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The Ongoing Saga of Optimal Blood Pressure Level in Patients With Diabetes Mellitus and Coronary Artery Disease

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Although it is well established that increased blood pressure (BP) is a major contributor to the increased risk of cardiovascular events in diabetes mellitus (DM), there is still ongoing controversy regarding the optimal level of BP attained with therapeutic interventions that is safe and provides cardiovascular protection, especially in patients with DM and coexistent coronary artery disease (CAD).^{1,2} The article in this issue of the *Journal of the American Heart Association (JAHA)* provides yet more evidence for the wealth of data already available in showing that intensive reduction of BP to levels <130/80 mm Hg as recommended by the recent 2017 American College of Cardiology (ACC)/American Heart Association (AHA) Hypertension Guidelines might indeed not be safe in diabetic patients with coexistent CAD.^{3–9} In the present study by White et al, the investigators have performed a retrospective analysis to evaluate the optimal level of BP in patients with DM and recent acute coronary syndrome enrolled in the EXAMINE (Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care trials) trial. The primary objective of this analysis was to evaluate the appropriate target BP in these high-risk patients with DM and CAD, given the recent recommendations of the 2017 ACC/AHA BP Guidelines for the target BP <130/80 mm Hg in patients with DM. These investigators examined the relationship between the clinician-measured BP values and risks of major adverse cardiac events and heart failure using the BP values of 131 to 140 mm Hg for systolic and 81 to 90 mm Hg for diastolic as a referent as recommended by the 2015 ACC/AHA/ASH (American Society of

Hypertension) Guidelines and the American Diabetes Association (ADA) 2017 guidelines.^{3–5} The results revealed a U-shaped relationship between cardiovascular outcomes and BP values. Specifically, the findings demonstrated that the risk of major adverse cardiac events and cardiovascular death or heart failure were higher for both systolic BP <130 mm Hg as well as diastolic BP <80 mm Hg.³ These findings described by White et al raise concern about the appropriateness of the BP goal of <130/80 mm Hg across the board for all patients with DM as recommended by the 2017 ACC/AHA guidelines.⁴ It is important to note that the 2017 Guidelines recommendations for BP control in DM are in contrast to several other national and international guidelines, which recommend a BP target of <140/90 mm Hg for diabetic patients and suggest considering BP goal of <130/80 mm Hg in selected high-risk patients when it can be achieved without any harm.^{5,6,10} We might then question as to what evidence or data compelled the 2017 ACC/AHA guidelines to recommend the goal of <130/80 mm Hg. Although there does not appear to be any specific overwhelming evidence in support of this recommendation, it has been stated that it is based on evaluation of the prediabetes cohort in the SPRINT database (diabetics were excluded) as well as the findings from some of the recent meta-analyses.^{11,12} It is crucial to keep in mind that these analyses did not specify patient characteristics and might not have included diabetic patients with CAD who are likely to be adversely affected by excessive lowering of BP. Furthermore, the recommendations made by the 2017 ACC/AHA guidelines are clearly in contrast to the findings available from previous large prospective randomized clinical trials (RCTs) that have specifically examined the BP target of <130/80 mm Hg in diabetics and high risk patients with CAD/cardiovascular disease.^{13,14} These studies including the results from the ACCORD (Action to Control Risk of Diabetes) study revealed that there was no significant demonstrable benefit of lowering BP values to <130/80 mm Hg for overall risk reduction in major adverse cardiac events (although ACCORD results did show reduction in nonfatal stroke rates with intensive BP reductions).^{13,14} The findings described in the present study by White et al lend further support to the findings of previous studies and further demonstrate the potential for harm with aggressive BP-lowering therapy

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specifically in patients with DM and recent acute coronary syndrome.³ Their findings also emphasize the adverse consequences of intensive BP reduction in high-risk patients with DM and CAD reported in the recent analyses of the data from the INVEST (The International Verapamil-Trandolapril Study), CLARIFY (Prospective Observational Longitudinal Registry of Patients with Stable Coronary Artery Disease), as well as the ONTARGET (Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial) and TRANSCEND (Telmisartan Randomised Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease) studies.^{7–9} All of these studies showed that systolic BP of <120 mm Hg and diastolic BP <70 mm Hg were associated with adverse cardiovascular outcomes except for reduced risk of stroke in those achieving lower BP values.^{7–9}

The Concept of “Lower Is Better”

It is then natural to ask why has there been so much focus on lowering the BP to the lowest possible levels in DM. In order to get proper insight into this prevailing concept, we have to examine the historical perspective of this concept. Epidemiologic observations in several landmark studies had demonstrated that there is progressive increase in the risk of macrovascular and microvascular events with increasing levels of systolic BP starting at 115 mm Hg.^{1,2,15} In addition, some of the earlier interventional RCTs had shown the benefit of aggressive BP-lowering strategy in reducing the increased risk of both macrovascular and microvascular events.^{1,2,15,16} It is, however, important to recognize that in both studies the achieved systolic BP in the aggressive intervention arm was 144 mm Hg. Based largely on this prevailing concept (even in the absence of any evidence from prospective RCTs), previous guidelines had recommended that in patients with DM and hypertension, the target BP should be <130/80 mm Hg (and even lower to 120/75 mm Hg in those with renal impairment).^{1,2}

