

Aggressive Blood Pressure Lowering Is Dangerous: The J-Curve

Pro Side of the Argument

Giuseppe Mancia, Guido Grassi

Historically, the possibility that reducing blood pressure (BP) might have harmful effects has gone through 3 temporal steps. In the first half of the last century, it was a widespread belief that an elevated BP provided the necessary hydraulic gradient to preserve organ perfusion in the face of an increase in systemic vascular resistance, the implication being that hypertension was a compensatory mechanism and no BP-lowering intervention was justified.¹ This was largely forgotten in the subsequent 2 to 3 decades where the results of the antihypertensive treatment trials dominated the scene and emphasized the beneficial effects of BP reductions at most if not all degrees of BP elevation.²⁻⁶ The possibility that antihypertensive treatment might produce harm rather than benefit resurfaced in the late 70s and 80s,^{7,8} however, due in particular to a report that in patients with a high cardiovascular risk the incidence of myocardial infarction was diminished by reducing diastolic BP to 85 to 90 mm Hg but increased when a more pronounced reduction occurred.⁸ Despite its important limitations (small number of patients, few cardiac events, and retrospective nature of the observations), the report was widely referred to and revived the popularity that has since characterized the J-curve phenomenon, that is, the possible J-shaped rather than linear relationship of BP reductions by treatment with incident cardiovascular events.

The present article will argue in favor of this hypothesis. It will be acknowledged that at present this is not supported by undisputable evidence such as that provided by randomized trials. It will be emphasized, however, that the J-curve hypothesis is supported by common sense, physiological data, and results from large-scale observational studies, often derived

from antihypertensive treatment trials on individuals at high or very high cardiovascular risk. This makes it not just a remote but a real possibility, which deserves to be addressed by future studies.⁹ Its important implications for clinical practice should make investigation on the J-curve phenomenon a priority for cardiovascular medicine.

Background Considerations in Favor of the J-Curve

As discussed in a recent editorial,¹⁰ the hypothesis that the BP achieved with treatment bears a J-shaped relationship with incident cardiovascular events owes an important portion of its persistent popularity to common sense considerations and physiological data. Common sense tells that a BP value below which organ perfusion and function are compromised ought to exist, and that a too low BP target must have an adverse effect on morbidity and mortality. This is confirmed by physiological studies that have shown that in vital organs such as the brain, the heart, and the kidneys, autoregulatory mechanisms cause vasodilatation and maintain perfusion constant when BP is progressively reduced.¹¹⁻¹³ They have further shown, however, that there is a BP value below which a further progressive reduction is accompanied by a steep progressive blood flow fall, and that this BP threshold or nadir is reset to higher values in hypertension¹⁴ and is increased also in the presence of asymptomatic organ damage or overt disease, presumably because in a damaged organ alterations of structure and function impair the vascular smooth muscle ability to relax, compromise the vasodilatory reserve, and make perfusion more critically dependant on an adequate arteriovenous BP

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From the Centro Interuniversitario di Fisiologia Clinica e Iperensione, Università Milano-Bicocca and Istituto Auxologico Italiano, Milano, Italy (G.M.); Clinica Medica, Dipartimento di Scienze della Salute, Università Milano-Bicocca, Milano, Italy (G.G.); and Multimedica, Sesto San Giovanni (Milano), Italy (G.G.).

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Correspondence to Giuseppe Mancia, Centro di Fisiologia Clinica e Iperensione, Via Francesco Sforza, 35, 20121 Milano, Italy. E-mail giuseppe.mancia@unimib.it

