described below) that focused on the 2180 very old (>80 years) participants demonstrated age-dependent J-shaped relationships between on-treatment SBP and DBP and the primary outcome (all-cause mortality, nonfatal MI, or nonfatal stroke) [21]. The SBP nadir increased with increasing age from 110 mm Hg in the youngest (<60 years) to 135 mm Hg in the 60 to <70 years group to 140 mm Hg in the very old. The DBP nadir was 75 mm Hg for those <60 to <80 years and 70 mm Hg for the very old. The observation that reduction of SBP to <140 mm Hg is associated with increased adverse events and outcomes in the very old suggests that BP management should be less aggressive in this group than in the general hypertensive population.

Coronary Artery Disease

The International Verapamil-Trandolapril study (INVEST) tested the hypothesis that a calcium channel blocker (CCB) or a beta blocker (BB) strategy would be equally effective in preventing CVD events in a population of 22,576 high risk hypertensive patients with stable CAD [22]. A secondary analysis of data from INVEST evaluated the relationship between average on-treatment BP and risk for the primary outcome (all-cause mortality, nonfatal MI, or nonfatal stroke) [23]. In the study as a whole there was a J-shaped relationship with a nadir of 119/84 mm Hg (129/74 mm Hg after adjustment for time to primary outcome) between both SBP and DBP and all-cause mortality and MI in both treatment groups. In contrast, there was no J-shaped relationship for stroke, and at lower DBP there were substantially more MIs than strokes. INVEST also reported an interaction between decreased DBP and history of revascularization [24].

An analysis that focused on 6166 previously revascularized (coronary artery bypass grafting (CABG), percutaneous coronary intervention (PCI), or both) INVEST participants and compared them with 16,410 non-revascularized participants (control group) showed a significant intervention effect. Lower DBP was associated with a lower risk of the primary outcome in revascularized patients than in those without re-vascularization. The J-shaped relationships between SBP, DBP and CVD events seen in the study as a whole were also present in revascularized patients, but there was an upward shift for the SBP nadir and a downward shift for the DBP nadir in this group, suggesting that revascularization improved coronary perfusion and therefore tolerability of lower DBP (coronary perfusion pressure).

An additional subanalysis of INVEST tested whether treating to a target BP of <130/80 mm Hg compared with the usual target of <140/90 mm Hg was associated with improved outcomes in 2699 patients with CAD and concomitant peripheral arterial disease (PAD), a particularly high risk group [25]. The primary outcome occurred less frequently at an achieved BP of 135–145/60–90 mm Hg compared with those with lower and higher BPs. Thus, there were J-shaped relationships between both SBP and DBP and the primary outcome. These findings were interpreted by the authors as not supporting the target BP of <130/80 mm Hg in this patient population.

The Treating to New Targets (TNT) trial randomized 10,001 patients with CAD to a less vs more intensive lipid-lowering regimen (10 mg vs 80 mg atorvastatin) without regard to BP status [26]. The trial showed that cardiac events were significantly reduced in the intensive

lipid-lowering arm. A subanalysis relating in-trial SBPs and DBPs to fatal and nonfatal cardiac events revealed J-shaped relationships with nadirs at 146.3 and 81.4 mm Hg [27]. The J-curves were relatively flat for BPs of 140–120/80–70 mm Hg, with increases in cardiac events at SBPs <120–110 and DBPs <70–60 mm Hg. For stroke, there was a J-shaped relationship for DBP (nadir 80 mm Hg), but not for SBP.

Diabetes

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial tested whether lowering glycated hemoglobin to normal levels with intensive therapy would reduce major CVD events (nonfatal MI, nonfatal stroke, or CVD death) in 10,251 high risk diabetic patients [28]. In the ACCORD-Lipid trial a subgroup of 5518 participants were further randomized to simvastatin plus fenofibrate or placebo to test whether major CVD events would be reduced by addition of a fibrate to statin therapy [29]. In the ACCORD-BP trial the remaining 4733 participants were further randomized to either intensive therapy with a SBP target of <120 mm Hg or standard therapy with a SBP target of <140 mm Hg [30•]. Achieved BP in the intensive-treatment group was 119/64 mm Hg; in the standard-treatment group, 134/71 mm Hg. There was no significant difference between treatment groups for the primary outcome (major CVD events) or most of the secondary outcomes. However, in the intensive-treatment group, stroke was reduced significantly (hazardratio [HR], 0.59; 95 % confidence interval [CI], 0.39–0.89; $P=0.03$). Importantly, there was also an increased incidence of serious adverse events attributed to BP medications, including hypotension, syncope, bradycardia or arrhythmia and hyperkalemia in the intensive-treatment group. The results of ACCORD clearly do not demonstrate a linear relationship between BP and CVD outcomes, as the lower goal (and achieved) SBP was not associated with a reduction in CVD events. Whether the benefits of aggressive BP lowering in reducing stroke outweigh the increase in adverse events and the lack of CVD benefit in diabetic patients is a matter of ongoing debate among clinicians.

