



[Savoia, C.](#) and [Touyz, R.](#) (2017) Hypertension, diabetes mellitus, and excess cardiovascular risk importance of baseline systolic blood pressure. *Hypertension*, 70(5), pp. 882-883.  
(doi:[10.1161/HYPERTENSIONAHA.117.09764](https://doi.org/10.1161/HYPERTENSIONAHA.117.09764))

This is the author's final accepted version.

There may be differences between this version and the published version. You are advised to consult the publisher's version if you wish to cite from it.

<http://eprints.gla.ac.uk/145759/>

Deposited on: 11 August 2017

Enlighten – Research publications by members of the University of Glasgow  
<http://eprints.gla.ac.uk>

**Hypertension, diabetes and excess cardiovascular risk-importance of baseline systolic blood pressure.**

**Carmine Savoia<sup>1</sup> , Rhian M Touyz<sup>2</sup>**

<sup>1</sup>Clinical and Molecular Medicine Department, Cardiology Unit Sant' Andrea Hospital, Sapienza University of Rome, Rome, Italy.

<sup>2</sup>Institute of Cardiovascular and Medical Sciences, British Heart Foundation Glasgow Cardiovascular Research Centre, University of Glasgow, Glasgow, UK.

**Running Title: Blood pressure targets in diabetes**

**Correspondence:**

Carmine Savoia, MD, FAHA

Clinical and Molecular Medicine Department

Cardiology Unit,

Sant' Andrea Hospital

Sapienza University of Rome

Via di Grottarossa 1037/1039

00189 Rome, Italy

Tel +390633775561

Fax +390633775061

[carmine.savoia@uniroma1.it](mailto:carmine.savoia@uniroma1.it)

Over 50% of adults with type 2 diabetes also have hypertension, which doubles the risk of cardiovascular disease in this cohort of patients. Extensive clinical data has demonstrated unequivocally that lowering systolic blood pressure (SBP) reduces cardiovascular disease (CVD) (1), particularly in high risk patients such as those with diabetes, yet the optimal target for blood pressure (BP) reduction remains a topic of discussion. For most patients with hypertension, treatment guidelines still suggest that BP should be treated to a target <140/90 mmHg (2,3). However, the potential greater cardiovascular benefit of lowering BP to targets much lower than 140/90 mmHg, especially in patients with diabetes, has recently been debated. Based on data from the Systolic Blood Pressure Intervention Trial (SPRINT) (4) and several recent meta-analyses, some guidelines (CHEP, Australian, Taiwan) have now adopted goals of 120-130 mmHg in ‘SPRINT’-like patients. The concept of the “lower the better”, especially in patients with diabetes or previous cardiovascular or renal disease, may not necessarily hold true, since several studies have shown a “J-curve” effect of BP treatment, where BP lowering to levels beyond those required to maintain tissue perfusion may lead to additional cardiovascular events, particularly coronary heart disease or stroke (5). Although the notion of the J-curve has typically referred to diastolic BP (DBP) in terms of additional harm when DBP is reduced below 65 mmHg, there has been recent concern that excessive BP lowering in general could increase the risk of cardiovascular events. Moreover, in patients with diabetes, the previously recommended BP target of <130/85 mmHg was challenged after the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial (6) since in a population of 4733 patients with type 2 diabetes an intensive BP-lowering therapy (SBP <120 mmHg) versus standard BP target (SBP <140 mmHg) failed to show overall cardiovascular benefit. The recent EMPA-REG OUTCOME study, demonstrated significant reduction in cardiovascular mortality with empagliflozin and suggested that a decrease in SBP to 130 mmHg may explain, in part, the cardiovascular protective effects of the drug.

Thus, considering the recent trials and meta-analyses, together with the suggested impact of the ‘J-curve phenomenon’ confusion continues to grow regarding optimal goals for treatment of patients