Because of the lack of evidence from prospectively conducted RCTs during the past decade, 2 studies specifically examined the role of intensive BP-lowering strategy to achieve systolic BP <130 mm Hg (in patients with DM and hypertension) on various cardiovascular outcomes including cardiovascular mortality, nonfatal myocardial infarction, fatal and nonfatal strokes, all-cause mortality, and various microvascular events including nephropathy.^{13,14} The results of these studies did not find any substantive benefit of intensive BP control (systolic BP <130 mm Hg) in reducing the risk of coronary events defined as fatal or nonfatal myocardial infarctions. These findings were further corroborated by several other reports including a meta-analysis that specifically evaluated various levels of BP in DM and these also failed to reveal any significant benefit of intensive BP-lowering strategy over standard BP

control strategy on macrovascular events.^{7–9,17} It is, however, important to emphasize that both the data from individual RCTs and the meta-analysis did show that the risk of stroke was indeed reduced with intensive BP control.^{2,17}

Based on the available evidence, it is reasonable to conclude that despite the recommendations of the 2017 ACC/AHA BP guidelines, the totality of data from recent trials including the paper by White et al in this issue of *JAHA* do not support an across-the-board strategy to intensively lower BP to levels <130/80 mm Hg in patients with DM and hypertension, because many of them will have coexistent cardiovascular disease and CAD. Furthermore, the data from some studies including the paper by White et al suggest that aggressive BP reduction (which generally requires multiple antihypertensive drugs) can be associated with increased risk of adverse events including the risk of symptomatic hypotension in high-risk patients with DM and CAD (especially those with recent acute coronary syndrome).^{2,3,13,14,17}

The reason for the adverse effects of excessive lowering of BP in patients with pre-existing CAD (especially in presence of structural heart disease such as left ventricular hypertrophy or left ventricular dysfunction) could be secondary to decrease in the coronary perfusion pressures across the diseased segments of the coronary arteries, because of impairment of coronary autoregulation when BP decreases.¹⁸

In contrast, the data from several RCTs and the meta-analyses do demonstrate benefit of intensive BP control to SBP <130 mm Hg in reducing the risk of stroke in diabetic patients with hypertension.^{2,13–17} The observed stroke reduction with lower BP levels is consistent with data from observational studies that showed a linear relationship between increasing SBP levels and risk of stroke, and the decrease in stroke risk with lowering of SBP to levels <120 mm Hg.^{1,2,13–17} Furthermore, the data from the PROGRESS (Perindopril Protection Against Recurrent Stroke) study showed that in survivors of prior stroke, there was a progressive reduction in the recurrence of ischemic as well as hemorrhagic strokes as the on-treatment SBP went down to <115 mm Hg.¹⁹ In that study, there was no evidence for J-curve phenomenon in survivors of stroke and the benefit of lowering SBP on recurrence of stroke was evident even in those who started with baseline median SBP of 114 mm Hg.¹⁹ These data could be explained by 2 reasonings: first being the direct and close relationship of stroke with SBP, and second related to the fact that there is an excellent autoregulation of the cerebral blood flow, which allows the continued perfusion of the brain even at low BP values.²⁰

Clinical Implications and Future Direction

Despite the recommendations of the 2017 ACC/AHA BP guidelines looking at the totality of evidence including the

present paper by White et al, it is hard to recommend an across-the-board BP goal of <130/80 mm Hg for all patients with DM and hypertension.^{1–5} It seems evident that there is heterogeneity of the effects of intensive BP-lowering on coronary versus cerebral events, and the effects can also vary based on the presence or absence of comorbid conditions in a given individual (such as those with recent acute coronary syndrome as described in the present study by White et al.^{1–3,7–9} The available evidence from RCTs suggest that in patients with preexisting cardiovascular disease, specifically coronary heart disease, it is prudent not to lower SBP \leq 130 mm Hg; however, for those at higher risk of stroke (such as black and Asian patients) who do not have preexisting coronary heart disease, it may be beneficial to reduce SBP <120 mm Hg if this can be done without any harm. Overall, it seems reasonable that a BP target of <140/90 mm Hg as recommended in several recent guidelines will be safe and effective in reducing the risk of coronary events in patients with DM and hypertension.^{1–3,5,6,10} Lower BP targets might be appropriate in those at higher risk of stroke and other microvascular complications such as chronic kidney disease. As suggested by White et al and in view of the ongoing controversy regarding optimal BP level in high-risk patients with DM and CAD, prospective RCTs are needed to examine and demonstrate appropriate target BP that can be safely attained and beneficial.

Disclosures

None.

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