The Action in Diabetes and Vascular disease–PreterAx and DiamicroN–MR Controlled Evaluation (ADVANCE) trial compared the effects of administering an angiotensin converting enzyme (ACE) inhibitor-diuretic combination to placebo on major macrovascular and microvascular events (death from CVD disease, nonfatal stroke or nonfatal MI, new or worsening diabetic renal or eye disease) in 11,140 high risk diabetic patients (38 % Asian) [31, 32]. There were no BP criteria for inclusion and use of other antihypertensive agents was permitted. Active treatment resulted in lower achieved BPs (135/74 mm Hg vs 140/76 mm Hg) and significant reductions in combined macrovascular and microvascular endpoints compared with placebo. There was no evidence of a J-curve. A subsequent report assessed the effects of lowering BP to levels below currently recommended thresholds (130/80 and 125/75 mm Hg for people with diabetes and nephropathy respectively) for renal outcomes among participants in the ADVANCE trial [33]. Active treatment reduced the risk for renal events by 21 % ($P<0.0001$), an outcome driven by reduced risks for microalbuminuria and macroalbuminuria ($P<0.003$). Treatment effects were consistent across subgroups defined by baseline SBP or DBP, and lower SBP levels during followup were linearly related to reductions in renal outcomes, even to values <110 mm Hg. Risk for renal events was lowest among those with a median achieved SBP of 106 mm Hg and an achieved DBP in the range

62–93 mm Hg. Thus, ADVANCE demonstrated no J-curve relationship for either SBP or DBP with renal events in patients receiving fixed combination ACE inhibitor-diuretic treatment.

An observational subgroup analysis of data from the 6400 participants in INVEST who had diabetes at baseline tested whether tight SBP control (SBP <130 mm Hg) would reduce CVD outcomes [34••]. The tight SBP goal (<130 mm Hg) was not associated with reduced CVD morbidity compared with the conventional SBP goal of <140 mm Hg. Further, there was an increase in all-cause mortality in the tight BP control group.

Chronic Kidney Disease

The African-American Study of Kidney Disease and Hypertension (AASK) trial compared the effects of 2 levels of BP control (standard: mean arterial pressure (MAP) 102–107 vs intensive: MAP 92 mm Hg) and of 3 antihypertensive drug classes (ACE inhibitor, BB or CCB) on kidney function and mortality in 1094 non-diabetic African American patients with CKD [35]. Achieved BPs were 141/85 (MAP 104) mm Hg in the standard group and 128/78 (MAP 95) mm Hg in the intensive group. There was no difference between groups in the primary outcome (reduction in glomerular filtration rate (GFR), end stage renal disease (ESRD), or death). Similarly, an analysis of CVD outcomes during the active treatment phase of AASK revealed that neither achieved BP nor antihypertensive drug class affected CVD events [36•]. However, the small number of events limited the interpretation of the study.

Following the active treatment phase, AASK participants were invited to enroll in an extension (cohort) phase in which all participants were treated with an ACE inhibitor (or angiotensin receptor blocker [ARB] if not tolerated) to a BP target of <130/80 mm Hg [37•]. Total follow-up (trial and cohort phase) was 8.8 years to 12.2 years. During the cohort phase, mean BPs were 130/78 mm Hg in the intensive group and 141/86 mm Hg in the standard group. As in the active phase, there was no difference between groups in risk of the primary outcome. However, among participants with urinary protein-to-creatinine ratios >0.22, those in the intensive group had a significant reduction in risk of the primary outcome. Overall, the findings of AASK do not reveal benefit of intensive BP control on either progression of CKD or mortality in non-diabetic African-American patients with CKD in the absence of proteinuria.

