



REVIEW ARTICLE

## Hypertension, coronary heart disease and stroke: Should the blood pressure J-curve be a concern?☆

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**Abstract** The paradoxical increase in cardiovascular events in patients with treatment-induced low blood pressure (BP), particularly in hypertensives with pre-existing coronary artery disease, especially those with critically low diastolic BP, which conflicts with data from epidemiologic observational studies, is referred to as a J-curve. It was first described over 30 years ago and is still the subject of considerable controversy. Recent large clinical outcomes trials (INVEST, TNT, ONTARGET, PROVE IT-TIMI 22, SMART) and meta-analyses strongly support its existence for systolic and diastolic BP. The diastolic J-curve is commonly more pronounced. In contrast to cardiovascular complications related to coronary artery disease, no J-curve phenomenon was noted for stroke in most of these studies. This is explained by differences in cerebral and coronary autoregulation and because coronary perfusion occurs only during diastole. On the basis of this review, we suggest a cautious, individualized approach to treatment, particularly in hypertensive patients with coronary heart disease or high risk for impaired coronary blood flow. In these patients we advise against treatment that lowers systolic BP below 120–125 mmHg and, particularly, diastolic BP below 70–75 mmHg.

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**PALAVRAS-CHAVE**

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**Hipertensão arterial, doença coronária e acidente vascular cerebral. A curva em J deve preocupar-nos?**

**Resumo** O aumento paradoxal de eventos cardiovasculares quando a diminuição da pressão arterial ultrapassa determinados níveis críticos, em particular de pressão diastólica e em especial em hipertensos com doença coronária, contrariando os dados de estudos epidemiológicos observacionais, que é conhecido como curva em J e foi descrito há mais de 30 anos tendo suscitado muita controvérsia, foi novamente posto em evidência em vários estudos clínicos recentes (INVEST, TNT, ONTARGET, PROVE IT TIMI 22, SMART) e meta-análises. Na maioria destes estudos, a curva em J foi mais pronunciada para a pressão diastólica (pelo facto de a perfusão coronária se fazer durante a diástole) e não se evidenciou curva em J para acidente vascular cerebral, o que estará relacionado com diferenças nas curvas de autorregulação cerebral e coronária. Com base na análise de todos estes estudos, é nossa opinião que a atitude a tomar deverá ser prudente e individualizada, em especial em hipertensos com doença coronária comprovada ou risco acrescido para fluxo coronário comprometido (idosos, presença de hipertrofia ventricular esquerda), devendo evitar-se que se atinjam com a terapêutica anti-hipertensiva valores de pressão sistólica inferiores a 120-125 mmHg e, em particular, valores de pressão diastólica inferiores a 70-75 mmHg.

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Meta-analyses of epidemiological observational studies have demonstrated a linear relationship between systolic and diastolic blood pressure (BP) levels and risk of cerebrovascular and cardiovascular events for pressures as low as 115/70 mmHg upwards. The Prospective Studies Collaboration meta-analysis of 61 studies involving a million individuals without initial cardiovascular or cerebrovascular disease showed a doubling of mortality from stroke or myocardial infarction (MI) for every 20-mmHg increase in systolic BP or 10-mmHg increase in diastolic BP.<sup>1</sup>

However, in a 1979 paper published in the *Lancet*, Stewart<sup>2</sup> suggested that there was a paradoxical increase in the incidence of MI with lower diastolic BP levels. In 169 patients with severe hypertension, those with diastolic BP (defined as disappearance of Korotkoff sounds) less than 90 mmHg with antihypertensive medication were at greater risk of MI.

