Editorial

Is a Blood Pressure Target of <130/80 mm Hg Still Appropriate for High-Risk Patients?

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Thresholds and targets for lowering blood pressure have been controversial and contested from the earliest days, starting with the treatment of malignant hypertension to the present day, when guidelines advocate blood pressure–lowering drug treatment for high-risk patients with blood pressures in the normal or high-normal range.1–3 The perennial question has been, Can we be sure we are doing more good than harm? The challenge has been to provide convincing evidence for recommended thresholds and targets. The J curve debate first appeared with articles from Stewart4 and Cruikshank,5 and has surfaced to systolic blood pressure.

With renewed vigor in the past few years.6–8

The debate is certainly worth having, given that hypertension is a risk factor rather than a disease, and it affects ≈25% of the adult population worldwide and >50% of the population >60 years of age.9 It is clear that there must be a J curve relating blood pressure to cardiovascular risk because, at pressures below the lower limits for autoregulation, perfusion of vital organs must fail. The key question is whether there is a J curve within the usual range of blood pressures to which patients might be exposed by treatment. Important related issues are whether any such J curve is related to the patients’ inherent risk profile or directly to blood pressure–lowering treatment; whether there is heterogeneity between different outcomes, especially in groups with different background vascular disease, such as coronary disease or stroke; and whether any such J curve is related more to diastolic than to systolic blood pressure.

In this issue of Circulation, Mancia et al10 present observational analyses from the Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial (ONTARGET) suggesting that cardiovascular protection is not improved in high-risk patients when the blood pressure targets achieved move from <140/90 mm Hg to tighter levels <130/90 mm Hg. This article follows a previous observational study from the ONTARGET trialists, in which they describe a “J-Curve (nadir around 130 mmHg) in the relationship between on-treatment systolic blood pressure and all outcomes except stroke.”19 In the present article, the authors first pool all the patients originally assigned to the 3 randomized treatment groups: ramipril alone, telmisartan alone, or the 2 together. They then divide the patients into 4 groups according to the proportion of postrandomization visits in which the blood pressure was reduced to either <140/90 mm Hg or <130/80 mm Hg (<25%, 25%–49%, 50%–74%, ≥75%). After adjustment for various baseline variables, they find that the risk of stroke or renal end points decreases progressively as the proportion achieving either of these targets increases. They find little association between the risk of myocardial infarction or heart failure and the frequency of blood pressure control for either target. Composite end points and mortality were favorably affected by achieving the less tight target of <140/90 mm Hg, but not the tighter target of <130/90 mm Hg. However, none of the evidence presented for any of the outcomes shows any sign of a J curve, ie, of an upturn in risk in the group achieving the tightest (>75%) control of blood pressure for either target. The authors suggest that more evidence is needed from prospective randomized trials to establish the optimal blood pressure targets for high-risk patients. They suggest that guidelines for the management of hypertension should revise their targets for high-risk patients because lowering blood pressure to <130/80 mm Hg confers no greater cardiac protection than achieving a target of <140/90 mm Hg. They also suggest that guidelines might differ in different populations with different patterns of vascular disease, eg, in many parts of Asia, where stroke presents the greatest burden.

The difficulty facing us is that the recent evidence for either a J curve or a lack of benefit with tighter blood pressure control, including this latest contribution, comes from nonrandomized, post hoc observational studies, and is subject to confounding. The main problem is the potential for systematic bias in observational studies of treatments, because it is difficult to distinguish differences in outcome that are the direct consequence of the indication for treatment from differences in outcome that are conferred by the treatment itself. This indication bias is well exemplified with reference to the use of digitalis for patients with heart failure or atrial fibrillation in the 1980s11 and of calcium antagonists for patients with hypertension or coronary disease in the 1990s.12 In each case, the suggestions of significant harm arising from observational studies were ultimately refuted through the weight of randomized evidence. Another example is provided by the refutation of the much touted cardiovascular benefits of hormone replacement therapy in women.13 At the core of the dilemma is the fact that this sort of confounding is difficult, if not impossible, to overcome with even the most sophisticated multivariable statistical analysis. The difficulty is exemplified in the present instance by imbalances in important determinants of risk, including a history of diabetes mellitus, myocardial infarction, or stroke at baseline.10
It is equally possible that indication bias is responsible for the recent reports of J curves or lack of further benefit with tighter blood pressure control to 130/80 mm Hg in high-risk patients.6–8,10 This possibility is reinforced by reports of similar J curves in the placebo groups of randomized trials. It is therefore important to seek randomized evidence to clarify the balance of risks and benefits and tighter blood pressure control. One rigorous contribution in this respect comes from the meta-analysis of 147 trials of blood pressure–lowering drugs that reported that “the percentage reductions in coronary heart disease events and stroke were similar in people with and without cardiovascular disease and regardless of blood pressure before treatment down to 110 mm Hg systolic and 70 mm Hg diastolic” (the Figure).14 This evidence from randomized trials increases the likelihood that the lack of further benefit observed with tighter blood pressure control in the present article,10 and the reports of J curves in other studies do not reflect direct effects of blood pressure–lowering treatment. Rather, they are likely to arise from the greater inherent risk present in the subjects with the lowest blood pressures ab initio as a result of indication bias or reverse causality.