The Irbesartan in Diabetic Nephropathy Trial (IDNT) compared the effects of an ARB vs CCB or placebo on the progression of CKD (doubling of serum creatinine, ESRD) or all-cause mortality in 1590 hypertensive patients with diabetic nephropathy treated to a BP goal 135/85 mm Hg [38]. Progression of CKD was reduced with the ARB compared with either the CCB or placebo independent of BP. In contrast, a post hoc analysis demonstrated J-shaped relationships between achieved SBP and CVD mortality and HF with a nadir of 120 mm Hg and between achieved DBP and all-cause mortality and MI with a nadir in the range of 80–85 mm Hg [39]. There was no J-curve for stroke. While these findings do not support use of intensive BP lowering to prevent CVD outcomes in patients with diabetes and CKD, interpretation is limited by the small number of events observed.

Left Ventricular Hypertrophy

The Losartan Intervention for Endpoint reduction in hypertension (LIFE) trial demonstrated that ARB-based treatment was superior to BB-based treatment in reducing a composite end-point (CVD death, nonfatal MI, or nonfatal stroke) in 9193 hypertensive patients with electrocardiographically documented LVH (ECG-LVH) despite equivalent BP responses [40]. A post hoc analysis tested whether lower achieved SBP (< 130 mm Hg) was associated with a reduced risk of CVD morbidity and mortality and all-cause mortality compared with usual SBP control (131–141 mm Hg) and inadequate SBP control (≥ 142 mm Hg) [41•]. Usual SBP control (131–141 mm Hg) was associated with a reduction in CVD events compared with the 2 other groups. There was a J-shaped relationship with a nadir at 130 mm Hg for SBP. Participants with an achieved SBP ≥ 130 mm Hg had no further reduction in MI or stroke, a tendency toward increased CVD mortality and significantly increased all-cause mortality. These outcomes were independent of achieved DBP and treatment modality. Similar to findings in diabetic hypertensive patients, these data do not support treating patients with ECG-LVH to lower SBP goals in order to prevent CVD outcomes and death.

High Cardiovascular Risk

The Valsartan Antihypertensive Long-Term Evaluation (VALUE) trial tested whether for the same level of BP control an ARB would reduce CVD morbidity and mortality compared with a CCB in 15,245 hypertensive patients at high CVD risk because of multiple risk factors or pre-existing CVD [42]. The primary composite endpoint was not significantly different between treatment groups despite a greater BP decrease in the CCB arm. Post hoc analyses revealed a J-shaped relationship between DBP and CVD events with a nadir of 78 mm Hg that was seen only for participants with CAD at baseline (46 % of the cohort) [43, 44].

The Cardiovascular Effects of Systolic Blood Pressure Control (Cardio-Sis) trial tested the hypothesis that tight-control of SBP (< 130 mm Hg) compared with usual-control (< 140 mm Hg) would be beneficial in preventing ECG-LVH and a composite of CVD events in 1111 non-diabetic patients with SBP ≥ 150 mm Hg [45]. Achieved BPs were 131.9/77.4 mm Hg in the tight-control vs 135.6/78.8 mm Hg in the usual-control group ($P < 0.0001$). Outcomes were significantly reduced in the tight-control group, and adverse effects of treatment were rare and did not differ between groups. The absence of a J-curve led the authors to conclude that their findings support a lower BP goal than currently recommended for non-diabetic patients with hypertension. Weaknesses of the study include its small size, short duration of follow-up, and use of an intermediate endpoint (ECG-LVH) as the primary outcome.

The Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial study (ONTARGET) randomized 25,588 high risk patients (≥ 55 years with known atherosclerotic disease or diabetes with vascular damage (9603 patients) to an ACE inhibitor, an ARB or both to test whether the ARB was not inferior to the ACE inhibitor and whether a combination of the 2 was superior to the ACE inhibitor alone in preventing CVD events and stroke [46]. ONTARGET showed that the ARB was equivalent to the ACE inhibitor and was associated with fewer serious adverse effects (angioedema); the combination was associated

with no outcome benefit and with more adverse events than the ACE inhibitor despite greater BP reduction. Post hoc analyses examined the effects of achieved SBP and DBP on CVD outcomes in the cohort as a whole and in the diabetic subgroup [47••, 48]. For the cohort as a whole there was a J-shaped relationship (nadir 130 mm Hg) between achieved SBP, categorized into deciles, and risk of all CVD outcomes except stroke [47••]. For any level of achieved SBP, the highest risk of a CVD event or stroke was seen in participants in the lowest quartile of in-trial DBP (< 72 mm Hg). CVD risk was significantly higher in the diabetic subgroup than in non-diabetic participants in ONTARGET, regardless of the SBP achieved during treatment [48]. As in the cohort as a whole, there was no benefit in fatal or nonfatal CVD outcomes from reducing SBP to < 130 mm Hg.

