The J-Curve in Arterial Hypertension: Fact or Fallacy?

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Key Words

Hypertension · Systolic blood pressure · Diastolic blood pressure · J-curve · Coronary perfusion pressure

Abstract

It is known that a large proportion of patients with arterial hypertension are undertreated. This may result in an increase of the incidence of cardiovascular events. On the other hand, aggressive reduction of blood pressure may increase cardiovascular events (J-curve phenomenon) in certain populations. This phenomenon may be seen in patients with coronary artery disease and left ventricular hypertrophy when the diastolic blood pressure decreases below 70–80 mm Hg, and the systolic blood pressure decreases below 130 mm Hg. This phenomenon is not seen in patients with stroke or renal disease. Thus, a safer and more conservative strategy should be applied in patients with coronary artery disease, left ventricular hypertrophy, elderly, and in patients with isolated systolic hypertension. This is depicted in the recently published European Society of Hypertension/European Society of Cardiology guidelines in which higher targets of blood pressure are suggested in certain cardiovascular diseases and in the elderly.

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Historical Background

Elevated blood pressure (BP) has not always been considered the most common modifiable cause of cardiovascular morbidity and mortality. During the first half of the 20th century there was even a widespread belief that elevated BP is an indispensable compensatory mechanism for preserving organ perfusion, especially when there was an increase in systemic vascular resistance [1]. Clinical trials, however, in the 1960s and 1970s demonstrated that the hypertensive therapies were definitely beneficial and leading to the recommendation by experts ‘the lower the better’ [2, 3]. In patients at high cardiovascular risk, however, aggressive treatment might be rather harmful than beneficial. The idea that a reduction of BP below a certain point may increase cardiovascular events (J-curve) was introduced by Stewart [4] in 1979, and by Cruickshank et al. [5] 10 years later. These reports revealed an increased risk of myocardial infarction but not stroke or renal disease, in patients at high cardiovascular risk, when diastolic BP (DBP) was reduced <85–90 mm Hg [6]. This J-shaped relationship between BP level and cardiovascular morbidity and mortality has been described as the J-curve phenomenon.

Coronary Flow and Blood Pressure

Coronary blood flow is mainly a diastolic event. Left ventricular (LV) contraction during systole results in an increase of myocardial tissue pressure, which impedes flow in the intramyocardial vessels. There is even back-flow into the intramural and small epicardial coronary arteries [7].

The normal systolic and diastolic function of the heart is closely connected to the balance between myocardial oxygen supply and demand. Oxygen delivery to the heart is determined by the arterial oxygen content, which is equal to the product of hemoglobin concentration and arterial oxygen saturation and coronary blood flow. Therefore, an increase of coronary blood flow is the major compensatory mechanism to meet an increase in myocardial oxygen demand since myocardial oxygen extraction is almost maximal at rest [8, 9].

The major factors determining coronary blood flow are coronary artery resistance, coronary perfusion pressure and diastolic time (fig. 1). Coronary artery resistance regulates coronary blood flow and when the demand for myocardial oxygen increases, coronary artery resistance decreases. Diastolic time is another important factor regulating myocardial perfusion, since the majority of myocardial blood flow occurs in diastole, while subendocardial blood flow is exclusively diastolic. Diastolic time has a non-linear relationship to heart rate, thus small changes in heart rate, especially at slower rates (<75 beats/min) produce significant changes in diastolic time (fig. 2). Coronary perfusion pressure is the pressure gradient between the coronary arteries and the right atrium or LV diastolic pressure. The lowest perfusion pressure where coronary flow can be autoregulated is 40–50 mm Hg [9, 10]. Coronary perfusion pressure in patients with coronary artery disease (CAD) is related to the coronary artery diastolic pressure distal to a significant coronary obstruction. Coronary artery diastolic pressure distal to a significant obstruction, however, is lower than the aortic diastolic pressure and thus, even if aortic diastolic pressure is satisfactory, the diastolic pressure distal to a coronary artery stenosis may not be adequate. Thus, aortic diastolic pressure is a poor indicator of coronary perfusion pressure in patients with obstructive CAD; LV diastolic pressure under these circumstances becomes a major determinant of coronary perfusion pressure. Hence, not only changes in aortic pressure, but changes in LV diastolic pressure should be considered when estimating coronary perfusion pressure. In patients without obstructive CAD, the necessary aortic diastolic pres-

Fig. 1. Major factors that determine the balance between myocardial oxygen supply and demand [from 10].

