Curr Hypertens Rep (2013) 15:575–581
DOI 10.1007/s11906-013-0402-z



# Blood Pressure Levels and Stroke: J-curve Phenomenon?

**Jolanta Malyszko · Paul Muntner · Jacek Rysz · Maciej Banach**

Published online: 25 October 2013


**Abstract** The blood pressure J-curve discussion has been ongoing for more than 30 years, yet there are still questions in need of definitive answers. On one hand, existing antihypertensive therapy studies provide strong evidence for J-curve-shaped relationships between both diastolic and systolic blood pressure and primary outcomes in the general hypertensive patient population, as well as in high-risk populations, including subjects with coronary artery disease, diabetes mellitus, left ventricular hypertrophy, and the elderly. On the other hand, we have very limited data on the relationship between systolic and diastolic blood pressure and stroke prevention. Moreover, it seems that this outcome is more a case of "the lower the better." Further large, well-designed studies are necessary in order to clarify this issue, especially as existing available studies are observational, and randomized trials either did not have or lost statistical power and were thus inconclusive.

**Keywords** Blood pressure · Cerebrovascular event · Hypertension · J-curve relationship · Stroke

J. Malyszko
2nd Department of Nephrology and Hypertension with Dialysis Unit, Medical University, Bialystok, Poland

P. Muntner
Department of Epidemiology, School of Public Health, University of Alabama at Birmingham, Birmingham, AL, USA

J. Rysz
Department of Nephrology, Hypertension and Family Medicine, Medical University of Lodz, Lodz, Poland

M. Banach (✉)
Department of Hypertension, Medical University of Lodz, Zeromskiego 113, 90-549 Lodz, Poland
e-mail: maciejbanach@aol.co.uk

## Introduction

Stroke is a devastating and debilitating disease, currently the leading cause of disability and fourth leading cause of death [1, 2]. Each year, approximately 16 million people worldwide are affected by stroke, and the estimated prevalence of stroke survivors is over 60 million [3]. The impact of stroke on quality of life, productivity, and the cost of health care is immense [4]. Stroke prognosis is influenced by a wide variety of factors, including age, stroke severity, stroke mechanism, infarct location, comorbid conditions, clinical findings, and related complications [5], and the medical community is obliged to identify risk factors and introduce preventive regimens [6]. Cerebrovascular disease is caused by one of several pathophysiologic processes involving the blood vessels of the brain, including: the intrinsic process related to the vessel, such as atherosclerosis, lipohyalinosis, inflammation, amyloid deposition, arterial dissection, developmental malformation, aneurysmal dilation, or venous thrombosis; an embolic process originating remotely (heart or extracranial circulation) and lodging in the intracranial vessel; inadequate cerebral blood flow due to decreased perfusion pressure or increased blood viscosity; and finally, rupture of a vessel in the subarachnoid space or intracerebral tissue [7]. It is therefore possible to differentiate between ischemic and hemorrhagic origin of cerebrovascular disease. The first three processes may result in transient brain ischemia (transient ischemic attack or TIA) or permanent brain infarction (ischemic stroke), whereas the last can lead to either subarachnoid hemorrhage or intracerebral hemorrhage (primary hemorrhagic stroke) [7, 8]. Approximately 80 % of strokes are due to ischemic cerebral infarction and 20 % to brain hemorrhage [1, 8].

Hypertension is still the most common and leading risk factor for stroke [1, 7–9]. This includes isolated systolic hypertension, frequently observed in elderly patients [10,

11]. As demonstrated in epidemiological and observational studies, there is a gradually increasing incidence of both coronary heart disease (CHD) and stroke as the blood pressure (BP) rises above 110/75 mmHg [7, 12]. In addition, both prior and current BP values are important risk factors for stroke [13]. It is somewhat difficult to prove a causal relationship between hypertension and stroke, as a rise in blood pressure could also be caused by other risk factors such as body weight gain and obesity that are often associated with dyslipidemia, glucose intolerance, and metabolic syndrome [14]. However, in assessing improved cardiovascular outcomes following antihypertensive therapy, it appears that elevated BP does play a causal role. The best evidence of the relationship between elevated BP and stroke comes from an overview of 14 hypertension treatment trials, where a long-term (mean 5 years) 5–6 mmHg decrease in normal diastolic blood pressure (DBP) was associated with a 35–40 % reduction in stroke [8].

