Should blood pressure reduction be aggressive in patients with hypertension and coronary artery disease?

In *The Lancet*, Emmanuelle Vidal-Petiot and colleagues show that in patients with hypertension and stable coronary artery disease included in the multicountry CLARIFY registry, non-fatal and fatal outcomes decreased as blood pressure was reduced to a 120–139 mm Hg systolic or a 70–79 mm Hg diastolic range over 5 years of treatment. Blood pressure reductions to less than 120/70 mm Hg, however, were accompanied by a marked increase of cardiovascular risk that involved cause-specific events such as myocardial infarction and heart failure, only sparing stroke, whose risk remained similar to that seen at the higher blood pressure values. This finding warns against an extensive extrapolation of the results of the SPRINT trial (ie, that an approach of the lower the achieved blood pressure, the better, should be pursued in all individuals at high cardiovascular risk). According to this new analysis, in patients with atherosclerotic lesions of the coronary arteries, excessive blood pressure reductions might lead to clinically relevant coronary underperfusion.

The findings of the CLARIFY registry are in line with those from post-hoc analyses of several trials, which have similarly seen the association between treatment-induced blood pressure reduction and outcomes to have a J-curve. In most if not all instances, however, the increased outcome seen at the lowest blood pressure values could have been explained by the greater baseline cardiovascular risk exhibited by the patients in the ascending J-curve limb. However, in the study by Vidal-Petiot and colleagues’ baseline risk differences were not especially pronounced (ie, several major cardiovascular risk factors such as age, male prevalence, smoking, diabetes, dyslipidaemia, and renal dysfunction were not appreciably different between groups with different on-treatment blood pressures). Furthermore, although in previous studies the number of patients located in the ascending J-curve limb was often a few hundred, in Vidal-Petiot’s study, there were more than 2000. Finally, baseline differences can hardly explain why a J-curve was seen for cardiac but not for cerebrovascular outcomes. This offers valid arguments for a J-curve origin from an excessive blood pressure reduction rather than from reverse causality (ie, an increased incidence of outcomes due to a greater initial cardiovascular risk).

The latter explanation cannot be excluded, however, because having a history of myocardial infarction, myocardial revascularisation, and heart failure was more common in patients with low on-treatment blood pressures than in those with higher on-treatment blood pressures, suggesting that a greater cardiac compromisation might have favoured both a greater blood pressure-lowering effect of treatment and a higher incidence of cardiac events. The authors coped with this limitation by adjusting the data for the available clinical variables. But adjustment represents an attempt to correct for confounding, not a guarantee that this is achieved. To conclusively show the origin of the J-curve from an excessive blood pressure reduction, prospective studies that allow comparisons between randomised groups with superimposable baseline characteristics will be needed.

The study by Vidal-Petiot and colleagues also shows that the risk of cardiovascular outcomes did not differ at systolic blood pressure values of between 120 and 139 mm Hg. It further shows that there were some age-dependent differences in the association between achieved blood pressure and outcomes. Patients younger and older than 75 years of age both showed a J-curve distribution of outcomes as systolic blood pressure decreased below 120 mm Hg range and exhibited a maximum outcome reduction at achieved diastolic blood pressures between 70–79 mm Hg. Conversely, although in patients aged 75 years or younger the cardiovascular risk increased progressively as blood pressure increased above 129 mm Hg, in older patients, it increased only at values of 150 mm Hg or more. This suggests that the diastolic blood pressure target recommended by guidelines for coronary patients (ie, <90 mm Hg) might be too high. It provides support, however, to the guidelines’ recommendation on systolic blood pressure targets (ie, that in patients with coronary artery disease and hypertension there is no need to achieve a blood pressure of <130 mm Hg) because at less than 140 mm Hg there is no loss on treatment-dependent
protection, which in very elderly patients can be obtained by setting the target at less than 150 mm Hg. This is important because low blood pressure targets markedly increase the incidence of treatment-related side-effects,\(^1,^6\) with an increase in treatment discontinuation, which leads to an increase in risk of cardiovascular events\(^7\) that might attenuate the treatment-dependent benefits.

Finally, the finding that in patients with hypertension and coronary artery disease, a low on-treatment blood pressure does not adversely affect the risk of stroke confirms previous observations that cerebrovascular events might progressively diminish down to blood pressure values of less than 120/70 mm Hg.\(^8,^9\) A question under discussion is whether this finding reflects a greater ability of the brain to autoregulate blood flow. Another question is whether there might be circumstances in which achieving a greater cerebrovascular protection by aggressive blood pressure reduction might overcome the disadvantage of an increase of cardiac events. This is not the case for patients with coronary artery disease in whom myocardial infarction and heart failure are more frequent than stroke. It might apply to Asian patients (in whom strokes largely exceed coronary events) or patients with a previous stroke because stroke recurrence is more common than a first cardiac event.\(^10\)

The adoption of a lower blood pressure target for secondary stroke prevention, however, will require the demonstration that existing cerebrovascular damage does not extend a J-curve to stroke, an issue on which present data are not unequivocal.\(^11,^12\)

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I report personal fees from Bayer, Boehringer Ingelheim, CVRx, Daichi Sankyo, Medtronic, Menarini International, Menck Serono, Novartis, Recordati, Sanofi, and Servier.

8 Chrysant SG, Chrysant GS. Effectiveness of lowering blood pressure to prevent stroke versus to prevent coronary events. Am J Cardiol 2010; 106: 825–29.