Fig. 2. Diastolic time has a non-linear relationship to heart rate, thus minor changes in heart rate, especially at lower heart rates (<75 beats/min), result in significant changes in diastolic time. R-R = Cardiac cycle duration; QS₂ = systolic period [onset of the Q wave in the ECG to the second heart sound (S₂)]; (R-R) – (QS₂) = total diastolic period [from 11].

Fig. 3. Coronary perfusion pressure in relation to distal coronary artery pressure and left ventricular end-diastolic pressure (LVEDP). **a** Subjects with normal coronary arteries and LVEDP. **b** Subjects with stenotic coronary arteries and/or high left ventricular diastolic pressure [from 12].

sure for adequate myocardial perfusion should be between 50 and 65 mm Hg assuming that LV diastolic pressure is within normal limits (5–12 mm Hg). In cases with increased LV diastolic pressures, as is the case in heart failure, higher aortic diastolic pressures are required for an adequate pressure gradient [11, 12] (fig. 3). In patients with LV hypertrophy, subendocardial ischemia might occur even in the absence of coronary artery stenosis if the LV diastolic pressure is high [13, 14]. There are reports that abrupt reduction of DBP even at levels of 85–90 mm Hg can cause ischemic T-wave changes in hypertensive patients [15]. Heart rate, myocardial contractility and myocardial wall tension are the major factors which determine myocardial oxygen demand, while LV pressure and LV volume determine LV wall tension (Laplace's law: $T = Pr/h$, where T = wall tension, P = pressure, r = radius of the cavity, h = wall thickness) (fig. 1).

In conclusion, the imbalance between the major factors that determine myocardial oxygen delivery and demand may produce myocardial ischemia. Anemia, arterial oxygen desaturation or reduced coronary blood flow due to decreased coronary perfusion pressure, diastolic time or increased coronary artery resistance, result in reduced myocardial oxygen supply. Furthermore, in-

creased contractility, heart rate or LV pressure or volume result in augmented myocardial oxygen consumption (fig. 1).

Possible Explanations for the J-Curve Phenomenon

There are certain mechanisms that could explain this phenomenon, including the following:

Comorbidities

Populations with poor health and chronic illnesses such as neoplasms, chronic infection, malnutrition, and heart failure due to ischemic or non-ischemic cardiomyopathy tend to have a lower BP. Thus, low DBP may be related to comorbidities and thus, comorbidities and not DBP are responsible for the adverse events. In the National Institute of Aging sponsored Established Populations for Epidemiologic Studies of the Elderly (EPESE), more than 10,000 elderly patients were followed for over 5 years in order to assess the relationship between BP and cause-specific mortality. At 2 years, systolic BP (SBP) showed a J-curve relationship with all-cause mortality. All-cause mortality, cardiovascular mortality, and cancer mortality were highest in the low DBP group (<75 mm Hg). Nevertheless, there was evidence of the J-curve phenomenon even in the placebo group that not only involved cardiovascular events, but also non-cardiovascular mortality. Thus, the low BP was not the primary cause of death, but most likely the underlying disease. Further, there is a marked decrease in survival in patients with heart failure and associated low BP, which is an important index of the severity of disease [16].

Stiff Aorta

During LV systole, blood ejected into the ascending aorta generates a pulse wave that is perceived in the periphery as the arterial pulse. When the pulse wave reaches the periphery, it then returns back to the aorta as reflective waves. The aortic pulse wave velocity (PWV) depends on the elastic properties of the aorta. When the elastic properties of the aorta are normal, the PWV is slow; when the aorta is stiff, as seen with aging, diabetes mellitus and arterial hypertension, the PWV increases resulting in arteriolar damage in target organs, especially in the kidneys and brain [17]. In a stiff aorta, the reflective waves reach the root of the aorta at the end of systole resulting in an increase in systolic and a decrease in diastolic aortic pressure [18, 19], which results in an increase in the pulse pressure. Thus, a low DBP in the elderly or

other groups of patients is most likely related to a stiff aorta, which is related to adverse cardiovascular events [20, 21].