In 1987, Cruickshank et al.<sup>3</sup> also detected a J-curve relationship between diastolic BP and mortality from MI but only in hypertensive patients with ischemic heart disease, a finding the authors attributed to the fact that coronary perfusion takes place during diastole. A subsequent meta-analysis by the same lead author of six studies involving over 14 000 hypertensive patients confirmed the J-curve relation, particularly between diastolic BP and ischemic heart disease, as well as in patients with a history of coronary heart disease (CHD).<sup>4</sup> The relationship between diastolic BP and coronary mortality was also seen in the Framingham study, but only in individuals with a history of MI<sup>5</sup>; there was no evidence of a J-curve for systolic BP. Similarly, a meta-analysis of 13 studies (48 000 hypertensives) by Farnett et al. demonstrated a J-curve relationship between diastolic BP and cardiovascular morbidity and mortality, more pronounced in the elderly and those with a history of ischemic heart disease.<sup>6</sup>

Although some studies have found a similar relationship with stroke,<sup>7</sup> most have not, and the PROGRESS trial showed that antihypertensive therapy actually reduced the risk of recurrent stroke with progressive lowering of BP.<sup>8</sup> Rashid et al. confirmed this finding in a subsequent review of randomized trials,<sup>9</sup> while Turan et al.<sup>10</sup> showed similar results in patients with ischemic stroke attributable to intracranial arterial stenosis, in whom the risk of stroke in the same territory was less in individuals with lower BP. A recent meta-analysis in nearly 74 000 diabetic patients showed a progressive reduction in stroke with reductions in BP, although the same was not seen for MI.<sup>11</sup>

However, Kannel et al.,<sup>12</sup> using data from the Framingham study, reported that the increased risk of cardiovascular events with diastolic BP <80 mmHg was only found when systolic BP was higher than 140 or 160 mmHg. According to these authors, the J-curve is thus related to differential (pulse) pressure, which reflects increased arterial stiffness, already identified as an important cardiovascular risk factor. In support of this hypothesis, the SHEP trial and other studies in the elderly with isolated systolic hypertension have also shown the existence of a J-curve for diastolic BP <65/70 mmHg.<sup>13</sup>

A meta-analysis of seven randomized clinical trials involving more than 40 000 hypertensive patients<sup>14</sup> showed that there is a J-curve (or U-curve) in both medicated and non-medicated hypertensives for both cardiovascular and non-cardiovascular mortality. This may be due to reverse causality, the paradoxical increase in events with lower BP levels being the consequence of poor health conditions – the result of cancer or other wasting disease, or heart failure with severely impaired systolic function.

There are thus three possible explanations for the increase in cardiovascular events with lower BP (Table 1):

**Table 1** Pathophysiological mechanisms of the blood pressure J-curve.

1.	Reduction in coronary perfusion (which occurs in diastole) with critically low diastolic BP levels;
2.	Increased differential (pulse) pressure due to low diastolic BP, secondary to increased arterial stiffness;
3.	Reverse causality.

reduced coronary perfusion with lower diastolic BP exceeding the lower limit of the autoregulation curve; increased pulse (differential) pressure due to low diastolic BP reflecting increased arterial stiffness; and reverse causality.

Whether or not the J-curve or U-curve actually exists, the important question is whether there are benefits in setting lower BP target levels, for example 130/80 rather than 140/90 mmHg. After the publication of the HOT<sup>15</sup> and UKPDS<sup>16</sup> trials, the guidelines began to recommend target BP levels below 130/80 mmHg for high-risk hypertensives (those with diabetes, renal failure or cerebrovascular or cardiovascular disease). However, as pointed out in the reappraisal of European guidelines on hypertension management by the European Society of Hypertension and the European Society of Cardiology,<sup>17</sup> these levels are rarely attained, and benefits are seen when BP falls below 140/90 mmHg, even if it does not reach 130/80 mmHg.

A Cochrane review published in 2009,<sup>18</sup> based on a meta-analysis of randomized clinical trials, also concluded that there was no justification for setting target BP levels below those usually recommended. However, the ADVANCE trial,<sup>19</sup> in patients with type 2 diabetes (who have a similar risk to those with previous MI), showed a significant reduction in microvascular and macrovascular events when systolic BP of 135 mmHg was attained compared to 140 mmHg, mainly due to fewer renal events. In the ACCORD trial,<sup>20</sup> a landmark study of 4733 patients with type 2 diabetes comparing the effects of intensive antihypertensive therapy to lower systolic BP below 120 mmHg with standard treatment (target of below 140 mmHg) in a mean follow-up of 4.7 years, the risk of fatal and non-fatal cardiovascular events did not differ significantly between the group with mean systolic BP of 119.3 mmHg and those with mean systolic BP of 133.5 mmHg except for stroke, which was significantly less common in the lower BP group.