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gradient. The top panel of Figure 1 shows that a diastolic BP reduction to <90 mmHg, obtained via intravenous injection of nitroprussiate, led to a marked reduction of coronary blood flow in hypertensive patients with left ventricular hypertrophy, whereas in hypertensive patients without left ventricular hypertrophy, no alterations of coronary perfusion occurred down to diastolic values of ≈ 70 mmHg.¹⁵ The bottom panel shows that reducing diastolic BP to <80 mmHg markedly increased the incidence of cardiovascular (mainly cardiac) events in patients with coronary disease, the effect being much less pronounced in those who had undergone a revascularization procedure.¹⁶ The available physiological data have several important implications. One, the J-curve hypothesis needs a reformulation. The question should not be whether a J-curve phenomenon exists: it obviously does, with an ascending limb that will reach a 100% mortality at zero BP. It should rather be whether the ascending limb can become manifest at the BP values achieved with drugs that lower BP. Two, there is not just a single but probably many nadir BP values to refer to in order to avoid organ underperfusion and increased risk, depending on the characteristics of the patients. Three, although anti-hypertensive treatment may move blood flow autoregulation back toward the normotensive range,¹⁴ in hypertension as well as in cardiovascular disease the risk of reducing BP below the range over which perfusion is preserved may be greater.

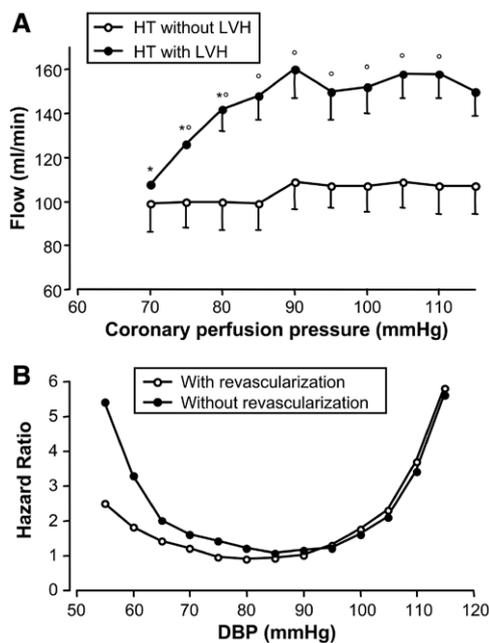


Figure 1. A, The effects of reducing coronary perfusion pressure by intravenous infusion of nitroprussiate on coronary blood flow (measured in the great cardiac vein) in hypertensive patients with and without left ventricular hypertrophy (LVH). **B**, The cardiovascular event incidence at different achieved diastolic blood pressure (DBP) levels in patients with coronary artery disease (CAD) who did not undergo coronary revascularization compared with those who had the procedure. HT indicates hypertension. Adapted with permission from Polese et al¹⁵ and Messerli et al.¹⁶ Authorization for this adaptation has been obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.

Evidence in Favor of the J-Curve

A large number of observational studies, many of which obtained by post hoc analyses of event-based trials, have observed a J-shaped relationship between BP reductions and some or all measured cardiovascular events, that is, no additional but rather an attenuation or a disappearance of the BP-dependant cardiovascular protective effects with greater compared with more modest BP reductions from the initially higher levels.^{16–37} The results can be summarized as follows. One, an increased incidence of cardiovascular outcomes has been seen for more versus less pronounced reductions of both systolic and diastolic BP. Two, in line with the view that nadir BP values differ in different subjects, the systolic and diastolic BP below which the cardiovascular risk increased has shown marked between-study differences.¹⁰ Three, the J-curve phenomenon has been observed for fatal and nonfatal events as well as major cardiovascular (heart failure, myocardial infarction, and stroke) and renal complications (serious deterioration of renal function or end-stage renal disease). Four, the above observations have been made in widely different patient populations, although in most instances individuals with a high or very high cardiovascular risk (because of conditions such as a marked initial systodiastolic BP elevation, isolated systolic hypertension, old age, multiple cardiovascular risk factors, organ damage, or clinical cardiovascular disease) have been involved. To quote some representative examples from recent large-scale studies with several years of follow-up, in the 22 576 hypertensive patients with coronary disease recruited for the International Verapamil SR/T Trandolapril trial (INVEST), the incidence of cardiovascular morbidity and mortality showed a reduction in patients in whom diastolic BP was reduced to between 80 and 89 mmHg, with a clearcut progressive increase, however, in those in whom values <80 and <70 mmHg were achieved.¹⁶ In the 25 620 high- or very high-cardiovascular risk (previous cardiovascular event or diabetes mellitus with organ damage) patients of the Ongoing Telmisartan Alone and in Combination with Ramipril Global End Point trial (ONTARGET), the incidence of cardiovascular events decreased when systolic BP was reduced from 145/82 to 133/76 mmHg, but it increased again in the groups in which treatment achieved lower BP values (125/72 and 116/68 mmHg; Figure 2).²⁸ In the 6400 patients with diabetes mellitus of the INVEST trial,³⁰ the cardiovascular event incidence showed a major reduction when, during the 4-year treatment period, systolic BP was reduced from >140 to between 130 and 139 mmHg. The incidence increased, however, when BP values <130 mmHg were achieved, with a risk that became more than double that of patients in the higher BP category when on-treatment BP fell to 110 mmHg (Figure 3). Finally, in the 20 332 patients with a history of stroke of the Prevention Regimen for Effectively Avoiding Second Strokes trial (PRoFESS), reducing systolic BP from ≥ 150 to 140 to 149 and to 130 to 139 mmHg was found to reduce progressively and markedly the risk of cardiovascular morbidity and mortality. A further reduction to <130 and <120 mmHg increased the risk again (+16% and +31%, respectively), however, with values that were even greater than those exhibited by patients remaining at the 140 to 149 mmHg on-treatment BP range³⁷ (Figure 4, left).