Effects of Specific Antihypertensive Therapies

The major benefit of therapy with antihypertensive medications in patients with hypertension is mostly related to the reduction in BP. The various hypertensive medications, however, have different effects on the cardiovascular system. It has been suggested that angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and calcium channel blockers may have more of a beneficial effect on the elastic properties of the aorta and reflective waves compared to β -blockers. Further, antihypertensive medications have varying effects on heart rate. It is known that a higher heart rate is a risk factor for future cardiovascular events in several diseases including hypertension. Thus, the so-called J-curve phenomenon may be related to an increase in heart rate, decrease in BP, or a combination of the two, and not only from a decrease in BP per se [22–31]. In addition to the properties of hypertensive medications, which may be crucial for outcomes regarding cardiovascular morbidity and mortality, the duration of time in which there is adequate BP control also is important.

Clinical Trials Supporting the J-Curve Phenomenon

In the International Verapamil SR Trandolapril Study (INVEST) [32, 33], verapamil or atenolol-based treatment was compared in 22,576 patients with arterial hypertension and CAD. In hypertensive patients with stable CAD, the primary outcomes (death, myocardial infarction, stroke) decreased when DBP was reduced to 80–89 mm Hg; however, when lower BP levels were achieved (DBP <80 and <70 mm Hg) cardiovascular events increased, especially when DBP levels were <60 mm Hg. The nadir for SBP was 119 mm Hg. Patients with CAD who did not undergo revascularization were more susceptible to adverse cardiovascular events related to aggressive treatment of hypertensive than those who underwent revascularization.

In the Randomized Olmesartan and Diabetes Microalbuminuria Prevention study (ONTARGET) [34, 35], 25,620 hypertensive patients with previous cardiovascular events or diabetes mellitus with organ damage (high or very high cardiovascular risk) were studied. There was a reduction in cardiovascular events when BP levels decreased from 145/82 to 133/76 mm Hg; however, further

BP reduction revealed a J-curve phenomenon regarding cardiovascular events for lower BP values (125/72 and 116/68 mm Hg), but not for stroke. The risk of cardiovascular events even doubled in diabetic patients when SBP was low (110 mm Hg) compared to less strict BP control.

The Treating to New Targets (TNT) double-blinded study [36] evaluated 10,001 patients (35–75 years of age) with clinically evident CAD (previous myocardial infarction, angina with objective evidence of atherosclerotic CAD, or a history of coronary revascularization) and low-density lipoprotein levels <130 mg/dl. They were randomized to 80 or 10 mg atorvastatin and were stratified according to BP measurements in 10 mm Hg increments from SBP $\leq$ 110 to >160 mm Hg and from DBP $\leq$ 60 to >100 mm Hg. The primary outcome was a composite of death from CAD, non-fatal myocardial infarction, resuscitated cardiac arrest, and fatal or non-fatal stroke. 982 patients (9.82%) experienced a primary outcome at 4.9 years (median) follow-up. Although it was a lipid-lowering trial, rather than hypertension, the TNT study exhibited a J-curve relationship between SBP and DBP, and fatal and non-fatal cardiovascular events with a nadir of 146.3/81.4 mm Hg, except for the outcome of stroke, where there was an increased risk of the primary outcome for a BP <110–120/60–70 mm Hg. In addition, in patients with vascular disease, recent diagnosis of CAD, age >65 years, or pulse pressure >60 mm Hg (indirect evidence of a stiff aorta), a BP >143/82 mm Hg was associated with lower vascular events compared to a BP <143/82 mm Hg (Second Manifestations of Arterial Disease Trial, SMART) [37].

Evidence Contradicting the J-Curve Effect

The Hypertension Optimal Treatment (HOT) trial [38] was a prospective randomized study that enrolled approximately 19,000 hypertensive patients between 50 and 80 years of age (median 61.5) who were randomly assigned to a target DBP <90, <85, or <80 mm Hg. The nadir of cardiovascular events was observed at a mean BP level of 139/82.6 mm Hg and the lowest risk of cardiovascular death was at a mean DBP of 86.5 mm Hg. Although additional BP reduction <82.6 mm Hg was not beneficial, it was safe and no J-curve phenomenon was observed for major cardiovascular events (myocardial infarction, stroke, cardiovascular mortality); however, a twofold increase in cardiovascular events was found in the group of smokers with a DBP <80 mm Hg.