A large collaborative meta-analysis of 102 prospective studies from the Emerging Risk Factors Collaboration that enrolled a total of 698,782 persons without a history of vascular disease or diabetes at baseline confirmed the J-shaped relationship between SBP and CHD that was observed in ONTARGET [49]. This analysis stratified participants into 10 mm Hg increments of baseline SBP and found a nadir in CHD risk at a SBP of 130 mm Hg. Interestingly similar J-shaped relationships were found between CHD events and other major risk factors, including fasting blood glucose and total and non-HDL cholesterol.

A secondary analysis of ONTARGET compared the benefits and risks of treating to BP targets of $< 140/90$ vs $< 130/80$ mm Hg on CVD and renal events and stroke [50•]. For the analysis, treatment groups were pooled, and participants were divided into 4 groups according to the percentage of in-treatment visits in which BP was found to be controlled (to $< 140/90$ or $< 130/80$ mm Hg) prior to occurrence of an event. After adjustment for demographic and clinical variables, a progressive increase in the proportion of visits in which BP was reduced to $< 140/90$ or $< 130/80$ mm Hg was associated with a progressive reduction in stroke, new onset microalbuminuria or macroalbuminuria or return to normoalbuminuria in albuminuria patients, but no progressive reduction in MI or HF was seen. The risk of CVD events was reduced by increasing the frequency of BP control to $< 140/90$, but not to $< 130/80$ mm Hg. These findings provide evidence that in high-CVD risk patients, reducing BP to $< 140/90$ mm Hg, but not to a lower BP, is associated with CVD protection. Achievement of lower BP goals appeared to be useful in preventing stroke and renal outcomes, however.

Conclusion

Randomized controlled trials of antihypertensive treatment provide evidence for J-shaped relationships between both SBP and DBP and important outcomes (all-cause mortality CVD mortality, nonfatal and fatal MI, HF) in the general population of hypertensive patients, as well as in high-risk special populations, (eg, the elderly, those with pre-existing CVD [CAD, PAD, LVH], CKD, diabetes, or multiple CVD risk factors). Most analyses point towards a nadir of 130–140/70–85 mm Hg in the J-curve without providing evidence that treatment targeted to < 130 or < 120 mm Hg is beneficial for any outcome except stroke and renal outcomes. These J-curve data from randomized trials are supported by findings of the recently published Secondary Manifestations of Arterial Disease (SMART) study, an observational study of a cohort of 5788 patients with symptomatic vascular disease (CAD,

PAD, CVD, or a combination) at baseline [51, 52•]. The relationship between BP and all vascular events followed a J-shaped curve with a nadir of 143/82 mm Hg. For SBP and stroke, no non-linearity was found, while DBP and stroke were non-linearly related.

Most of the current evidence supporting the J-curve concept comes from post hoc analyses that are subject to confounding. Well-designed, appropriately powered randomized controlled trials designed to prospectively evaluate the J-curve as a primary outcome are needed to sort out cause-effect relationships between achieved BPs and CVD outcomes, as well as to define optimal treatment of well phenotyped hypertensive populations [53]. Further, prospective analyses of the effects of different classes of antihypertensive agents on the J-curve relationship and its potential reversibility are also needed to assist clinicians in managing their high risk hypertensive patients.

The ongoing Systolic Blood Pressure Intervention Trial (SPRINT) is enrolling a population of 9250 older hypertensive patients with a rich admixture of antecedent CKD and CVD, but without diabetes, in order to test the hypothesis that aggressive BP treatment (SBP goal <120 mm Hg) compared with standard goal (<140 mm Hg) will reduce CVD and renal outcomes and delay the progression of cognitive decline and development of dementia [54, 55]. Pending results of SPRINT, which are expected to be available in 2018, little enthusiasm currently exists for attempting to lower BP into the normal range (<120 mm Hg) with pharmacologic antihypertensive therapy in high risk hypertensives.