Advancing age has a major adverse impact on stroke morbidity, mortality, and long-term outcomes [15–18], as evidenced in both major and minor strokes. Older adults (>65 years) have increased risk of death during the two months after stroke [19, 20]. Age is similarly a risk factor for hypertension. Egan et al. [21] showed that hypertension is a common problem in elderly persons (>60–65 years) in the U.S., reaching a prevalence as high as 60–80 %. In addition, one of the reports from the Framingham Heart Study indicated a progressive increase in the development of hypertension in patients over age 65 (16 %, 26 %, and 50 % in the optimal, normal, and high-normal groups, respectively) [22]. A second report estimated that non-hypertensive individuals aged 55–65 have a 90 % lifetime risk of developing stage 1 hypertension (BP 140 to 159/90 to 99 mmHg) and a 40 % lifetime risk of developing stage 2 hypertension (BP ≥160/≥100 mmHg) [23].

Severe uncontrolled hypertension is a major risk factor for intracranial hemorrhage, particularly in a young person admitted to the hospital with the acute onset of a focal neurologic deficit and BP greater than 220/120 mmHg. Song et al. [24] showed that each 20 mmHg increase in systolic blood pressure (SBP) was associated with a much greater increased relative risk for hemorrhagic stroke than for ischemic stroke (3.18 vs. 2.23). Moreover, for BP ≥180/≥110 mmHg, the difference in relative risk between hemorrhagic and ischemic stroke subtypes was even more pronounced (28.83 vs. 9.56). Chronic hypertension, which promotes the formation of atherosclerotic lesions, is therefore the single-most important treatable risk factor for both thrombotic extracranial and intracranial large artery and penetrating artery disease [24, 25].

Approximately 60 % of strokes in men and women of all ages are attributable to hypertension [1]. Hypertension is associated with an increased likelihood of subclinical or silent stroke, which in turn has been linked to an elevated risk of vascular dementia and recurrent stroke [26–28]. In addition to mean BP elevation, there is mounting evidence that visit-to-visit variability in SBP is an independent risk factor for stroke [29–31]. Conversely, the absence of a history of hypertension or present hypertension fundamentally reduces the likelihood of cerebrovascular disease [32]. In their 2011 guidelines, the American Heart Association (AHA) and American Stroke Association (ASA) recommended antihypertensive treatment for all patients with ischemic stroke and TIA who are more than 24 hours from symptom onset [33]. In patients with acute ischemic stroke, it is important not to lower BP too quickly. In addition, lifestyle modifications are recommended as part of the antihypertensive regimen, as these modifications have been associated with BP reduction [33]. Important modifications include weight loss; salt restriction; a diet rich in fruits, vegetables, and low-fat dairy products; regular aerobic physical activity; and limited alcohol consumption [33, 34]. The 2013 European Society of Hypertension (ESH) / European Society of Cardiology (ESC) Guidelines for the Management of Arterial Hypertension [35] recommend antihypertensive treatment in all hypertensive patients with a history of stroke or TIA, even when initial SBP is in the 140–159 mmHg range. They suggest a SBP goal of <140 mmHg, although the SBP values for intervention and SBP goal may be somewhat higher in elderly hypertensives [35]. The guidelines also suggest a SBP treatment target of 150–140 mmHg in elderly patients under the age of 80, although a target of less than 140 mmHg may be considered in the fit elderly. The recommendation for hypertensive patients aged 80 and above is a target of 150–140 mmHg [22]. These recommendations are in line with current AHA/American College of Cardiology Foundation (ACCF) guidelines (2011) [36].

## Search Strategy

We searched using the MEDLINE (1966–October 2013), EMBASE and SCOPUS (1965–October 2013), and DARE (1966–October 2013) electronic databases. Abstracts from national and international cardiovascular meetings were searched as well. Where necessary, relevant authors were contacted to obtain further data. The main search terms were: blood pressure, hypertension, intensive (aggressive) hypotensive therapy, J-curve, stroke, therapy, and treatment.

## J-curve – Does it Exist in Stroke Patients?

The J-curve phenomenon has been the subject of much discussion since it was first introduced by Stewart in 1979 with the presentation of the results of studies conducted in 169

patients with severe arterial hypertension. A fivefold increased risk of myocardial infarction (MI) was noted in individuals who had achieved DBP reduction below 90 mmHg over individuals with a BP range of 100–109 mmHg [35, 37]. Subsequent reports published in the 1980s confirmed these observations [38]. Subsequent detailed analysis has led to the conclusion that BP reduction may increase the risk of CV complications – similar to the effects of an excessive rise in BP – and this relationship takes on a characteristic *J-curve* shape [37, 39, 40].

