CONTROVERSIES IN HYPERTENSION

Aggressive Blood Pressure Lowering Is Dangerous: The J-Curve

Con Side of the Argument

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Blood pressure (BP) is poorly controlled in the population, a phenomenon with adverse prognostic impact.[1] However, a more aggressive approach toward BP lowering has been tempered over the last 2 to 3 decades by some reports suggesting a paradoxical increase in morbidity and mortality associated with an excessive reduction in BP, the so-called J-shaped curve hypothesis. Many investigations addressed this issue, and some excellent reviews discussed strengths and limitations of these studies in detail.[2–5] We conducted an updated critical review of the most relevant studies and meta-analysis from our and other groups. We recognize that there is some evidence that a diastolic BP target <80 mm Hg,[6] or an achieved diastolic BP <70 mm Hg,[7] might be associated with an increased risk of myocardial infarction[6] (MI) or total cardiovascular events[7] in hypertensive patients with established coronary artery disease (CAD). However, with the possible exception of hypertensive patients with CAD, there are no convincing data behind the conclusion that an aggressive reduction of BP could be a direct cause of adverse outcome. Several studies that reported a J-shaped association between achieved BP and outcome have methodological limitations.[2–5] In particular, several clinical conditions including, but not limited to, heart failure, previous MI, and cancer might have been the dominant and direct cause of adverse outcome in these patients, antihypertensive treatment being thus a sort of innocent bystander. As an implication of this line of thinking, dangerous would not be the excessive reduction in BP but rather the excessively low BP. The difference is not trivial.

Insight From Direct Epidemiology

In subjects with or without risk factors, but free from overt cardiovascular disease, the log-linear relation between BP and rate of mortality from CAD or stroke appears to begin at values around 115/75 mm Hg, without any J-shaped relation.[8] Indeed, these values are rarely reached in treated hypertensive patients. The risk of end-stage renal disease also showed a direct linear relation with BP, with no evidence of a J-curve.[9] In patients with history of stroke, a J-shaped relation between BP and recurrent stroke has been noted during the first 3 to 6 months after the index event,[10] but not later.[11] With increasing time elapsed from acute stoke, patients may be more stable and their cerebral circulation less vulnerable to the effects of BP lowering.[10]

Post Hoc Analyses of Observational and Interventional Studies

In these analyses, the average BP recorded during follow-up (ie, achieved BP) is plotted against the incidence of death or major events to explore the shape of the relation between BP and rate of events. In the post hoc analyses of intervention studies, 2 or more randomized groups are generally pooled together. About 35 years ago, a post hoc analysis of the Framingham Heart Study was the first to document an increased risk of MI in patients with diastolic BP <90 mm Hg during follow-up, thereby suggesting that the relation between unsmoothed BP and risk was not linear.[12] A plethora of studies then followed. As suggested in previous reviews,[2–5] the main limitations of post hoc studies can be summarized as follows:

1. Lack of Randomization. In such analyses, patients are not randomized to groups with different levels of achieved BP. Hence, the risk factors for an adverse outcome are not evenly distributed by randomization, but may differ across the groups. For example, the International Verapamil-Trandolapril Study (INVEST), which included 22 576 patients with hypertension and