Other authors have also suggested, on the basis of analyses from the International Verapamil-Trandolapril Study (INVEST), that there is a J curve in the relationship between achieved blood pressure and coronary events, but not stroke and renal events, and have produced evidence that applies particularly to diastolic blood pressure.6 The explanation proposed is that, because coronary perfusion is achieved predominantly during diastole, patients with coronary artery disease are especially at risk when diastolic pressure is low.6 The main problem with this suggestion is that patients with low diastolic blood pressure during the trial, ie, after randomization, likely had a low diastolic pressure at entry to the trial. Indeed, analyses from the Framingham study have reported that a statistically significant excess of cardiovascular events was observed only at diastolic pressures of <80 mm Hg when accompanied by a systolic pressure >140 mm Hg, with an increasing tendency to J curve with successive increments of accompanying systolic blood pressure.15 Thus, the patients with low diastolic pressure are more likely to have coronary events during the trial, not because active blood pressure lowering has caused the event but because they have isolated systolic hypertension reflecting stiffening of the large arteries with advancing age. In this situation, the low diastolic blood pressure may well predict the occurrence of major coronary events but does not cause them.

Another approach to interpreting the difference in the relation between in-trial blood pressure and coronary disease on the one hand and stroke on the other lies in the epidemiological basis of the relationship as reported in previous large-scale observational studies.16,17 These studies have demonstrated that the relationship between blood pressure and stroke is much stronger and steeper than that with coronary disease. This raises the second issue that bedevils the interpretation of clinical trials: the need to minimize random errors, which are inversely proportional to the number of individuals observed to experience events during follow-up.11 Thus, much larger numbers are needed to establish with precision the relationship between blood pressure and coronary events than with stroke. This is in part responsible for the difficulty the ONTARGET trialists have in establishing a clear association of blood pressure control with coronary events;
the large confidence limits observed (Table 2) make it difficult to overcome the limitations imposed by the weaker and shallower relationship between blood pressure and coronary events than with stroke. Similar considerations help explain the lack of significant reduction in both the primary outcome and myocardial infarction in the blood pressure arm of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial.\(^{18}\) Both end points were reduced by >10%, but these reductions were not significant, and, as acknowledged by the ACCORD investigators, lack of power, reflecting the much-lower-than-expected event rate, was such that the wide confidence limits could not exclude a benefit as high as 27% for the primary outcome and 32% for myocardial infarction.\(^{18}\)

In summary, Mancia et al present analyses from ONTARGET suggesting that tighter blood pressure control to <130/80 mm Hg confers additional protection against stroke and renal disease but not myocardial infarction or heart failure, with no suggestion of a J curve. These data stem from observational analyses and must be regarded as hypothesis generating until confirmed by randomized evidence from rigorously conducted prospective trials. The findings are relevant to ongoing reappraisal of the targets recommended in current guidelines, partly on the grounds that the evidence for the tighter target of <140/90 mm Hg is still limited.\(^{19}\) However, it should be noted that at the present time only a minority of patients meet the currently recommended blood pressure targets for either the general population with hypertension (<140/90 mm Hg) or high-risk individuals, especially those with diabetes mellitus or established vascular disease or renal disease (<130/90 mm Hg).\(^{14-16}\) It is therefore important that these targets not be revised unless and until there is more solid randomized evidence from rigorous large-scale clinical trials that achievement of either of these targets causes real harm in terms of major outcomes. Otherwise, we risk discrediting current guidelines unnecessarily and exacerbating the already poor compliance with guideline recommendations for blood pressure control. This could jeopardize the cardiovascular health of millions of people with blood pressure–related disease worldwide on the basis of inadequate evidence.

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References


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