The Systolic Hypertension in the Elderly Program (SHEP) trial included 4,376 elderly patients (mean age 72) with a mean SBP/DBP of 170/77 mmHg at baseline [10]. The patients were randomly assigned to antihypertensive therapy or placebo, and the goal of therapy was at least a 20 mmHg reduction in SBP to a level below 160 mmHg. The patients were treated with chlortalidone, with atenolol or reserpine added when as necessary. BP attained was 143/68 mmHg in the treated group and 155/72 mmHg in the placebo group [10]. Despite the low diastolic pressure attained by the treated group, this group had significantly better outcomes, including significantly lower incidence of stroke at 4 to 5 years (5.5 % vs. 8.2 % with placebo) [10, 41]. These benefits were noted in both men and women and in all age groups, including patients over the age of 80. However, it was also noted that the achievement of low DBP was a factor predisposing to CV events – coronary artery disease (CAD) and other cardiovascular diseases (CVD) – in the actively treated patients [10, 41]. The relative risk of composite CV events was significantly higher for DBP values greater than 70 mmHg, and close to a twofold increase for DBP greater than 55 mmHg [10, 41]. Thus, a discrepancy was noted between cardiovascular and cerebrovascular outcomes.

The benefit of treating hypertension in extremely elderly patients was directly addressed in the Hypertension in the Very Elderly Trial (HYVET) [42••], in which the primary endpoint was fatal or nonfatal stroke. The trial included 3,845 patients over 80 years of age (mean age 84) with a sustained SBP of at least 160 mmHg (mean 173/91 mmHg), who were randomly assigned to either the thiazide diuretic indapamide or placebo. In addition, if they failed to meet the target BP of 150/80 mmHg, they randomly received either the angiotensin-converting enzyme inhibitor perindopril or placebo [42••]. At two years, the mean BP was 15.0/6.1 mmHg lower with active therapy (approximately 143/78 vs. 158/84 mmHg), similar to the values achieved in the SHEP trial [10, 41]. Active therapy was associated with a significant reduction in fatal stroke (6.5 vs. 10.7 %) and near significant reduction in all strokes (12.4 vs. 17.7 %, $p<0.06$). All-cause mortality was reduced from 59.6/1,000 persons per year in the placebo group to 47.2/1,000 persons per year in the active treatment group [42••].

The Systolic Hypertension in Europe (Syst-Eur) trial [11] involved 4,695 patients over the age of 59 (mean age 70 years) with isolated systolic hypertension (mean initial-sitting BP of 174/86 mmHg). Active treatment consisted of nitrendipine or nitrendipine plus enalapril and hydrochlorothiazide if necessary [11]. The drop in BP was greater with active therapy (23/7 vs. 13/2 mmHg). After 4 years, significant reductions were noted in stroke (7.9 vs. 13.7 total endpoints/1,000 patient years) and fatal and nonfatal cardiac endpoints [11]. It was estimated that treatment of 1,000 patients for 5 years would prevent 53 cardiovascular endpoints and 29 strokes. No J-curve relationship was observed [11]. Subgroup analysis found that the mortality benefit increased significantly with a higher SBP at study entry, fell with increasing age [43], and was more pronounced in patients with diabetes mellitus [44].

In the treatment of elderly patients with isolated systolic hypertension, there are still no clear data indicating optimal levels of BP lowering. Studies are needed to provide guidance as to minimum SBP/DBP that can be tolerated. Analysis from the SHEP trial noted, on one hand, a clear benefit in reduced incidence of stroke in the active treatment group (lower-the-better relationship), but on the other hand, found significant increases in cardiovascular events with diastolic blood pressure ≤60 mmHg (*J-curve* relationship) [45–49]. Only the subgroup analysis of elderly patients in the FEVER study showed a benefit for lowering SBP to levels below 140 mmHg [50]. The FEVER study included almost 10,000 Chinese hypertensives, in whom cardiovascular outcomes were significantly reduced by more intense therapy (achieving a mean SBP of 138 mmHg), compared with less intense therapy (achieving a mean SBP of 142 mmHg). Significant reductions in stroke were found in uncomplicated hypertensives, in hypertensives with randomization SBP <153 mmHg, and in elderly hypertensives (mean age 69.5) (-44 %, $p<0.001$) when their SBP was lowered by more intense treatment [50]. Adding a small dose of a generic drug to achieve mean SBP values <140 mmHg was shown to prevent 5.2 CV events in every 100 patients treated for 3.3 years. There was, again, a lower-the-better trend and *no J-curve*-shaped relationship [50].