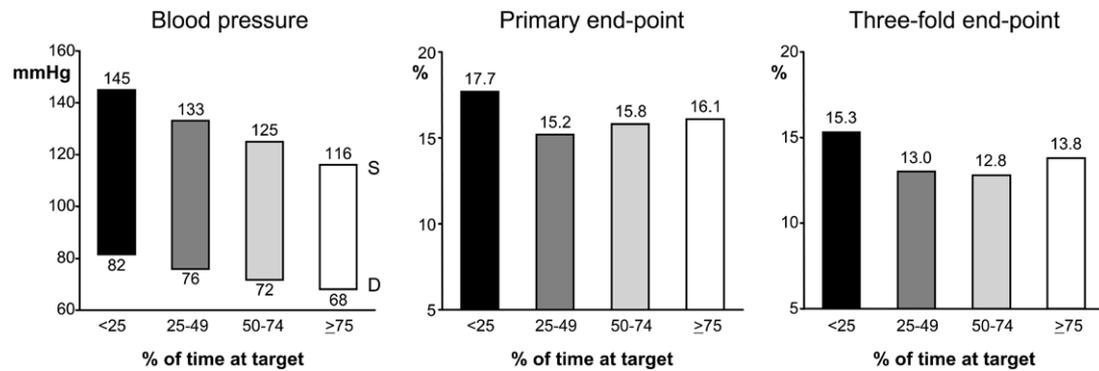


Figure 2. Incidence of cardiovascular outcomes (primary end point) according to the percentage of visits in which blood pressure (BP) was reduced to <130/80 mmHg with resulting different on-treatment mean BP values (left). The 3-fold end point to cardiovascular morbidity and mortality except for incident heart failure. D indicates diastolic; and S, systolic. Data from the ONTARGET trial. Adapted with permission from Mancia et al.²⁸ Authorization for this adaptation has been obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.

Limitations of the Evidence in Favor of the J-Curve

The evidence in favor of a J-shaped relationship between BP and cardiovascular morbidity and mortality has well-known limitations. The most important ones are that the number of patients and events in the lowest BP subgroups (those in whom an increased risk occurs), can be very small, and that the post hoc approach to data analysis involves comparisons among nonrandomized groups, those in whom the BP reduction is largest or the achieved absolute value is lowest usually showing a worse cardiovascular risk profile than those in whom the BP reduction is less pronounced or the achieved BP value is higher. This raises the possibility that the results are accounted for by reverse causality, that is, that an originally greater cardiovascular risk leads to a greater BP fall and an increased number of incident events. This finds support in the observation that a J-curve phenomenon has been reported to occur also in placebo-treated groups^{34,38} and involve not only cardiovascular events but

also fatal events of noncardiovascular nature, which should be unaffected by the achieved BP levels. However, in studies such as INVEST and ONTARGET, the groups in which an increased event incidence was observed included thousands of patients and were thus by no means small.^{17,27–30} Furthermore, there is no evidence that BP reductions and control to target values can be more easily obtained when cardiovascular risk is high, and usually the opposite seems to be the case.^{39,40} Finally, and most importantly, in several large-scale studies, a J-shaped relationship between achieved BP values and cardiovascular outcomes has been observed also after adjustment for a large number of baseline covariates, thereby addressing the potential role of different risk-associated demographic and clinical characteristics in the compared groups. It must be acknowledged that because between-group differences might extend to unmeasured variables, adjustment procedures may not entirely dispose of this limitation of the post hoc approach and that reversed causality cannot be entirely ruled out. Because an impaired

