

Hypertension, Diabetes Mellitus, and Excess Cardiovascular Risk

Importance of Baseline Systolic Blood Pressure

Carmine Savoia, Rhian M. Touyz

See related article, pp 907–914

More than 50% of adults with type 2 diabetes mellitus also have hypertension, which doubles the risk of cardiovascular disease (CVD) in this cohort of patients. Extensive clinical data have demonstrated unequivocally that lowering systolic blood pressure (SBP) reduces CVD,¹ particularly in high-risk patients, such as those with diabetes mellitus; 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 <140/90 mmHg, especially in patients with diabetes mellitus, has recently been debated. Based on data from the SPRINT trial (Systolic Blood Pressure Intervention Trial)⁴ and several recent meta-analyses, some guidelines (CHEP [Canadian Hypertension Education Program], Australian, and Taiwan) have now adopted goals of 120 to 130 mmHg in SPRINT-like patients. The concept of the lower the better, especially in patients with diabetes mellitus or previous cardiovascular or renal disease, may not necessarily hold true because 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 in terms of additional harm when diastolic BP 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 mellitus, the previously recommended BP target of <130/85 mmHg was challenged after the ACCORD trial (Action to Control Cardiovascular Risk in Diabetes)⁶ because in a population of 4733 patients with type 2 diabetes mellitus, 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 (Empagliflozin, Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients) 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 about 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 diastolic BP <90 mmHg seem safe in the J-curve effect, and hence, most guidelines still suggest these targets in patients with diabetes mellitus and hypertension.³ Some guidelines suggest lower targets (<140/85 mmHg).² Although the SPRINT⁴ findings certainly support intensive treatment to SBP of 120 mmHg, this study excluded patients with diabetes mellitus, 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 mellitus, stroke, and 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 to 124 mmHg, supporting intensive BP control with no evidence of a J-shaped effect in a large multimorbid hypertensive population, including those with diabetes mellitus.⁷ On the contrary, a recent meta-analysis⁸ clearly showed increased risk of CVD mortality in patients with diabetes mellitus who had a baseline SBP <140 mmHg, whereas another meta-analysis,⁹ including studies in adults with type 2 diabetes mellitus, reported a small reduction in the risk of stroke associated with more intensive BP reduction and inconclusive results for mortality and coronary heart disease. Hence, SBP treatment targets for adults with diabetes mellitus still remain unclear. Further unravelling the J-curve BP effect, Navar et al,¹⁰ in the current issue of the journal, questioned whether SBP at the extremes contributes to cardiovascular events in patients with type 2 diabetes mellitus. In particular, the study investigated the association between baseline on-treatment SBP and CVD in 12 275 adults with diabetes mellitus, prior CVD, and treated hypertension, from the TECOS (trial evaluating cardiovascular outcomes with sitagliptin) randomized trial of sitagliptin versus placebo. The study showed a U-shaped association between on-treatment SBP at baseline

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and CVD events in the entire population, suggesting that the relationship between SBP and risk of cardiovascular events is nonlinear. This phenomenon raises the question as to what the target BP should be when treating hypertension in patients with diabetes mellitus. Of significance, SBP in the range between 110 and 150 mmHg was associated with a similar risk of CVD in patients with diabetes mellitus, suggesting that the U-shape is driven primarily by low or high SBP. At low on-treatment SBP (<110 mmHg), there was no increased risk for CVD, fractures, or worsening kidney function, whereas 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, because these findings derive from an observational analysis of trial data in high-risk patients with previous cardiovascular 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 to 150 mmHg in hypertensive patients with type 2 diabetes mellitus. 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 mellitus. Although 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 mellitus, 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 mellitus, 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.

Disclosures

None.

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