In a meta-analysis of 13 randomized trials involving 37 736 diabetic or prediabetic patients<sup>21</sup> that compared microvascular and macrovascular events with more and less intensive antihypertensive therapy, systolic BP  $\leq$ 135 mmHg was associated with a 10% reduction in overall mortality and a 17% reduction in stroke compared to  $\leq$ 140 mmHg, although with 20% more serious adverse effects. However, there were no differences in other microvascular and macrovascular (cardiac, renal, and retinal) events. The authors also compared target BP of  $\leq$ 130 mmHg and  $\leq$ 135 mmHg and found no significant differences in microvascular and macrovascular events except for a larger reduction in stroke with lower BP, but with 40% more serious adverse effects.

Similarly, a subanalysis of the INVEST trial of 6400 diabetic hypertensives with CHD<sup>22</sup> showed that intensive therapy aiming at systolic BP  $<$ 130 mmHg was not associated with a reduction in cardiovascular events compared to less intensive BP control (130–139 mmHg).

In the HYVET study<sup>23</sup> in hypertensives 80 years of age or older, cardiovascular morbidity and mortality was reduced with antihypertensive therapy for BP levels below 150/80 mmHg, while the VALISH<sup>24</sup> and JATOS<sup>25</sup> studies, also in elderly hypertensives, showed no reduction in cardiovascular morbidity and mortality with systolic BP of  $<$ 140 mmHg compared to  $>$ 140 mmHg.

In the last five or six years the question of the J-curve has again come to the fore, particularly after the INVEST, VALUE, ONTARGET, Syst-Eur and TNT trials demonstrated a paradoxical increase in cardiovascular events, especially MI, when systolic or diastolic BP was reduced below certain levels. All these trials involved hypertensives with high cardiovascular risk, particularly for CHD. In a secondary analysis of the INVEST trial<sup>26</sup> in 22 576 hypertensives with CHD, there was an increase in the primary outcome (all-cause mortality, non-fatal MI and non-fatal stroke) and in all-cause mortality and MI in patients in whom antihypertensive therapy had reduced diastolic BP to below 70–80 mmHg and systolic BP to below 120–130 mmHg (although the J-curve was considerably less pronounced than for diastolic BP), these effects being more marked in patients who had not undergone revascularization. The nadir of the J-curve for systolic BP rose to 140 mmHg in patients aged over 80 and to 70 mmHg for diastolic BP.<sup>27</sup> In the VALUE trial<sup>28</sup> in hypertensive patients (46% with CHD), there was a higher incidence of stroke with systolic BP between 120 and 130 mmHg, while the Syst-Eur trial<sup>29</sup> showed increased risk for cardiovascular events with diastolic BP of less than 70 mmHg only for patients with CHD. Similarly, in a post-hoc analysis of the HOT trial, previously unpublished data revealed a J-curve relationship between diastolic BP and risk for MI, but only in patients with previous myocardial ischemia.<sup>30</sup> In the TNT trial,<sup>31</sup> in 10 001 CHD patients treated aggressively to attain cholesterol and BP reduction, a higher cardiovascular event rate was seen in the group with the lowest BP values than in those with systolic BP 130–140 mmHg and diastolic BP 70–80 mmHg; there was much greater risk in those with BP levels of 110–120 and 60–70 mmHg. In the ON-TARGET study<sup>32</sup> (75% of patients with CHD), cardiovascular mortality and MI (but not stroke) increased for systolic BP values below 126–130 mmHg. In a subgroup analysis of this study in 9603 diabetic patients, increased cardiovascular mortality was seen with systolic BP  $<$ 125 mmHg compared with  $<$ 130 mmHg,<sup>33</sup> while the VADT trial,<sup>34</sup> in around 1800 diabetic hypertensives, found increased cardiovascular risk for diastolic BP  $<$ 70 mmHg. In the subanalysis of the INVEST trial,<sup>22</sup> tighter BP control (systolic BP  $<$ 130 mmHg) in diabetic hypertensive patients with CHD was associated with higher overall mortality compared to 130–140 mmHg. However, this higher mortality was only seen with systolic BP  $\leq$  115 mmHg.