References

Papers of particular interest, published recently, have been highlighted as:

• Of importance

•• Of major importance

1. Build and Blood Pressure. Chicago: Society of Actuaries. 1959; 1
2. Lew EA. High blood pressure, other risk factors and longevity: the insurance viewpoint. *Am J Med.* 1973; 55:281–94. [PubMed: 4746556]
3. 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; 360:1903–13. [PubMed: 12493255]
4. Blood Pressure Lowering Treatment Trialists Collaboration. Effects of different blood-pressure lowering regimens on major cardiovascular events: results of prospectively-designed overviews of randomized trials. *Lancet.* 2003; 362:1527–35. [PubMed: 14615107]
5. Stewart IM. Relation of reduction in pressure to first myocardial infarction in patients receiving treatment for severe hypertension. *Lancet.* 1979; 313:861–5.
- 6••. Cruickshank JM, Thorp JM, Zacharias FJ. Benefits and potential harm of lowering high blood pressure. *Lancet.* 1987; 329:581–4. In this study the term J-curve is used for the first time for the nonlinear relationship between BP and cardiovascular risk.
- 7•. Farnett L, Mulrow CD, Linn WD, Lucey CR, Tuley MR. The J-curve phenomenon and the treatment of hypertension Is there a point beyond which pressure reduction is dangerous? *JAMA.* 1991; 265:489–95. [PubMed: 1824642]
8. Williams B. Hypertension and the J-curve. *JACC.* 2009; 54:1835–6. [PubMed: 19892234]
9. Canty JM Jr. Coronary pressure-function and steady-state pressure-flow relations during autoregulation in the unanesthetized dog. *Circ Res.* 1988; 63:821–36. [PubMed: 3168181]

10. Polese A, De Cesare N, Montorsi P, Fabbicchi F, Guazzi M, Loaldi A, Guazzi MD. Upward shift of the lower range of coronary flow autoregulation in hypertensive patients with hypertrophy of the left ventricle. *Circulation*. 1991; 83:845–53. [PubMed: 1825626]
11. Lucas SJ, Tzeng YC, Galvin SD, Thomas KN, Ogoh S, Ainslie PN. Influence of changes in blood pressure on cerebral perfusion and oxygenation. *Hypertension*. 2010; 55:698–705. [PubMed: 20083726]
12. Loutzenhiser R, Griffin K, Williamson G, Bidani A. Renal autoregulation: new perspectives regarding the protective and regulatory roles of the underlying mechanisms. *Am J Physiol Regul Integr Comp Physiol*. 2006; 290:R1153–67. [PubMed: 16603656]
13. Berglund G. Goals of hypertensive therapy: is there a point beyond which pressure reduction is dangerous? *Am J Hypertens*. 1989; 2:586–93. [PubMed: 2667576]
14. 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). SHEP Cooperative Research Group. *JAMA*. 1991; 265:3255–64. [PubMed: 2046107]
15. 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; 159:2004–9. [PubMed: 10510985]
16. Staessen JA, Fagard R, Thijs L, Celis H, Arabidze GG, Birkenhäger WH, et al. Randomized double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension. The Systolic Hypertension in Europe (Syst-Eur) Trial Investigators. *Lancet*. 1997; 350:757–64. [PubMed: 9297994]
17. Fagard RH, Staessen JA, Thijs L, Celis H, Bulpitt CJ, de Leeuw PW, et al. On treatment diastolic blood pressure and prognosis in systolic hypertension. *Arch Intern*. 2007; 167:1884–91.
18. Beckett NS, Peters R, Fletcher AE, et al. Treatment of hypertension in patients 80 years of age and older. *N Engl J Med*. 2008; 358:1887–98. [PubMed: 18378519]
19. JATOS Study Group. Principal results of the Japanese Trial to Assess Optimal Systolic Blood Pressure in Elderly Hypertensive Patients (JATOS). *Hypertens Res*. 2008; 31:2115–27. [PubMed: 19139601]
20. Ogiwara T, Saruta T, Raguki H, et al. Target blood pressure for treatment of isolated systolic hypertension in the elderly. *Hypertension*. 2010; 56:196–202. [PubMed: 20530299]
21. Denardo SJ, Gong Y, Nichols WW, Messerli FH, Bavry AA, Cooper-Dehoff RM, Handberg EM, Champion A, Pepine CJ. Blood pressure and outcomes in very old hypertensive coronary artery disease patients: an INVEST substudy. *Am J Med*. 2010; 123:719–26. [PubMed: 20670726]
22. Pepine CJ, Handberg EM, Cooper-DeHoff RM, et al. A calcium antagonist versus a non-calcium antagonist hypertension treatment strategy for patients with coronary artery disease. The International Verapamil-Trandolapril Study (INVEST): a randomized controlled trial. *JAMA*. 2003; 290:2805–16. [PubMed: 14657064]
23. Messerli FH, Mancia G, Conti CR, Hewkin AC, Kupfer S, Champion A, et al. Dogma disputed: can aggressively lowering blood pressure in hypertensive patients with coronary artery disease be dangerous? *Ann Intern Med*. 2006; 144:884–93. [PubMed: 16785477]
24. Denardo SJ, Messerli FH, Gaxiola E, Aranda JM Jr, Cooper-Dehoff RM, Handberg EM, et al. Coronary revascularization strategy and outcomes according to blood pressure (from the International Verapamil-Trandolapril Study [INVEST]). *Am J Cardiol*. 2010; 106:498–503. [PubMed: 20691307]
25. Bavry AA, Anderson D, Gong Y, Denardo SJ, Cooper-DeHoff RM, Handberg EM, et al. Outcomes among hypertensive patients with concomitant peripheral and coronary artery disease: findings from the International Verapamil-SR/Trandolapril Study. *Hypertension*. 2010; 55:48–53. [PubMed: 19996066]
26. LaRosa JC, Deedwania PC, Shepherd J, et al. Comparison of 80 versus 10 mg of atorvastatin on occurrence of cardiovascular events after the first event (from the Treating to New Targets [TNT] trial). *Am J Cardiol*. 2010; 105:283–7. [PubMed: 20102935]
27. Bangalore S, Messerli FH, Wun C, et al. J-curve revisited: an analysis of blood pressure and cardiovascular events in the Treating to New Targets (TNT) Trial. *Eur Hear J*. 2010; 31:2897–908.