The Multiple Risk Factor Interventional Trial (MRFIT) [39] was a multicenter primary prevention study with 16-year follow-up; it was initiated in 1972 and studied 12,866 patients with prior myocardial infarction. It was designed to determine whether certain interventions, such as smoking cessation, cholesterol reduction and control of high BP, would reduce mortality from CAD compared to usual care at that time. In the first 2 years of follow-up, an increase in all-cause mortality was observed in patients with SBP <120 mm Hg and a DBP <70 mm Hg; however, the high mortality rate in this group of patients was not seen during the next 15 years of follow-up. Instead, there was a decreased pattern of mortality in the aforementioned group. Thus, it appears that low DBP was not the cause of death because the rate of adverse events declined over the years and this higher incidence in the first 2 years may have been related to comorbidities. Low SBP and DBP were related to LV dysfunction, as the authors stated. Hence, LV dysfunction resulted in higher morbidity and mortality and not the low BP per se.

The association of SBP and DBP with cardiovascular events was observed in the Physician's Health Study (PHS) and Women's Health Study (WHS) in which 22,071 men and 39,876 women were followed for a median of 13 and 6.2 years, respectively [40]. No J-curve phenomenon was observed in either group, especially in the women's group (a slight J-curve was shown in men for a DBP <60 mm Hg).

In the Individual Data Analysis of Antihypertensive Intervention (INDANA) trial [41], 4,000 hypertensive patients were studied with a follow-up of 4 years. An increased risk for events was observed in patients with low BP; this phenomenon, however, was not attributed to antihypertensive treatment, but poor health related to underlying disease.

J-Curve Phenomenon in Certain Patient Populations

Diabetic Mellitus

The United Kingdom Prospective Diabetes Study (UKPDS) investigated 1,148 patients with type 2 diabetes mellitus and demonstrated that macro- and microvascular events were lower in patients with a mean BP <144/82 mm Hg [42]. In the Appropriate Blood Pressure Control study, in non-insulin diabetic patients there was no difference in cardiovascular risk between the group of 138 mm Hg compared to the intensive group of 132 mm Hg. However, many patients did not reach a SBP <130 mm Hg [43].

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) investigated 4,733 patients with type 2 diabetes mellitus [44]. The results have shown that the incidence of cardiovascular events was not related to the SBP (SBP 133 vs. 119 mm Hg) and a J-curve phenomenon was not apparent, although a group with intermediate BP were lacking.

The Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) trial investigated 11,140 patients with type 2 diabetes mellitus. The data demonstrated that there was a beneficial effect when SBP was within the range of 130–140 mm Hg regarding macro- and microvascular endpoints; however, the benefit of BP reduction gradually flattened at lower BP levels [45].

A retrospective cohort study that was recently published included 126,092 adult patients in the United Kingdom with newly diagnosed type 2 diabetes mellitus who were studied [46]. BP was measured at least once during the first year after the diagnosis of diabetes and the patients were categorized into three groups in relation to mean SBP and DBP; there was the tight control group (SBP <130 mm Hg, DBP <80 mm Hg), the standard control group (SBP between 130 and 139 mm Hg, DBP between 80 and 84 mm Hg), and the uncontrolled group (SBP ≥140 mm Hg, DBP ≥85 mm Hg). In patients with known cardiovascular disease, tight control of SBP (<130 mm Hg) and DBP (<80 mm Hg) was not associated with improved survival. On the contrary, low BP was associated with increased risk of all-cause mortality. Patients with a SBP of 110 mm Hg compared to patients with a SBP of 130–139 mm Hg (control) had a hazard ratio for all-cause mortality of 2.79. In patients with a DBP between 70 and 74 mm Hg and <70 mm Hg had hazard ratios of 1.32 and 1.89, respectively, when compared to patients with a DBP between 80 and 84 mm Hg (control). In patients without cardiovascular disease (similar associations were observed), a SBP <120 mm Hg and a DBP <75 mm Hg were associated with an increased risk of mortality. Therefore, the aforementioned study concluded that a BP <130/80 mm Hg was not associated with reduced risk of all-cause mortality in patients with newly diagnosed diabetes mellitus with or without established cardiovascular disease. An increased risk for poor outcomes was noticed for low BP, particularly <110/75 mm Hg.