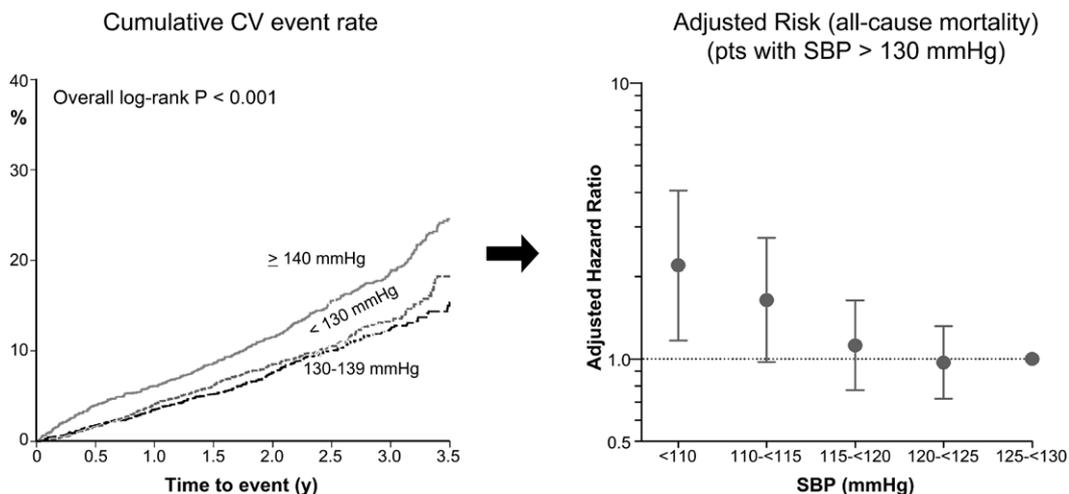


Figure 3. The cumulative event incidence of primary outcome (nonfatal myocardial infarction, nonfatal stroke, and all-cause mortality in 6400 patients with diabetes mellitus of the INVEST trial in whom systolic blood pressure (SBP) remained ≥ 140 mmHg or was reduced to between 130 and 139 mmHg and <130 mmHg (left). The risk of all-cause mortality in subgroups of patients achieving different systolic BP values <130 mmHg, having the 130 mmHg data as reference and adjusting the risk for baseline covariates (right). Adapted with permission from Cooper-Dehoff et al.³⁰ Authorization for this adaptation has been obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.

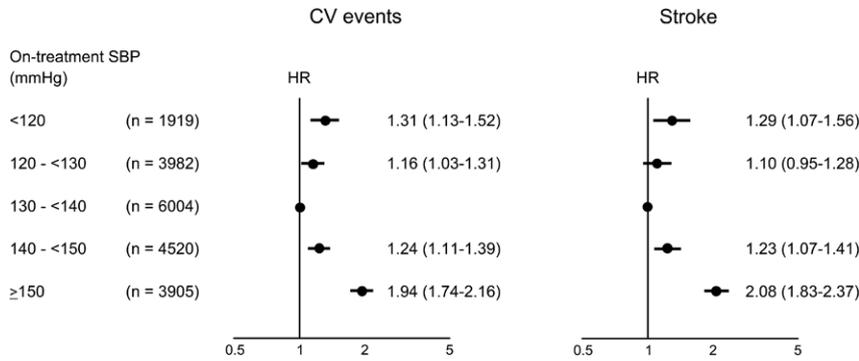


Figure 4. Risk of cardiovascular events and stroke recurrence according to different on-treatment systolic blood pressure (SBP) values in patients with a history of stroke. The group with on-treatment BP values between 130 and 139 mmHg is taken as reference. Data were adjusted for baseline covariates. Patients were recruited for the PROfESS trial. Adapted with permission from Ovbiagele et al.³⁷ Authorization for this adaptation has been obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.