28. Gerstein HC, Miller ME, Byington RP, et al. On behalf of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Study Group. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med*. 2008; 358:2545–59. [PubMed: 18539917]
29. ACCORD Study Group. Effects of combination lipid therapy in type 2 diabetes mellitus. *N Engl J Med*. 2010; 362:1563–74. [PubMed: 20228404]
- 30•. Cushman WC, Evans GW, Byington RP, et al. ACCORD Study Group. Effects of intensive blood-pressure control in type 2 diabetes mellitus. *N Engl J Med*. 2010; 362:1575–85. This large randomized controlled trial demonstrated for the first time no benefit of aggressive antihypertensive treatment to a goal SBP<120 mm Hg compared with conventional treatment to a goal SBP<140 mm Hg on CVD outcomes other than stroke in patients with hypertension and diabetes. [PubMed: 20228401]
31. Rationale and design of the ADVANCE study: a randomised trial of blood pressure lowering and intensive glucose control in high-risk individuals with type 2 diabetes mellitus Action in Diabetes and Vascular Disease: PreterAx and DiamicroN Modified-Release Controlled Evaluation. *J Hypertens Suppl*. 2001; 19(Suppl):S21–8.
32. 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; 370:829–40. [PubMed: 17765963]
33. de Galan BE, Perkovic V, Ninomiya T, Pillai A, Patel A, Cass A, et al. ADVANCE Collaborative Group. Lowering blood pressure reduces renal events in type 2 diabetes. *J Am Soc Nephrol*. 2009; 20:883–92. [PubMed: 19225038]
- 34•. Cooper-DeHoff RM, Gong Y, Handberg EM, Bavry AA, Denardo SJ, Bakris GL, et al. Tight blood pressure control and cardiovascular outcomes among hypertensive patients with diabetes and coronary artery disease. *JAMA*. 2010; 304:61–8. This subgroup analysis of data from INVEST demonstrated no benefit of tight SBP control (<130 mm Hg) compared with conventional SBP control (<140 mm Hg) on CVD outcomes or all-cause mortality. [PubMed: 20606150]
35. Wright JT Jr, Bakris G, Greene T, et al. African American Study of Kidney Disease and Hypertension Study Group. Effect of blood pressure lowering and antihypertensive drug class on progression of hypertensive kidney disease: results from the AASK trial. *JAMA*. 2002; 288:2421–31. [PubMed: 12435255]
- 36•. Norris K, Bourgoigne J, Gassman J, Hebert L, et al. Cardiovascular outcomes in the African American Study of Kidney Disease and Hypertension AASK (Trial). *Am J Kidney Dis*. 2006; 48:739–51. This analysis of CVD outcomes during the active phase of AASK showed no benefit of either intensive antihypertensive treatment or of any particular antihypertensive drug class. [PubMed: 17059993]
- 37•. Appel LJ, Wright JT, Greene T, et al. Intensive blood pressure control in hypertensive chronic kidney disease. *N Engl J Med*. 2010; 363:918–29. Long-term followup of AASK showed no benefit of intensive BP control on either progression of CKD or mortality in the absence of proteinuria. [PubMed: 20818902]
38. Lewis EJ, Hunsicker LG, Clarke WR, et al. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med*. 2001; 345:851–60. [PubMed: 11565517]
39. Berl T, Hunsicker LG, Lewis JB, et al. Collaborative Study Group. Impact of achieved blood pressure on cardiovascular outcomes in the Irbesartan Diabetic Nephropathy Trial. *J Am Soc Nephrol*. 2005; 16:2170–9. [PubMed: 15930097]
40. Dahlöf B, Devereux RB, Kjeldsen SE, et al. Cardiovascular morbidity and mortality in the Losartan Intervention for Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. *Lancet*. 2002; 359:995–1003. [PubMed: 11937178]
- 41•. Okin PM, Hille DA, Kjeldsen SE, Dahlöf B, Devereux RB. Impact of lower achieved blood pressure on outcomes in hypertensive patients. *J Hypertens*. 2012; 30:802–10. Post-hoc analysis of LIFE showed for the first time that lowering SBP to 130 mm Hg had no benefit on CVD outcomes or stroke and increased all-cause mortality in patients with ECG-LVH. [PubMed: 22343536]