Isolated Systolic Hypertension

Antihypertensive treatment remains a goal even for elderly patients with isolated systolic hypertension. It should be mentioned, however, that the fall of SBP is ac-

accompanied by a fall in DBP as well. Many clinical trials have reported the existence of a J-curve phenomenon between DBP and cardiovascular events, especially in patients with isolated systolic hypertension and CAD at baseline [21]. The Systolic Hypertension in the Elderly Program (SHEP) trial [20] showed that a lower DBP was associated with an increased incidence of cardiovascular disease with significant effects observed first at 70 mm Hg and more pronounced at 60 mm Hg. There was even a twofold increase in cardiovascular disease for a DBP <55 mm Hg.

The revised European Society of Hypertension/European Society of Cardiology Guidelines for the management of hypertension recommend the reduction of SBP between 150 and 140 mm Hg in elderly patients <80 years of age; <140 mm Hg could be considered in fit individuals. Additionally, it was recommended to reduce SBP between 150 and 140 mm Hg in patients >80 years of age only if they were in good physical and mental health [47].

Stroke

Data from several studies have demonstrated that antihypertensive treatment prevents the incidence of stroke even for SBP <120 mm Hg and thus, 'the lower the better' seems to be accurate in this group [32, 33, 36, 41, 48]. Even in patients with cerebrovascular disease, the Perindopril Protection Against Recurrent Stroke Study (PROGRESS) [49] showed that the lower risk of recurrence was among those with the lowest follow-up BP levels (median 112/72 mm Hg). The explanation for this phenomenon may be related to the fact that cerebral autoregulation (which is between 40 and 125 mm Hg) is more effective than that of the heart and that cerebral blood flow is mainly a systolic event, whereas myocardial perfusion of the myocardium is mostly diastolic.

In the Prevention Regimen for Effectively Avoiding Second Strokes (PROFESS) trial [50], the effect of therapy with the angiotensin receptor blocker telmisartan soon after stroke had a more favorable outcome on patients when the BP was reduced from 150 mm Hg or higher to 140–149 and 130–139 mm Hg. However, SBP levels <130 or 120 mm Hg resulted in increased risk of cardiovascular morbidity and mortality, even for stroke. It should also be noted that after the acute phase of a cerebrovascular event, the autoregulatory mechanism of the cerebral blood flow may be disrupted. As a result, aggressive BP control in this period may lead to the expansion of the ischemic zone surrounding an ischemic, thrombotic or embolic stroke, especially for SBP levels <130 or 120 mm Hg.

Chronic Kidney Disease

Regarding renal outcomes, most of the studies have focused on the progression of microalbuminuria or albuminuria and the progressive decline in renal function. SBP <130/80 mm Hg prevents the progression of proteinuric nephropathy and no J-curve phenomenon has been demonstrated. However, abrupt lowering of SBP to <130 mm Hg or <120 mm Hg in hypertensive patients with chronic kidney disease (CKD) may cause reduction in the glomerular filtration rate (GFR) and urine output [51–54]. The medical records of 651,749 US veterans (mostly men) with CKD (62.3% had an estimated GFR between 45 and 59 ml/min/1.73 m²) were reviewed between 2005 and 2012 to evaluate the possible associations among SBP and DBP with mortality. Patients with a SBP >160 mm Hg and a DBP >100 mm Hg had a 5% greater risk of death than patients with BP levels between 120–139 and 80–89 mm Hg. Patients with a SBP <120 mm Hg and a DBP <80 mm Hg had greater risk of death when compared to patients with BP between 120–139 and 80–89 mm Hg. Patients with a SBP between 130 and 159 mm Hg combined with a DBP between 70 and 89 mm Hg had lower mortality rates than those with very high or very low BPs. It is interesting that 'ideal' SBP levels may not be advantageous if this is accompanied by a 'lower-than-ideal' DBP in patients with CKD. The limitation of the study was that the study population consisted mainly of elderly men with a mean age of 73.8 years [55, 56].

