

HYPERLIPIDEMIA & HYPERTENSION UPDATE

Hypertension Control: J-Curve Revisited

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ABSTRACT

Over the last three decades there is an increasing number of investigators and meta-analyses focusing on the dangers of lowering blood pressure below certain levels. Several studies such as Invest, Ontarget, Value and TNT showed a significant decrease in cardiovascular morbidity and mortality by lowering blood pressure levels. However, blood pressure decrease below a certain level had exactly the opposite effect. The increase of cardiovascular morbidity and mortality was attributed to the excessive reductions in blood pressure which may explain why in major clinical trials blood pressure below certain levels increases cardiovascular adverse events mainly in patients with coronary heart disease. In these patients a fall in diastolic blood pressure might lower perfusion pressure distal to a stenosis below a critical level at which autoregulation is effective. This phenomenon led the European Society of Hypertension to propose a “J-shaped curve” relationship between blood pressure and cardiac morbidity and mortality, whereby lowering blood pressure below a critical point is no longer beneficial and possibly even deleterious. The challenge is to better define the limits of intervention and to define groups of people who are particularly vulnerable to over-aggressive lowering of blood pressure.

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Hypertension is an established risk factor for major cardiovascular events; its entity was recognized from antiquity, even with different definition (“hard pulse disease”), where ancient historical records as far back as 2600 BC report different treatment strategies (usually by acupuncture and venesection) to manage this disease.¹ Over the years treatment strategies were changed; in the late 1930s, elevated blood pressure was considered by many expert physicians to be necessary for the adequate perfusion of vital organs; JH Hay affirms that “the greatest danger to a man with high blood pressure lies in its discovery, because then some fool is certain to try and reduce it”.² Likewise, P Dudley White affirms that “Hypertension may be an important compensatory mechanism which should not be tampered with, even if it were certain that we could control it”.³ In the late 1950s, the benefit of blood pressure reduction reappears with the introduction of diuretics⁴ and the research for effective therapy and management of hypertension continued until the 1990s were the dogma “the lower the better” prevails after the HOT study results.⁵ The zeal of the physicians was so pronounced that they were tempted to decrease blood pressure especially diastolic blood pressure as low as possible without adverse effects, encouraged by contemporary guidelines in 1980s.⁶

However, in the last three decades there have been an increasing number of investigators and meta-analyses focusing on the dangers of lowering blood pressure below

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certain levels. Several studies such as Invest, Ontarget, Value and TNT⁷ showed a significant decrease in cardiovascular morbidity and mortality by lowering blood pressure levels. However, blood pressure decrease below a certain level had exactly the opposite effect.⁷ The increase of cardiovascular morbidity and mortality was attributed to the excessive reductions in blood pressure which may explain why in major clinical trials blood pressure below certain levels increases cardiovascular adverse events mainly in patients with coronary heart disease. Many authors attribute this phenomenon mainly among other reasons to the fact that most of coronary blood flow to the left ventricle occurs in diastole. In patients with chronic ischemic heart disease a fall in diastolic blood pressure might lower perfusion pressure distal to a stenosis below a critical level at which autoregulation is effective. This phenomenon leads the European Society of Hypertension to propose a “J-shaped curve” relationship between blood pressure and cardiac morbidity and mortality, whereby lowering blood pressure below a critical point is no longer beneficial and possibly even deleterious.⁷ The J curve describes the shape of the relationship between blood pressure and the risk of cardiovascular morbidity and/or mortality and the J shape reflects increased risk at high levels of blood pressure, with risk falling in parallel to blood pressure reduction until a nadir is reached, below which further blood pressure reduction begins to increase the risk.

However, the explanation of this blood pressure paradox seems to be more complicated. A plethora of reports have described the shape of the relationship between blood pressure and risk. Some reports have shown this relationship to be continuous and positive, while others have demonstrated an increased risk in participants with low blood pressure. However, these studies lacked control patients, thus, comparison with similar but untreated patients was impossible. These reports could not investigate whether drugs that reduce blood pressure have harmed hypertensive patients or it was low blood pressure or co-morbidities from the beginning that increased cardiovascular events. The INDANA database offered the opportunity to assess the shape of the relationship between risk for events and level of blood pressure in both treated and initially untreated hypertensive patients.⁸ The authors affirmed that the increased risk for events observed in patients with low blood pressure was not related to antihypertensive treatment and was not specific to blood pressure-related events. They attributed the J-shaped curve as due to the poor health conditions that lead to low blood pressure and an increased risk for death.⁸

Therefore, there are different opinions regarding the same issue and critical questions remain to be answered.

How low can blood pressure be lowered and remain both safe and beneficial?

What is the lowest safe level of blood pressure beyond which potential harm offsets the benefits of treatment?

Whether the J-curve relationship is equally significant for systolic as it is for diastolic blood pressure and whether its impact is more relevant for stroke, renal events, myocardial infarction and heart failure

According to the guidelines of the European Society of Hypertension (ESH), in the general hypertensive population the blood pressure target is <140/90 mmHg and in high risk patients with coronary artery disease, stroke, diabetes or renal dysfunction, the target is <130/80 mmHg. The concept in the latter group is that of a flexible threshold/target for treatment in relation to total cardiovascular risk due to J-curve phenomenon.⁷ However, there is no evidence for this affirmation since there are practically no data regarding the beneficial effect of lowering blood pressure below this threshold in this high risk group.

In the ACCORD study, the authors concluded that in patients with type 2 diabetes at high risk for cardiovascular events, targeting a systolic blood pressure of less than 120 mmHg, as compared with less than 140 mmHg, did not reduce the rate of a composite outcome of fatal and nonfatal major cardiovascular events.⁹ Moreover, in the HOT study, reanalyzing the data, there was no evidence of a J-shaped curve for the relation of major cardiovascular events, myocardial infarction, stroke, and cardiovascular mortality with achieved blood pressures.

Based on the previously published trials, it seems that there is no J curve for stroke and renal events, however in the field of coronary heart disease we need well designed prospective randomized studies to answer the question for the existence of a J curve or not. Clearly, there is a point at which both diastolic and systolic blood pressure become too low to sustain life.

In conclusion, advanced cardiovascular disease is a mixture of different clinical conditions which require individualization of decisions. Despite the need to reduce cardiovascular risk by blood pressure reduction, blood pressure control is more difficult to achieve due to the presence of underlying vascular and renal organ damage. The challenge is to better define the limits of intervention and to define groups of people who are particularly vulnerable to over-aggressive lowering of blood pressure; to this end, we are in dire need for new prospective randomized trials addressing this question.

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