

**Category:**

**Study type:**

**Author's declarative title:** Patients with coronary heart disease and very low blood pressure are at increased risk of cardiovascular events but whether this should affect treatment decisions is not clarified

**Citation:**

### **Commentary**

#### **Context**

Very large observational studies have provided evidence against a “J-shaped association” between systolic (SBP) or diastolic blood pressure (DBP) and risk of cardiovascular disease (CVD).<sup>1</sup> The log-linear relationship observed in these studies indicates that, within the normal physiological BP range, there is no threshold below which associations change qualitatively. In order to mitigate the risk of confounding and reverse causality, these studies appropriately excluded people with known CVD. However, this selection has contributed to continued controversy over possible thresholds, particularly among those with established coronary heart disease (CHD); over 20 studies have reported conflicting findings on the existence of a threshold, its exact level and the population and outcomes that might be affected by it.<sup>2</sup>

#### **Methods**

The CLARIFY study<sup>3</sup> aimed to investigate the ‘optimum’ BP level in a prospective international cohort of 22679 patients with known stable CHD and hypertension. Investigators used adjusted Cox proportional hazards models to assess associations between BP and risk of a range of CVD outcomes over 5 years. By contrast with most previous studies that have used *baseline* BP as their exposure variable or have corrected these for regression dilution bias<sup>4</sup>, they defined their primary exposure variable as the arithmetic mean of all BP values from baseline to the last available measurement before an event (average BP). Presumably, because average BP might increase the risk of reverse causality, they also report associations for baseline BP as an alternative exposure variable.

#### **Findings**

Patients in the reference categories 120-129 mmHg SBP or 70-79 mmHg DBP were found to have the lowest risk of cardiovascular death, myocardial infarction (MI) or stroke. No formal statistical tests for trend or departure from trend were reported. Restricted cubic splines showed apparent J-shaped associations for all outcomes. However, for stroke the confidence intervals in the lowest SBP and DBP categories included 1 and hence were not statistically different from the reference category. In supplementary models with baseline BP as the exposure variable, associations were weaker for all outcomes in the high as well as low BP categories. For instance, for MI HRs (95% CI) for the lowest SBP category changed from 1.48 (1.17-1.87) to 1.11 (0.87-1.42) and for the highest SBP category from 2.92 (2.32-3.67) to 1.36 (1.09-1.69), and

the test for heterogeneity was no longer significant. A similarly weak association was observed for stroke ( $p=0.06$ ).

### ***Commentary***

The CLARIFY registry shows that the risk of CVD differs by patients' average BP during follow-up with possible reverse associations at the lower end of BP spectrum. However, whether these apparently J-shaped associations are robust and causal is less clear. The authors argue that the models with baseline BP as the exposure variable showed broadly consistent results to their main analyses, thus dismissing the possibility of reverse causality. However, their supplementary results show a flattening of associations with no significant heterogeneity by baseline SBP for MI or stroke. This may be due to lack of power and does not support the existence of J-shaped associations. They further argue that the absence of an association between low BP and stroke is biologically plausible and supports the harmful role of low BP on MI but not stroke. In making this judgement, the authors seem to interpret the lack of evidence for a significant association between low BP and stroke as evidence against it. An alternative explanation for this observation is that BP is a stronger risk factor for stroke than MI<sup>5</sup> and therefore less sensitive to confounding and bias.

### ***Implications for practice***

CLARIFY reminds us that patients with CHD and very low BP (as well as high BP) are at increased risk of CVD events. However, such patients may still benefit from BP lowering treatment based on more reliable evidence from meta-analyses of randomised trials that have shown no heterogeneity of effects by baseline BP or between those with or without CHD.<sup>6</sup>

### **References**

1. Rahimi K, Emdin CA, MacMahon S. The epidemiology of blood pressure and its worldwide management. *Circ Res* 2015;116(6):925–36.
2. Messerli FH, Panjra GS. The J-Curve Between Blood Pressure and Coronary Artery Disease or Essential Hypertension. *J Am Coll Cardiol* 2009;54(20).
3. Vidal-Petiot E, Ford I, Greenlaw N, et al. Cardiovascular event rates and mortality according to achieved systolic and diastolic blood pressure in patients with stable coronary artery disease: an international cohort study. *Lancet* 2016;388(10056):2142–52.
4. Emdin CA, Anderson SG, Salimi-Khorshidi G, et al. Usual blood pressure, atrial fibrillation and vascular risk: evidence from 4.3 million adults. *Int J Epidemiol* 2016;
5. Prospective Studies Collaboration. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* 2002;360:1903–13.
6. Ettehad D, Emdin CA, Kiran A, et al. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. *Lancet* 2015;387(10022):957–967.

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**Competing interests**

None