42. Julius S, Kjeldsen SE, Weber M, et al. Outcomes in hypertensive patients at high vascular risk treated with regimens based on valsartan or amlodipine: the VALUE randomized trial. *Lancet*. 2004; 363:2022–31. [PubMed: 15207952]
43. Messerli FH, Mancia G, Weber MA, Kjeldsen SE, Holzhauer B, Hua TA, et al. Low blood pressure is associated with increased cardiovascular morbidity (J-shaped curve) in treated hypertensive patients with increased cardiovascular risk: The VALUE Randomized Trial. *J Am Coll Cardiol*. 2009; 53(Suppl A):A46.
44. Zanchetti A, Julius S, Kjeldsen S, McInnes GT, Hua T, Weber M, et al. Outcomes in subgroups of hypertensive patients treated with regimens based on valsartan and amlodipine: an analysis of findings from the VALUE trial. *J Hypertens*. 2006; 24:2163–8. [PubMed: 17053536]
45. Verdecchia P, Staessen J, Angeli F, et al. Usual versus tight control of systolic blood pressure in non-diabetic patients with hypertension (Cardio-sis): an open-label randomized trial. *Lancet*. 2009; 374:525–33. [PubMed: 19683638]
46. ONTARGET Investigators. Telmisartan, ramipril, or both in patients at high risk for vascular events. *N Engl J Med*. 2008; 358:1547–59. [PubMed: 18378520]
- 47•. 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; 27:13609. This post-hoc analysis of ONTARGET showed no benefit on fatal or nonfatal CVD outcomes from reducing SBP to <130 mm Hg.
48. Redon J, Mancia G, Sleight P, et al. Safety and efficacy of low blood pressures among patients with diabetes: subgroup analyses from the ONTARGET trial. *J Am Coll Cardiol*. 2012; 59:74–83. [PubMed: 22192672]
49. SarwarN, Gao P, Seshasai SR, Gobin R, Kaptoge S, Di Angelantonio E, et al. Emerging Risk Factors Collaboration. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. *Lancet*. 2010; 375:2215–22. [PubMed: 20609967]
- 50•. Mancia G, Schumacher H, Redon J, Verdecchia P, Schmieder R, Jennings G, et al. Blood pressure targets recommended by guidelines and incidence of cardiovascular and renal events in ONTARGET. *Circulation*. 2011; 124:1727–36. A secondary analysis of ONTARGET demonstrated that in high-CVD risk patients reducing BP to <140/90 mm Hg, but not to a lower BP, is associated with CVD protection; achievement of lower goals may be useful in preventing stroke and renal outcomes. [PubMed: 21947289]
51. Simons PC, Algra A, van de Laak MF, Grobbee DE, van der Graaf Y. Second manifestations of ARTerial disease (SMART) study: rationale and design. *Eur J Epidemiol*. 1999; 15:773–81. [PubMed: 10608355]
- 52•. Dorresteyn JA, van der Graaf Y, Spiering W, et al. Secondary Manifestations of Arterial Disease Study Group. Relation between blood pressure and vascular events and mortality in patients with manifest vascular disease: J-curve revisited. *Hypertension*. 2012; 59:14–21. This large cohort study of patients with symptomatic vascular disease at baseline demonstrated a J-curve with a nadir of 143/82 mm Hg for all vascular events except stroke. [PubMed: 22068865]
53. Panjraht GS, Chaudhari S, Messerli FH. The j-point phenomenon in aggressive therapy of hypertension: new insights. *Curr Atherosclerosis Rep*. 2012; 14:124–9.
54. ClinicalTrials.gov Systolic Blood Pressure Intervention Trial (SPRINT). [Accessed April 2012] <http://clinicaltrials.gov/ct2/show/NCT01206062?term=SPRINT&rank=2> ClinicalTrials.gov Identifier-NCT01206062
55. Systolic Blood Pressure Intervention Trial (SPRINT). [Accessed April 2012] Wake Forest School of Medicine. <https://www.sprintrial.org/public/dspHome.cfm>