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obstructive CAD, was a potentially suitable setting to investigate the J-curve phenomenon.[13] Coronary blood flow, which occurs predominantly in diastole, may cease at BP values <40 mm Hg.[14] Coronary autoregulation, which may be crucial to maintain an adequate blood flow distally to a major epicardial stenosis, tends to become defective in the presence of left ventricular hypertrophy.[15] Hence, hypertensive patients with CAD may be particularly vulnerable to excessive reduction in diastolic BP. Indeed, a post hoc analysis of INVEST by Messerli et al[13] concluded that an excessive reduction in diastolic BP should be avoided in patients with CAD who are being treated for hypertension. This suggestion is based on a J-shaped relation between achieved BP and risk of primary outcome, particularly MI. However, when compared with patients with achieved diastolic BP 81 to 90 mm Hg, those with BP ≤60 mm Hg (ie, the extreme left of the J-curve) were ≈10 years older (74 versus 64 years) and had a higher prevalence of previous MI (47% versus 29%), stroke (12% versus 6%), heart failure (22% versus 4%), diabetes mellitus (44% versus 26%), and cancer (11% versus 2%). The J-shaped relation between BP and outcome noted in the univariable analysis (Figure, A) almost completely disappeared in the multivariable analysis (Figure, B) that adjusted for these and other potential confounders. The potential impact of the above confounders leaves open the possibility that the worse outcome in patients with lower BP is attributable not to a direct causative effect of treatment but to the effect of concomitant diseases causing a reduction in BP together with adverse outcome (ie, reverse causality). This view is supported by the results of the Coronary Revascularization Demonstrating Outcome Study in Kyoto (CREDO-Kyoto), performed with 9877 patients with CAD and coronary revascularization.[16] The study showed a higher incidence of cardiovascular death (P<0.001) in patients with diastolic BP <70 mm Hg than in those with a higher diastolic BP at the time of the procedure. However, after adjustment for several potential confounders, including age, left ventricular dysfunction, previous MI, diabetes mellitus, pulse pressure, and peripheral vascular disease, the difference between the 2 groups was no longer significant.[16] A further proof of the limitations of post hoc analyses based on achieved BP comes from an analysis of the African-American Study of Kidney Disease and Hypertension (AASK).[17] This randomized study compared 2 different BP goals (mean BP 102–107 mm Hg versus ≤92 mm Hg). The 2 primary end points (rate of decline in the glomerular filtration rate, composite of rate of decline in glomerular filtration rate, dialysis, transplantation, or death) did not differ between the 2 groups in the intention-to-treat analysis. In contrast, a post hoc analysis of the 2 groups pooled together showed a direct relation between achieved BP and decline in glomerular filtration rate (0.35 mL/min per 1.73 m^2 faster glomerular filtration rate decline for each 10 mm Hg higher mean BP during follow-up).[17] In an attempt to explain such discrepancy, the authors noted that achieved BP was confounded by comorbidities, a worse phenotypic profile, and less adherence to treatment.[17] A post hoc analysis of the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) also reported a J-shaped relation between average in-treatment systolic and diastolic BP and adjusted 4.5-year risk of primary event and cardiovascular mortality, but not for MI or stroke.[18] In patients with baseline systolic BP ≤130 mm Hg, a further reduction in BP from baseline to follow-up was associated with a significant increase of cardiovascular mortality.[18] Also in this study, however, despite adjustment for several potential confounders, patients with low baseline BP had a generally worse phenotypic profile, with a higher prevalence of men and patients with previous MI and coronary revascularization (all P<0.001).[18] In a post hoc analysis of Treating to New Targets (TNT) trials, Bangalore et al[19] found a J-shaped curve between systolic and diastolic BP and the primary outcome (composite of coronary death, nonfatal MI, resuscitated cardiac arrest, and stroke), with a nadir at 146/81 mm Hg. The TNT trial is another suitable context to investigate the potentially adverse impact of the J-curve because all these patients had a history of CAD. Even in this analysis, however, despite ample statistical adjustment for several imbalances between the groups, patients with low achieved BP had a much worse phenotype compared with patients with higher BP.[19] For instance, when compared with patients with achieved diastolic BP 81 to 90 mm Hg, those with BP ≤60 mm Hg were ≈6 years older (65 versus 59 years) and had a higher prevalence of diabetes mellitus (33% versus 13%), congestive heart failure (29% versus 5%), peripheral vascular disease (27% versus 8%), and