Concluding Remarks

'... I have attempted to maintain a proper balance between man and his instruments, between experienced opinion and statistics, between traditional views and heterodox, between bed-side medicine and special tests, between the practical and the academic, and so to link the past with the present' – Paul Wood [57].

Optimal treatment of hypertension remains a fundamental therapeutic target. The facts demonstrate that high BP is a strong and modifiable risk factor of cardiovascular morbidity and mortality. BP control confers measurable benefits as the risk of cardiovascular events is diminished by about 50% for every 20 mm Hg of SBP and for every 10 mm Hg of DBP reduction. On the other hand, the existence of a J-curve phenomenon that may become clinically relevant for a SBP <130 mm Hg and for a DBP <70–80 mm Hg in certain patients remains a matter of controversy (tables 1–3). For these reasons, the

Table 1. Clinical studies in favor of a J-shaped relationship between low BPs and adverse events (MI, stroke, cardiovascular death, all-cause mortality)

Studies	n	Subjects included	Nadir SBP/DBP, mm Hg	Events related in J-shaped manner with BP	Comments
INVEST 2006 [32, 33]	22,576	hypertension, CAD	SBP/DBP: 129/74 mm Hg in the adjusted model for time to primary outcome	all-cause death, non-fatal MI, non-fatal stroke	diastolic J-curve was less prominent for patients with revascularization than those without; diastolic J-curve was more pronounced than systolic J-curve; J-shaped relationship with DBP was observed to a lesser extent for stroke than for MI or mortality
INVEST Subanalysis 2010 [32, 33]	6,400	hypertension, CAD, type 2 DM	SBP: 130	all-cause mortality	rise in mortality, particularly evident towards levels of achieved SBP <115 mm Hg
ONTARGET 2009 [34, 35]	25,588	>55 years, CAD, PAD or cerebrovascular disease or DM with organ damage	SBP: 130	cardiovascular mortality, MI	J-curve did not occur for stroke; in patients with SBP <130 mm Hg, adjusted for covariates, cardiovascular mortality increased with further SBP reduction ($p < 0.0001$)
TNT 2010 [36]	10,001	35–75 years clinically evident CAD and LDL >130 mm Hg	SBP/DBP: 146.3/81.4	cardiovascular events (death from CAD, non-fatal MI, resuscitated cardiac arrest)	no J-curve for the outcome of stroke with SBP; exponential increase in the risk of primary outcome for BP <110–120/60–70 mm Hg, BP <110–120/60–70 mm Hg
SMART 2012 [37]	5,788	symptomatic vascular disease (CAD, CVD, PAD)	SBP/DBP: 143/82 PP: 62	vascular events (MI, stroke, vascular death) and all-cause mortality	elevated blood pressure not associated with higher vascular event rate and mortality in patients with recent diagnosis of CAD, >65 years, PP >60 mm Hg
Syst-Eur 2009 [21]	4,695	>60 years, isolated systolic hypertension	DBP: <70	cardiovascular events	J-curve only in patients with coronary heart disease at baseline
SHEP 1999 [20]	4,736	>60 years, isolated systolic hypertension	DBP: 70	CVD	increased risk for cardiovascular events with DBP <70 mm Hg was observed in the treated group of patients
Cruickshank et al., 1987 [5]	902	moderate to severe treated hypertension	DBP: 85–90	MI mortality	J-curve confined to those with evidence of ischemic heart disease
Stewart, 1979 [4]	169	uncomplicated, middle-aged, treated hypertension	DBP: 90	MI	findings suggest that BP should seldom be reduced by more than 22%
PROFESS 2011 [50]	20,330	>50 years recent non-cardioembolic ischemic stroke	SBP: 120	first recurrence of stroke (any type)	results adjusted for major health conditions (stroke subtype, heart failure) baseline BP and independent of follow-up BP, antihypertensive medication

DM = Diabetes mellitus; CVD = cardiovascular disease; LDL = low-density lipoprotein; MI = myocardial infarction; PAD = peripheral artery disease; PP = pulse pressure.