Debate has often been contentious regarding the issue of BP in the elderly. Decades ago, it was thought that isolated systolic hypertension in the elderly was to be expected and that it was well-tolerated. In the observational Rotterdam study, an increase in risk of stroke began at DBP below 65 mmHg [51]. These observations, however, are not conclusive proof of a cause-and-effect relationship between lower DBP and adverse cerebrovascular outcomes, particularly as the opposite is most often observed, which suggests a lower-the-better relationship. In a meta-analysis that included two trials of isolated systolic hypertension, a J-shaped curve relationship was noted in mortality outcome for both SBP and DBP but was not noted for cerebrovascular

outcomes [52]. Moreover, the J-curve seen in treated and untreated patients was not specific for cardiovascular mortality. The authors concluded that the J-curve could probably be explained by poor health associated with lower blood pressure (poor tolerability) and not as an adverse effect of antihypertensive therapy [52].

In a recent study, Dorresteijn et al. [53] revisited the concept of BP and the J-curve in 5,788 symptomatic vascular disease patients enrolled in the Secondary Manifestations of Arterial Disease (SMART) study in a follow-up for the occurrence of new vascular events (i.e., myocardial infarction, stroke, or vascular death). SBP level was positively related to the occurrence of stroke ($p<0.01$), but no nonlinearity was observed ($p=0.08$) [53]. Therefore, low SBP level was not associated with increased occurrence of stroke. No association was found between mean baseline SBP level and occurrence of myocardial infarction. However, the relationship among SBP, DBP, and vascular mortality was J-shaped ($p=0.03$). In this study, the effect of BP on vascular events was modified by presence or absence of recently diagnosed coronary artery disease, age (<65 versus ≥65 years), and pulse pressure (<60 versus ≥60 mmHg). Interestingly, elevated BP was not associated with increased morbidity and mortality in patients with recently diagnosed coronary artery disease ≥65 years and having >60 mmHg pulse pressure. Importantly, low BP in these could be a symptom rather than a cause of disease. The authors suggested that BP below and above 143/82 mmHg was an independent risk factor for recurrent vascular events in patients with established vascular disease [53]. In the observational analyses of the Treating to New Targets (TNT) trial, the nadir BP, where the mortality rate was the lowest, was 146/81 mmHg [54]. The study enrolled over 10,000 patients with a history of coronary artery disease. A nonlinear J-curve was not found for systolic blood pressure and stroke, although this relationship did exist between systolic blood pressure and vascular events [54].

In the REGARDS (REasons for Geographic and Racial Differences in Stroke) analysis, the researchers attempted to assess the optimal blood pressure level of 13,948 individuals located in the U.S. stroke belt (North and South Carolina, Georgia, Alabama, Mississippi, Tennessee, Arkansas, and Louisiana) [55••, 56]. Patients were divided according to baseline treated SBP levels: <120, 120–129, 130–139, 140–149, and >150 mmHg. The primary outcomes were incident stroke, coronary heart disease, cardiovascular disease, and all-cause mortality. For participants aged 55–64 and 65–75, no relationship between SBP and stroke incidence was observed. For participants ≥75 years of age, stroke incidence increased across the full range of SBP. After multivariable adjustment, SBP ≥150 mmHg was associated with an increased hazard ratio of stroke ($p=0.091$), but no increased risk was observed for SBP levels of 120–149 mmHg. When SBP was modeled as a continuous variable, lower SBP was associated with a decreased risk for stroke, especially among participants ≥75 years of age (lower–the-better relationship) [55••]. However, the authors noted that considerable caution should be exercised for BP values <120, particularly 110 mmHg, especially for cardiovascular and coronary heart disease events as well as all-cause mortality (but not for stroke), because a J-curve shaped relationship might be observed [55••]. The authors concluded that the results of the REGARDS cohort study generated a hypothesis that for all patients >55 years, the recommended level of SBP should be <140 mmHg, with optimal values possibly in the 120–139 mmHg range [55••].

This is a bold hypothesis to be extrapolated from the data, but it does highlight the need for continuing research in this area. The analysis was limited by the fact that only baseline BP measurements were available (2 measurements on a single occasion), leading to the potential misclassification of patients, and there was a relatively low number of stroke and CHD incidents in some subgroups. Despite these acknowledged limitations, the REGARDS trial holds tremendous value, especially as it included a large number (almost 14,000) of high-risk patients. The study also appears to indicate no J-curve association between these hypertension and stroke. Therefore, intensive hypertension therapy (with targeted BP <120 mmHg) should be the subject of further investigation [55••].