with hypertension in different classes of cardiovascular risk, especially in the subset of diabetic patients who are at particularly high risk. SBP <140 mmHg and DBP <90 mmHg seem safe in the J-curve effect, and hence most guidelines still suggest these targets in patients with diabetes and hypertension (3). Some guidelines suggest lower targets (<140/85 mmHg) (2). While the SPRINT (4) findings certainly support intensive treatment to SBP of 120 mmHg, this study excluded patients with diabetes and hence uncertainty remains as to whether benefits observed in SPRINT hold true for high-risk individuals such as diabetic patients. A network meta-analysis of 42 studies including 144,220 patients with various comorbidities (including diabetes, stroke, chronic kidney disease), age ranges, and mean BP levels at baseline, showed that the lowest risks for CVD and all-cause mortality were evident at SBP 120-124 mmHg, supporting intensive BP control with no evidence of a J-shaped effect in a large multi-morbid hypertensive population, including those with diabetes (7). On the other hand a recent meta-analysis (8) clearly showed increased risk of CVD mortality in patients with diabetes who had a baseline SBP <140 mmHg, while another meta-analysis (9), including studies in adults with type 2 diabetes, reported a small reduction in the risk of stroke associated with more intensive BP reduction and inconclusive results for mortality and CHD. Hence SBP treatment targets for adults with diabetes remain still unclear. Further unravelling the J-curve BP effect, Navar and colleagues, in the current issue of the journal, questioned whether SBP at the extremes contributes to cardiovascular events in patients with type 2 diabetes (10). In particular, the study investigated the association between baseline on-treatment SBP and cardiovascular disease in 12,275 adults with diabetes, prior cardiovascular disease, and treated hypertension, from the Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) randomized trial of sitagliptin vs. placebo. The study showed a U-shaped association between on-treatment SBP at baseline and CVD events in the entire population, suggesting that the relationship between SBP and risk of cardiovascular events is non-linear. This phenomenon raises the question as to what the target BP should be when treating hypertension in patients with diabetes. Of significance, SBP in the range between 110-150 mmHg was associated with a similar risk of CVD in patients with diabetes,

suggesting that the U-shape is driven primarily by very low or very high SBP. At very low on-treatment SBP (< 110 mmHg) there was no increased risk for CVD, fractures or worsening kidney function, while at SBP >150 mmHg, risk of worsening kidney function was increased. Hence it is reasonable to assume that there is a wide safety margin for SBP targets (110-150 mmHg). However, since these findings derive from an observational analysis of trial data in high risk patients with previous CV events, caution should be used to extend them to the general hypertensive and diabetic population, especially in primary prevention. Nevertheless, an important lesson learned from the Navar study is the broad safety margin for treatment within the SBP range of 110-150 mmHg in hypertensive patients with type 2 diabetes. This is critical because there has been much debate about how far BP should be lowered to prevent cardiovascular events in high risk patients, including those with diabetes. While the Navar study demonstrated a U-shaped curve between SBP and cardiovascular outcomes, it should be highlighted that the U (or J)-curve relationship between BP values and ‘cardiovascular risk’ differ to the relationship between BP and ‘cardiovascular events’ and that many factors, such as age, sex, obesity, smoking, existing/previous CVD and diabetes may modify the relation between cardiovascular risk and outcome. Moreover, there are limitations when comparing data derived from epidemiological studies, clinical trials, intervention studies and meta-analyses, because study designs differ, population cohorts are variable and primary/secondary outcomes differ. Taking into consideration these limitations, and while we continue to discuss absolute BP values as ideal targets in the treatment of hypertension in patients with diabetes, the growing overall evidence indicates that beneficial cardiovascular effects of BP lowering likely depend on baseline SBP. However, this is not simple, because this relationship may differ depending on different subsets of patients. Further stratification studies with deeply phenotyped patients will likely reveal different ‘ideal’ BP targets for specific subsets of hypertensive patients, including those with diabetes mellitus.

**Source of Funding: None**

**Disclosure: None**

## **References**

1. Sowers JR. Recommendations for special populations: diabetes mellitus and the metabolic syndrome. *Am J Hypertens*. 2003;16(11 Pt:41S–5S).
2. Mancia G, Fagard R, Narkiewicz K, et al. 2013 ESH/ESC guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Eur Heart J*. 2013;34:2159-2219.
3. James PA, Oparil S, Carter BL, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *JAMA*. 2014;311:507-520.
4. The SPRINT Research Group. A randomized trial of intensive versus standard blood pressure control. *N Engl J Med*. 2015;373:2103–2116.
5. Williams B. Hypertension and the “J-curve”. *J Am Coll Cardiol* 2009;54:1835–1836.
6. ACCORD Study Group. Effects of intensive blood-pressure control in type 2 diabetes mellitus. *N Engl J Med*. 2010;362: 1575.
7. Bundy JD, Li C, Stuchlik P, et al. Systolic blood pressure reduction and risk of cardiovascular disease and mortality: a systematic review and network meta-analysis *JAMA Cardiol*. 2017;2:775-781.
8. Brunström M, Carlberg B. Effect of antihypertensive treatment at different blood pressure levels in patients with diabetes mellitus: systematic review and meta-analyses. *BMJ*. 2016; 352:i717.
9. McBrien K, Rabi DM, Campbell N, et al. Intensive and standard blood pressure targets in patients with type 2 diabetes mellitus: systematic review and meta-analysis. *Arch Intern*

*Med.* 2012; 172:1296-1303.

10. Navar AM, Gallup DS, Lokhnygina Y, et al. Hypertension Control in Adults With Diabetes and Recurrent Cardiovascular Events: Global Results From the TECOS Trial. *Hypertension*. 2017; in press.