recent European Society of Hypertension/European Society of Cardiology guidelines suggest a more conservative strategy, especially for high-risk patients. The optimal treatment goal now is a BP <140/90 mm Hg and <140/85 mm Hg for diabetics, instead of <130/80 mm Hg

as previously suggested. As is the case with almost all diseases, a fine balance between under- and overtreatment of arterial hypertension should be defined. In addition to pharmacologic agents, lifestyle modifications and treatment of other cardiovascular risk factors such

Table 2. Clinical trials without clear evidence of a J-curve

Studies	n	Subjects included	Nadir SBP/DBP, mm Hg	Events related in a J-shaped manner with BP	Comments
HOT (1998) [38]	18,790	mean 61.5, hypertension	DBP: 83	myocardial infarction	findings were observed in the subgroup with ischemic heart disease; no J-curve for non-ischemic patients
ACCORD (2007) [44]	4,733	type 2 diabetes mellitus	SBP goal: <120 vs. <140 BP achieved: 119/64	major cardiovascular event (non-fatal myocardial infarction, non-fatal stroke, cardiovascular death)	higher rate of severe adverse events in intensive treatment group
AASK (2002) [52]	1,094	African-American with hypertensive nephropathy	128/78 vs. 141/85 mm Hg	rate of change of GFR –2.21 vs. –1.95 ml/min/1.73 m ² /year; deaths 8.1 vs. 11%	no difference in cardiovascular endpoints
MDRD (1994) [51]	840	no diabetes	MAP <92 (<98 if >60 years old) vs. <107 (<113 if >60)	rate of change of GFR –3.7 vs. –4.1 ml/min/1.73 m ² /year	significant interaction with proteinuria

Table 3. Clinical studies contradicting the J-curve effect between low BPs and adverse endpoints

Studies	n	Included subjects	Nadir SBP/DBP, mm Hg	Events	Comments
IDNT (2001) [48]	1,590	30–70 years, hypertension overt diabetic nephropathy	SBP: 120, DBP: 85	cardiovascular death, chronic heart failure, myocardial infarction, total mortality	stroke risk continued to decrease even with DBP <85 mm Hg
INDANA (meta-analysis) (2002) [41]	40,233	hypertension	untreated subjects: DBP 90 treated subjects: DBP 84 untreated subjects: DBP 84 treated subjects: DBP 85	total mortality; cardiovascular mortality	J-curve not related to antihypertensive treatment
ABCD normotensive (1993) [43]	480	type 2 diabetes mellitus	128/75 vs. 137/81 mm Hg	change in creatinine clearance (exact numbers not reported); death 7.6 vs. 8.2%	reduced strokes; nearly half not treated in control group
UKPDS (1977–1997) [42]	1,148	type 2 diabetes mellitus	BP goal: <150/85 vs. 180/105 mm Hg BP achieved: 144/82 vs. 154/87 mm Hg	first clinical endpoint related to diabetes 50.9 vs. 67.4 events/1,000 patient-years: death related to diabetes 13.7 vs. 20.3; all-cause death 22.4 vs. 27.2	target in control group was unacceptably high; many patients in the control group were not treated
PROGRESS (2001) [49]	6,105	hypertensive and non-hypertensive patients with a history of stroke or transient ischemic attack (mean age 64; range 26–91 years); follow-up 4 years; active treatment with an ACE inhibitor-based BP-lowering regimen (perindopril) with or without addition of the diuretic indapamide, or matched placebo	combination therapy reduced BP by 12/5 mm Hg; single-drug therapy reduced BP by 5/3 mm Hg	total stroke (fatal and non-fatal)	active treatment reduced the incidence of total stroke by 28% and the rate of major vascular events by 26%; lower BP levels were BP continuously associated with lower risks of fatal strokes down to very low BP levels (as low as 115/75 mm Hg)

as obesity, lipid abnormalities, and smoking cessation should be emphasized [58]. It should be noted that anti-hypertensive pharmacologic agents have other effects beside their effect on BP such as heart rate, lipid profile, and others that may affect outcomes. Carefully designed prospective randomized trials may clarify some of the questions related to the J-curve phenomenon. It should be emphasized, however, that each patient has their own

individual profile and thus guidelines cannot replace clinical judgment and the common sense of a good caring physician.

Conflict of Interest

The authors have no conflicts of interest to disclose.

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