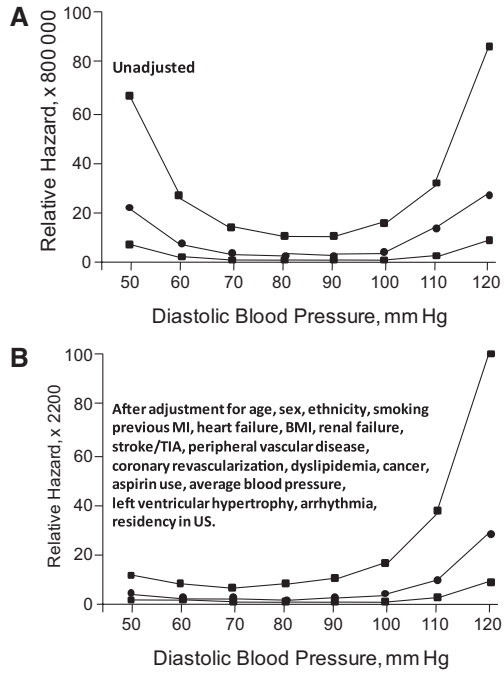

Figure. Unadjusted (**A**) and adjusted (**B**) relation between achieved (average in-treatment) diastolic blood pressure and risk of primary outcome in hypertensive patients with coronary artery disease enrolled in the International Verapamil-Trandolapril Study. MI indicates myocardial infarction; and TIA, transient ischemic attack. Reprinted from Messerli et al[13] with permission from *Annals of Internal Medicine*. Copyright © 2006, American College of Physicians.

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previous coronary bypass surgery (62% versus 44%).[19] An analysis of 5788 patients with recent diagnosis of atherosclerotic disease showed a J-shaped curve between BP (systolic, diastolic, and pulse) and risk of new vascular events, with a nadir at 143/82 mm Hg.[20] Importantly, however, the J-shaped curve between BP and vascular events was significantly more prominent in patients with pulse pressure >60 mm Hg, as well as in patients aged >65 years.[20] Both interactions were statistically significant.[20] Therefore, the adverse prognostic impact of a low achieved BP probably reflected the impact of aging and more stiff arteries, not that of lower BP values in itself. The authors openly recognized that these findings make the reverse causality hypothesis more plausible.[20]

2. Low Number of Patients With Low or Very Low Achieved BP. In the analysis of INVEST study, achieved BP was ≤60 mm Hg in only 176 of 22 576 patients.[13] Similarly, among the 10 001 patients in the TNT trial, achieved diastolic BP was ≤60 mm Hg in only 85 patients and systolic BP was ≤110 mm Hg in only 396 subjects.[19] The distribution of patients was better balanced between the groups in other trials.[17,18,20]

Analyses of Individual Patient Data

The first evidence that the J-curve is not directly induced by antihypertensive treatment came from a post hoc analysis of the European Working Party on High Blood Pressure in the Elderly (EWPHE), an intervention trial in which elderly patients were randomized to active treatment or placebo. Total mortality showed a J-shaped relation with achieved diastolic BP in the group allocated to placebo and with achieved systolic BP in the group allocated to active treatment.[21] Patients with the lowest achieved BP were also characterized by reduced body weight and hemoglobin levels, along with higher rates of noncardiovascular mortality.[21] Two analyses of the Individual Data Analysis of Antihypertensive Intervention Trials (INDANA) also offered the opportunity to accurately investigate the relation between BP and outcome in individual patients randomized to active treatment separately from those randomized to placebo or no treatment.[22,23] In a first analysis, a J-shaped relation between diastolic BP and risk of all-cause and cardiovascular death was noted not only in treated but also in untreated patients.[22] The authors concluded that the higher risk of events in patients with low BP was not related to antihypertensive treatment.[22] They speculated that poor health conditions leading to low BP and an increased risk for death were possible determinants of the J-shaped curve.[22] In a second analysis of INDANA database, the authors arranged a matched-pair analysis of treated versus untreated patients by quartiles of systolic and diastolic BP reduction.[23] The analysis showed that even in patients with a greater reduction in diastolic BP to levels <70 mm Hg, the active treatment reduced the risk of cardiovascular events, including total mortality (P<0.0001), cardiovascular mortality (P=0.01), all cardiovascular events (P=0.008), and MI (P=0.01).[23] Again, this analysis indicates that the J-shaped relation between BP and outcome is unlikely to be treatment-induced.[23] Finally, in a post hoc analysis of individual patients enrolled in the Systolic Hypertension in Europe (Syst-Eur) trial, the risk of cardiovascular events increased when the achieved diastolic BP was ≤75 mm Hg only in the active treatment group, not in the placebo group.[7] In contrast, patients randomized to placebo showed an increase in noncardiovascular mortality for progressively lower values of achieved BP, most likely as a consequence of reverse causation because of a variety of conditions leading to poor health and frailty.[7] Important limitations of the above analysis of the Syst-Eur trial included low prevalence of patients with CAD at baseline (14.7% in placebo group and 14.2% in active treatment group) and lack of interaction (P=0.19) between CAD at baseline and on-treatment diastolic BP.[7] Overall, these findings are in agreement with a retrospective analysis of the Hypertension Optimal Treatment (HOT) database[6] and suggest that the principal clinical context in which there is reasonable evidence that an excessive reduction on diastolic BP might be dangerous is that of patients with clear evidence of obstructive CAD. Even the aforementioned analysis of the INVEST trial,[13] despite its limitations outlined here, led to similar conclusions.