The PROVE-IT-TMI 22 trial<sup>35</sup> also demonstrated the existence of a J-curve relation with all-cause mortality and

cardiovascular events and mortality following antihypertensive therapy after acute coronary syndromes, more evident with diastolic BP, and only in terms of BP levels during follow-up, not baseline levels. In this study the nadir of the systolic curve was between 130 and 140 mmHg and that of the diastolic curve was between 80 and 90 mmHg, although the curve was relatively flat between 110–130 mmHg and 70–90 mmHg.

The beginning of 2012 saw the publication of the SMART trial<sup>36</sup> of 5788 patients with manifest vascular disease (CHD, stroke, or peripheral arterial disease), in which Dorresteijn et al. reassessed the existence of the J-curve, relating baseline systolic, diastolic and differential pressures with the occurrence of vascular events and all-cause mortality. They showed that there was a J-curve with a nadir of 143/82 mmHg, and, assuming reverse causality was unlikely to be the cause (although impossible to exclude), claimed that BP above or below this level could be considered an independent risk factor for cardiovascular events.

The studies reviewed above thus show the existence of a J-curve relationship with cardiovascular events, especially CHD, particularly for diastolic BP but also for systolic BP (although the latter is usually less pronounced). Stroke is consistently the exception (except in the acute phase<sup>37</sup> or, according to a recent study, in the subacute phase of non-cardioembolic ischemic stroke<sup>38</sup>), which may be related to differences in coronary and cerebral autoregulation – with more effective autoregulation of cerebral blood flow preserving tissue perfusion when BP is sharply reduced, or with selectively compromised coronary autoregulation.<sup>39</sup>

The controversy concerning the J-curve continues, and is at times lively, such as when Bryan Williams<sup>40</sup> suggests simply ignoring diastolic BP when systolic BP is elevated, since the latter mandates effective antihypertensive therapy to reduce stroke risk. By contrast, in a recent editorial,<sup>41</sup> NM Kaplan calls the J-curve “alive and threatening” and points out that the problem is the need to intensify antihypertensive therapy to control persistently high systolic BP, which can increase coronary risk through a parallel fall in diastolic BP, especially in the elderly with isolated systolic hypertension, who are more likely to have CHD.

The European Society of Hypertension document reappraising the 2007 hypertension guidelines states specifically that “on the basis of current data, it may be prudent to recommend lowering systolic/diastolic BP to values within the range 130–139/80–85 mmHg, and possibly close to lower values in this range, in all hypertensive patients.”<sup>17</sup> Similarly, Chrysant,<sup>42</sup> while pointing out that the J-curve is not a uniform phenomenon, highlights the fact that it is more likely to be found in elderly hypertensives at high risk due to concomitant CHD, diabetes or left ventricular hypertrophy, and recommends less aggressive BP control in such patients, avoiding levels below 130/80 mmHg. Flynn and Bakris<sup>43</sup> and Nilsson<sup>44</sup> set target BP levels in high-risk hypertensive patients with diabetes or chronic renal disease at less than 140/90 mmHg, stating that levels below 130/80 mmHg are only justified in cases of chronic proteinuric renal disease or when there is a high risk of stroke.

In conclusion, should the blood pressure J-curve be a concern? Although many questions on this subject remain unanswered and studies are scheduled to try to clarify the issue, we suggest a cautious, individualized approach to

treatment, particularly in hypertensive patients with CHD or high risk for impaired coronary blood flow (such as the elderly and those with left ventricular hypertrophy). In these patients we advise against systolic BP levels below 120–125 mmHg and, particularly, diastolic BP below 70–75 mmHg.

## Ethical disclosures

**Protection of human and animal subjects.** The authors declare that no experiments were performed on humans or animals for this study.

**Confidentiality of data.** The authors declare that no patient data appear in this article.

**Right to privacy and informed consent.** The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

## Conflicts of interest

The author has no conflicts of interest to declare.

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