cardiac function may reduce BP, reversed causality is probably the most likely explanation of the J-shaped relationship that exists between BP and mortality in treated heart failure patients, namely that there is a particularly marked reduction of survival in individuals in whom heart failure is associated with a low BP.⁴¹⁻⁴³ There is little question, however, that preservation of a J-shaped BP-outcome relationship after extensive multivariable adjustment for possible baseline differences in the compared groups speaks in favor of its origin from the achieved BP differences.

Evidence Against the J-Curve

Trials

Opponents of the J-curve hypothesis argue that, as reported in detail by old and recent review articles,^{44,45} not all post hoc analyses of large-scale trials have observed an increased risk of cardiovascular events in patients in whom BP was more aggressively reduced. More importantly, they emphasize that this has been the case also in the few event-based trials that have compared by a randomized design the effect of greater versus smaller BP reductions and higher versus lower BP targets, such as the United Kingdom Prospective Diabetes Study (UKPDS) and the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trials on patients with diabetes mellitus.^{46,47} However, in the UKPDS trial,⁴⁶ the achieved BP values of the more aggressively treated group remained well above (144/82 mmHg) the values that may more likely lead to an impairment of organ perfusion and an increase of cardiovascular risk. Furthermore, a conclusion about the existence of a J-curve phenomenon can only be reached when data from >2 groups of patients are available. This limits the contribution to the J-curve issue of both the UKPDS⁴⁶ and the ACCORD trial.⁴⁷ In the ACCORD trial,⁴⁷ the cardiovascular event incidence was similar at the achieved systolic BP of 133 and 119 mmHg, but this cannot exclude the possibility of a lower risk of events (and thus a J-curve) in a third group with an on-treatment BP value in-between. At present, the effects of different achieved BP values have been compared in 3 randomized groups only in the Hypertension Optimal Treatment trial (HOT), with no evidence of a J-curve either in the entire low cardiovascular risk trial population and in the small diabetic subgroup.⁴⁸ Unfortunately, in both instances the treated BP exhibited only small between-group differences as well as mean diastolic and systolic values, respectively >80 and 140 mmHg, that is, above the BP range where a J-curve is more likely to occur. Thus, although randomized trials do not

provide evidence in favor of the J-curve phenomenon, they do not disprove it either.

Epidemiology

A widely used argument against the J-curve phenomenon is that in a large number of epidemiological studies on a total of ≈1 million subjects, the relationship between BP and cardiovascular events seems to be linear from BP values of ≈180/110 mmHg to BP values of ≈110/70 mmHg, this being the case in both younger and older subjects, including those aged ≥80 years.^{49,50} This has greatly contributed to the belief that BP reductions exert a clearcut protective effect at any initial BP level, and treatment strategies should be based on the principle that the lower the BP the better is for the patient. However, a close look at the above epidemiological data allows to identify an upward deviation from linearity at the lowest diastolic BP values. Furthermore, the lowest explored BP values have been associated with an increased incidence of cardiovascular morbid and fatal events in several individual epidemiological studies, particularly in elderly subjects.⁵¹⁻⁵³ A recent example is provided by the large database obtained by the MONica, Risk, Genetics, Archiving and Monograph (MORGAM) Project, in which the risk of stroke showed a progressive reduction at progressively lower diastolic BP values, with a J-shaped increase, however, <71 mmHg in the elderly fraction of the study population.⁵³ Finally, the described linearity between BP and cardiovascular events has been recognized to be somewhat misleading because it originates from the use of a logarithmic scale to quantify the event incidence, which changes little in the lower portion of the BP range when absolute values are used. More in general, epidemiological evidence should never be considered a proxy for the effects of active treatment because (1) the risk may be totally or in part irreversible; (2) the treatment strategies that are used may have unforeseen effects that modify or mask the expected benefit; and (3) subjects recruited for epidemiological studies may differ from those in whom treatment is tested. This has been common in hypertension research in which the effects of BP-lowering interventions have mostly been studied in longstanding hypertensive patients, often with a history of cardiovascular events and almost invariably with a cardiovascular risk much higher than that of subjects recruited for epidemiological purposes. That this can make a difference for the risk of an event is supported by the observation that the relationship between BP and incident myocardial infarction is linear in subjects without and J-shaped in those with a history of coronary disease.⁵⁴