Lessons From Meta-Analyses

Major meta-analyses[24,25] suggest that the benefit of intense antihypertensive treatment is maintained down BP levels for which post hoc analyses of clinical trials documented a paradoxical increase in the cardiovascular risk. We conducted a meta-regression analysis of 31 intervention trials conducted in patients with type 2 diabetes mellitus, for a total of 73 913 patients (295 652 patient-years of exposure).[26] The risk of stroke decreased by 13% (P=0.002) for each 5-mm Hg reduction in systolic BP, and by 11.5% (P<0.001) for each 2-mm Hg reduction in diastolic BP. In contrast, the risk of MI did not show any association with the extent of BP reduction (systolic BP: P=0.793; diastolic BP: P=0832).[26] These data remove the potential concern for an increased risk of MI at low levels of achieved BP, which implies that these levels can be pursued in the clinical practice because the beneficial effect on stroke are unlikely to be neutralized or exceeded by harmful effects on MI.[26]

Conclusions

In patients with high systolic BP needing treatment, a concomitant reduction in diastolic BP to levels <70 mm Hg is unlikely to be the direct cause of a paradoxical rise in the risk of cardiovascular events, particularly MI. An exception might be represented by patients with clear evidence of obstructive CAD, but available evidence is limited.[6] Although the J-curve hypothesis is biologically reasonable, it remains an unproved hypothesis that needs further testing in randomized trials between different BP targets in patients exposed to a modern management of BP and other cardiovascular risk factors.

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Disclosures

None.

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

Giuseppe Mancia and Guido Grassi

Dr Verdecchia and colleagues share with us the view that a J-curve phenomenon must exist but conclude that its practical importance is trivial because (1) epidemiological data show cardiovascular events to be linearly related to blood pressure (BP) down to values (≈110/70 mm Hg) that encompass virtually the whole population, (2) a J-curve phenomenon has been observed in post hoc analyses of outcome trials, but the post hoc approach is scientifically weak, with only few patients and events forming the ascending limb of the J-curve, and (3) the results can be explained by reversed causality (ie, by a higher pretreatment risk and inherent frailty that accounts for both the worse outcome and, independently, the greater BP fall).

We do not deny that these are valid considerations and grant that differences in pretreatment risk profile are probably involved in the J-curve phenomenon. However, in our opinion, this does not exclude a causative role of low on-treatment BP as well, a conclusion based on evidence from studies in which the limitations mentioned by our opponents were minimized although admittedly not entirely removed. Limitations of the evidence apart, it is hard to forget that pathophysiological research has documented an impairment of autoregulation and organ perfusion at BP values well within the range achieved by BP-lowering treatments. Verdecchia and colleagues conclude that this may produce a J-curve in patients with coronary artery obstructions. This may not be a small number, and the size of the problem can be even greater if we consider that patients (the elderly in particular) may have arterial obstructions interfering with organ perfusion outside the heart. This makes the J-curve a possible effect of treatment that is of potential practical relevance.

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