Fig. 1.

Pressure flow relationship in the coronary circulation coronary blood flow is subjected to autoregulation. In the presence of a stenosis in a coronary artery, a fall in pressure across the stenotic lesion occurs and the microvessels dilate to compensate for the reduced distal arterial perfusion pressure, maintaining normal resting flow to a certain threshold. Beyond that point further reduction of perfusion pressure results in a decreased flow. (Hirata K, et al. Measurement of coronary vasomotor function: getting to the heart of the matter in cardiovascular research. Clin Sci 2004;107:449–60)

Randomized controlled trials - relationship of BP levels and cardiovascular outcomes

Table 1

Trial	FU duration, y	No. of participants	Age, y	% men	Race, %white	BMI, kg/m ²	BL SBP, mm Hg	BL DBP, mm Hg	FU SBP, mm Hg	FU DBP, mm Hg	J-point SBP, mm Hg	J-point DBP, mm Hg
SHEP [16, 17]	4.5	4736	72	43	86	–	170	77	149	70	–	<70
SystEur [18, 19]	2	4583	70	34	–	27	174	85	156	81	–	<70
HYVET [20]	2.1	3845	84	40	–	25	173	91	151	80	–	–
JATOS [21]	2	4418	76	39	0	24	172	89	140	76	–	–
VALISH [22]	2.85	3260	76	38	0	–	170	82	140	75	–	–
INVEST [23]	2	2180	84	39	54	26	150	86	–	–	140	70
INVEST [24, 25]	2	22,576	66	48	48	29	150	86	131	76	119	84
INVEST [26]	2	6166	66	66	74	29	150	86	131	76	125–145	55–80
INVEST [27]	2.7	2699	69	48	48	29	150	86	132	76	135–145	60–90
ACCORD-BP [28]	4.7	4733	62	52	61	32	139	76	126	67	–	–
ADVANCE [29, 30••]	4.3	11,140	66	57	–	28	145	81	139	79	–	–
INVEST [31]	2	6400	66	46	44	30	150	86	151	85	120–125	–
ASKK [32, 34••, 35]	4.1	1094	55	61	0	31	150	96	135	82	–	–
IDNT [36•, 37•]	2.6	1590	59	66	73	31	159	87	142	78	120	85
LIFE [39]	4.6	9193	67	46	85	30	174	98	147	79	130	–
VALUE [40, 41•, 42]	4.2	15,245	67	58	89	28	160	91	138	78	120–130	78
Cardio-sis [43]	2	1111	67	41	–	28	163	90	134	78.1	–	–
TNT [47••]	4.9	10,001	61	81	94	28	131	78	–	–	146	81
ONTARGET [50•]	4.6	9603	66	70	67	29	144	82	135	77	129	67–87
ONTARGET [51]	4.6	25,588	66	70	73	28	142	82	135	77	126–130	75–79 67
ONTARGET [52•]	2.75	12,554	67	72	–	28	144	82	135	77	130	80

Age, SBP, DBP, expressed as mean. BL, baseline; FU, follow up

ACCORD, Action to Control Cardiovascular Risk in Diabetes; ADVANCE, Action in Diabetes and Vascular disease; Perterax and Diamicron-MR Controlled Evaluation; IDNT, Irbesartan Diabetic Nephropathy Trial; INVEST, International Verapamil-Trandolapril Study

JATOS, Japanese Trial to Assess Optimal Systolic Blood Pressure in Elderly Hypertensive Patients; ONTARGET, Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial ; SHEP, Systolic Hypertension in the Elderly Program; Syst-Eur Systolic Hypertension in Europe; TNT, Treating to New Targets; VALUE, The Valsartan Antihypertensive Long-term Use Evaluation Trial; VALISH, Valsartan in Elderly Isolated Systolic Hypertension Study.