Organ Heterogeneity

In recent years, the hypothesis has been made that vital organs may respond differently to BP-lowering interventions. That is, BP reductions may have a limited protective effect on coronary events, with an ultimate flattening or even a reversal at low values, whereas they may progressively reduce the incidence of stroke and end-stage renal disease throughout the BP range achievable by antihypertensive treatment.^{55,56} As reviewed in some recent articles,^{57–59} the evidence is the following. One, in the ACCORD trial a systolic BP reduction to <120 mmHg did not have a significant effect on myocardial infarction, but it reduced substantially the risk of stroke.⁴⁷ Two, in the Perindopril Protection against Recurrent Stroke Study (PROGRESS), a reduction in the incidence of stroke recurrence was seen also at a baseline systolic BP between 120 and 139 mmHg, the treatment-induced BP fall leading to on-treatment systolic values well <130 mmHg.^{60,61} Three, in post hoc analyses of some trials (eg, INVEST, ONTARGET), reducing systolic BP to <130 or even <120 mmHg was accompanied by a reduction of stroke with an increased incidence of myocardial infarction.^{16,27,28} Four, similarly marked BP reductions have been shown to (1) more markedly reduce urinary protein excretion^{28,62,63}; (2) delay incipient nephropathy as identified by new onset microalbuminuria or proteinuria⁶³; and (3) attenuate the progressive decline of renal function accompanying renal disease.⁶⁴

These intriguing observations might find their explanation in a more effective blood flow autoregulation of the brain and the kidney compared with the heart, possibly because in extracardiac organs perfusion is not impaired during the systolic phase. It should be emphasized, however, that not all studies are consistent with the hypothesis that the brain and the kidney are not exposed to the J-curve phenomenon, within the BP range at which it seems to occur in the heart because (1) the ability of urinary protein excretion to predict renal outcomes is controversial,⁹ and (2) recent reports rather seem to indicate that reducing BP to <130 or <120 mmHg may worsen renal function and increase the risk of end-stage renal disease,^{35,65} adding support to the common experience that a marked BP reduction may lead to a marked increase in serum creatinine, with thus an impairment of renal function. Furthermore, some epidemiological data have shown an increase in the risk of stroke at the lower BP values exhibited by the study population,⁵³ and the relationship between BP reductions and stroke observed in trials seems to be much more complex than linear, an important role being played by the clinical condition of the patient, the timing of antihypertensive treatment initiation, the speed of the BP change, and the type of cerebrovascular event considered. It is well known that, if obtained few hours after a stroke, BP reductions may have deleterious effects, and a J-shaped increase in the incidence of stroke recurrence when BP was reduced to <130 or <120 mmHg (+10% and +29%, respectively; Figure 4, right) has recently been reported also when antihypertensive treatment was started at a few weeks distance from the acute cerebral event.³⁷ To date, a linear relationship with BP reductions down to low absolute levels seems to more consistently hold only for hemorrhagic stroke, which in the PROGRESS trial has exhibited a striking reduction in patients in whom

chronic antihypertensive treatment led to a systolic BP <120 mmHg,^{60,66} these low achieved BP values being associated also with the smallest incidence of intracranial bleeding in patients under anticoagulant treatment.^{66–68} However, hemorrhagic stroke accounts for only a minor fraction of the overall stroke prevalence.⁶⁸ Furthermore, a progressive risk reduction as BP falls to low values may not invariably occur even for this event. This is the implication of a recent trial in which an early systolic BP fall to <140 mmHg in patients with a hemorrhagic stroke did not produce any appreciable benefit.⁶⁹