Importantly, these results are strictly aligned with the results of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study [56]. ACCORD was a prospective randomized open-label study designed to evaluate the impact of treatment aimed at lowering SBP to <120 mmHg on the incidence of cardiovascular events (including stroke) in a high-risk group of diabetic patients (n=4,733 patients in the hypertension arm) [56, 57]. The composite primary endpoint of the study was nonfatal MI/stroke or death due to cardiovascular causes. Of the 4,733 patients enrolled in ACCORD BP, 2,362 were randomized to intensive treatment and 2,371 to standard therapy. After 1 year of treatment, the mean SBP was 119.3 mmHg in the intensive-treatment arm and 133.5 mmHg in the standard-therapy arm (difference: 14.2 mmHg), while the mean DBP values were 64.4 and 70.5 mmHg, respectively (difference: 6.1 mmHg) [56, 57]. The primary endpoint of nonfatal MI/stroke or cardiovascular death occurred in 445 patients (1.87 %/year in the intensive-treatment group, compared with 2.09 % in standard-therapy group; $p=0.20$). There were also no significant differences in secondary endpoints between the studied groups; however, the incidence of stroke was significantly higher in the group receiving standard treatment (0.53 % vs. 0.32 %; $p=0.01$). A similar relationship was found for nonfatal stroke (0.30 % vs. 0.47 %; $p=0.03$) [56, 57]. It is worth noting, however, that in patients from the group in which the SBP was lowered to <120 mmHg, the incidence of treatment complications, such as orthostatic hypotension, hyperkalemia, or renal function impairment not

requiring dialysis (GFR <30 ml/min/1.73 $m^2$),increased significantly (3.3 % vs. 1.3 %) [5, 57]. Interestingly, the results were quite similar to those observed in the Irbesartan Diabetic Nephropathy Trial (IDNT), where DBP <85 mmHg was associated with an increased trend in all-cause mortality, a significant increase in MI, but a decreased risk for stroke [58].

In summary, the ACCORD study suggested a lack of additional benefits from intensive BP reduction (apart from a significant effect on stroke incidence) in the group of patients with hypertension and Type 2 diabetes. It also indicated the potential negative aspects inherent in excessively intensive SBP lowering (possible J-curve mechanism). The research therefore illustrated the critical importance of defining the patient group in which significant BP reduction could be particularly dangerous and, conversely, identifying those at high risk of stroke who could benefit most from intensive hypotensive therapy [59].

Perhaps the many lingering questions surrounding the J-curve will be answered only by the Systolic Blood Pressure Intervention Trial (SPRINT) [60], the results of which are expected to be available in 2018, and the Optimal Blood Pressure and Cholesterol Targets for Preventing Recurrent Stroke in Hypertensives (ESH-CHL-SHOT) study [61••], which begins recruiting patients in autumn of this year. The ESH-CHL-SHOT trial was designed by ESH and the Chinese Hypertension League (CHL) in order to finally resolve the dilemma between the "lower the better" and the "J-curve" hypotheses. In this regard, ESH and CHL have promoted a randomized trial comparing antihypertensive treatment strategies aimed at 3 different SBP targets in a defined group of hypertensives, those with recent stroke or TIA [61••, 62].

## Conclusion

Despite the many achievements in clinical and preventive medicine, stroke remains a major cause of disability and death. Epidemiological studies indicate a gradually increasing incidence of both coronary disease and stroke as the blood pressure rises above 110/75 mmHg. Even with the increased data streams, however, optimal blood pressure levels have yet to be determined, particularly in the elderly. Recent studies do suggest that blood pressure should be reduced carefully in patients with hypertension and coronary artery disease, those with hypertension and diabetes, and those with hypertension and left ventricular dysfunction [39]. Blood pressure should not fall below 110–115/70–75 mmHg, as this may be associated with more cardiovascular events. Data are generally lacking on the relationship between hypertension and cerebrovascular events. From the scant data that does exist, there appears to be linear rather than a J-shaped curvilinear relationship between these two factors (the lower-the-better relationship). Most of the data, however, come from observational studies or randomized controlled trials that are inadequately powered to determine a direct relationship between stroke and intensive BP lowering. It has been suggested that large interventional randomized controlled trials are needed to provide definitive answers to these questions [25, 63–65].

### Compliance with Ethics Guidelines

**Conflict of Interest** Jolanta Malyszko, Paul Muntner, Jacek Rysz, and Maciej Banach declare that they have no conflict of interest. This review was written independently; no company or institution supported the authors financially or provided a professional writer. The authors have given talks, attended conferences, and participated in trials and advisory boards sponsored by various pharmaceutical companies.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.



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