Research and Practical Considerations

The fundamental role of BP for organ perfusion leaves no question that BP values below which underperfusion occurs must exist, and that the BP–cardiovascular outcome relationship is not linear but necessarily J shaped. This is supported by classical physiological data as well as by the results of a large number of observational studies that have observed that in a variety of clinical conditions, but especially in individuals exhibiting a high or very high cardiovascular risk, the ascending limb of the J-curve is seen at BP values achieved by antihypertensive treatment or more in general by drugs with BP-lowering properties. Because of their limitations, observational studies cannot provide conclusive evidence, and thus, whether and when during antihypertensive treatment a J-curve takes place will have to be conclusively proven by randomized trials aimed at comparing the effects of different achieved BP values in patients in whom the identity of the initial demographic and clinical characteristics is ensured. However, such trials will not be easy to design, perform, and interpret because (1) >2 groups of patients randomized to different BP targets will be needed; (2) the degree of BP reduction by treatment can be unpredictable; (3) different BP-lowering effects can only be obtained through different numbers and doses of antihypertensive drugs, which means that the role of BP versus the treatment differences may remain uncertain; and (4) the BP threshold below which underperfusion and damage occur may exhibit wide interpatient differences (as suggested by the marked discrepancies in the nadir BP values below which cardiovascular event rate increased as found by different J-curve–positive studies) and perhaps change over time and progression of the disease even within a given individual. This can make the prevailing type of effect offered by trials of limited help for the decision to take in any single patient.

At practical level, physicians will have to decide by the principle of *primum non nocere*, which means that the possible existence of a J-curve should never be overlooked and represent a primary concern in conditions such as coronary disease, pronounced degrees of organ damage, a recent cardiovascular event, or an old age, that is, when vital organs may be particularly exposed to the risk of underperfusion by treatment-induced BP falls. This concern should be shared by guidelines that should avoid recommending aggressive BP targets in the above conditions and rather opt for safer, more conservative strategies. This has been done in the recent European hypertension guidelines, which have elevated the BP values to be reached with treatment in patients with diabetes mellitus, a previous cardiovascular disease, or an advanced renal disease

from <130/90 to <140/90 mm Hg (140/85 mm Hg in diabetes mellitus), the systolic values to pursue in the elderly being between 140 and 150 mm Hg⁹

Disclosures

None.

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Response to Aggressive Blood Pressure Reduction Is Dangerous: The J-Curve: Pro Side of the Argument

Paolo Verdecchia, Fabio Angeli, Giovanni Mazzotta, Marta Garofoli, Gianpaolo Reboldi

We agree with Drs Mancia and Grassi when they state that the J-curve debate should not be focused on its existence (“it obviously does, with an ascending limb that will reach a 100% mortality at zero BP”) but on the possibility that the ascending limb will become manifest at blood pressure (BP) values usually achievable in the clinical practice.

However, we disagree with their interpretation that the increased event incidence at the extreme left of the J-curve is well supported in available studies because it occurred in 1000 patients. In the frequently cited post hoc analysis of the INternational VERapamil-trandolapril STudy (INVEST), a marked rise in the risk of myocardial infarction occurred at follow-up BP levels <110/60 mm Hg, which were achieved by ≈1% of the population (≈200 patients).¹ The J-shaped relationship between BP and outcome noted in the univariable analysis almost completely disappeared in the multivariable analysis that adjusted for several potential determinants of reverse causality.¹

We agree with their statement that “because of their limitations, observational studies cannot provide conclusive evidence” of the J-curve phenomenon. However, beyond remarking on the need for future randomized studies testing >2 BP targets, Drs Mancia and Grassi could have mentioned the point that no evidence in favor of the J-curve emerged to date from meta-regression analyses of randomized studies,² in which potential determinants of reverse causality (ie, older age, heart failure, cancer) were equally distributed by randomization between the treatment groups. In our opinion, this is a frequently forgotten but important point against the clinical relevance of the J-curve phenomenon at BP levels usually observed in trials and clinical practice.

In addition to randomized studies testing different BP targets, we also need more accurate analyses of existing databases addressing not only the visual inspection of the J-curve based on achieved BP values but also the changes in BP from baseline induced by treatment in relation to the subsequent outcome.

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Aggressive Blood Pressure Lowering Is Dangerous: The J-Curve: Pro Side of the Argument

Giuseppe Mancia and Guido Grassi

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