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DIABETES AND CARDIOVASCULAR DISEASE (ND WONG, SECTION EDITOR)

Evidence for and Against ACC/AHA 2017 Guideline for Target Systolic Blood Pressure of < 130 mmHg in Persons with Type 2 Diabetes

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Abstract

Purpose of Review We summarize the evidence for and against a target systolic blood pressure (SBP) < 130 mmHg in individuals with type 2 diabetes mellitus (T2DM).

Recent Findings The primary ACCORD trial pooled data from patients with more- and less-intense glycemic control and found no benefit to lowering SBP < 140 mmHg, findings consistent with multiple meta-analyses. However, a re-analysis of the ACCORD trial found that participants randomized to less-intense glycemic control (HbA1c 7.0–7.9%) benefited from targeting SBP < 120 vs. 140 mmHg. The SPRINT trial also found benefit for targeting SBP < 120 vs. 140 mmHg in participants at risk for cardiovascular events but excluded persons with T2DM.

Summary There is no consensus as to the optimal SBP target for patients with T2DM, though data suggest a benefit to targeting SBP < 130 mmHg in patients with less-intensive glucose control. Further research is also needed on BP control in the setting of newer anti-diabetic agents.

Keywords Diabetes · Clinical guidelines · Blood pressure

Introduction

Hypertension is the most commonly diagnosed chronic disease in the USA [1]. It is also a key non-communicable disease target for improving health outcomes globally [2]. Another common non-communicable disease that is similarly a major target for improving health outcomes is type 2 diabetes mellitus (T2DM) [1, 2]. Like hypertension, T2DM is highly prevalent and leads to premature morbidity and mortality while exacting high health care costs [3]. Many patients with T2DM have co-existing hypertension [2], and the combination of both conditions appears to be more deleterious than either alone [2]. Because of the high prevalence of hypertension in persons with T2DM and their link to developing premature cardiovascular (CV) and other related diseases, blood pressure (BP) control in persons with T2DM is a major clinical and public health issue [2, 4]. However, treatment goals for people with hypertension and T2DM have changed often over the last 30 years.

Recent randomized trials have prompted new recommendations by the American College of Cardiology/American Heart Association (ACC/AHA) that include a target systolic blood pressure (SBP) level of < 130 mmHg for patients with T2DM and hypertension [5••]. This represents a significant departure from the 2014 recommendations by the panel members appointed to the Eighth Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure which promoted a target SBP level < 140 mmHg for patients with T2DM [6]. These new ACC/

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AHA guidelines were driven in large part by the findings from the Systolic Blood Pressure Intervention Trial (SPRINT), which enrolled 9361 participants and found a 25% lower hazard ratio (HR) for the primary composite outcome of CV events and death, as well as a 27% lower HR for all-cause mortality in patients assigned to the lower target SBP of < 120 mmHg vs. those assigned to < 140 mmHg [7]. Although the low SBP target in this major study was < 120 mmHg, major concerns exist for extending this finding to general clinical recommendations. These include increased rates of adverse events noted at this lower BP goal [7], the use of unattended BP measurements possibly underestimating BP levels in clinical settings [8], and data from observational studies and meta-analyses suggesting increased rates of CV events and death when SBP levels fall below 120 mmHg [9, 10•]. Because the specific inclusion and exclusion criteria of a randomized controlled trial may limit extrapolation to a more general population with hypertension, and many of the key studies conducted BP measurements that were more consistent with the methods used in clinical practice, the ACC/AHA arrived at a recommended target SBP of < 130 mmHg, which is higher than the most effective target BP in SPRINT of < 120 mmHg [5••]. Importantly, for extending BP recommendations derived from SPRINT findings to persons with T2DM, it is important to underscore that SPRINT did not include diabetic patients. Indeed, when the over 4700 study participants with T2DM were randomized to intensive BP therapy (target SBP < 120 mmHg) or standard BP therapy (target SBP < 140 mmHg) in the Action to Control Cardiovascular Risk in Diabetes blood pressure trial (ACCORD), contrary to the SPRINT findings, there was no demonstrated difference found between BP groups in the primary composite outcome of CV events and mortality [11], leading many to suggest a target SBP < 140 mmHg for persons with T2DM and hypertension. These and other conflicting study results have led to an ongoing controversy among medical societies and clinical guideline committees regarding the optimal BP target in patients with T2DM and hypertension. In the clinical setting, many providers remain uncertain as to whether they should follow the guidelines recommending a SBP of ≥ 130 mmHg or those recommending a target of ≥ 140 mmHg.

Data from the 2010 National Health and Nutrition Examination Survey estimates that 72% of adult patients with diagnosed T2DM achieved BP < 140/90 mmHg, but only 51% actually achieved BP control to a level < 130/80 mmHg [12, 13]. Any proposed difference in targets would clearly affect treatment for a significant portion of the US population with T2DM. We review the data both in support for and against a target SBP of < 130 mmHg in persons with T2DM and review the contextual nuances of the different trial settings to provide the reader greater insight into this ongoing debate.

The Case for a Systolic Blood Pressure Target < 130 mmHg in Persons with T2DM

More-intensive BP-lowering treatment (target SBP < 120 vs. < 140 mmHg with achieved SBP 121 vs. 136 mmHg) in the SPRINT Trial was associated with a 25% reduction in major CV events (myocardial infarction, other acute coronary syndromes, stroke, heart failure, or death from CV causes) and a 27% reduction in all-cause death (but not from stroke or myocardial infarction alone) [7]. SPRINT did not include persons with T2DM but found intensive BP lowering was also more beneficial than the standard BP target in other traditionally high-risk patient groups such as those with chronic kidney disease [7].

Conversely, the primary results for ACCORD, a study which was limited to persons with T2DM, did not find a benefit from intensive BP control (target SBP < 120 mmHg vs. < 140 mmHg), with the exception of a reduction in the risk of stroke (HR, 0.59; 95% CI, 0.39–0.89) [11]. However, in a post hoc analysis of ACCORD data, Beddhu et al. stratified participants by both their BP goals (SBP < 120 mmHg vs. SBP < 140 mmHg) as well as their glycemic goals (intense control to HbA1c < 6.0% vs. less-intense control to HbA1c 7.0–7.9%). Participants in this analysis randomized to both the lower SBP goal and less-intensive glycemic control were found to have a significantly reduced hazard of the primary composite outcome, similar in magnitude to the SPRINT findings for those in the lower SBP arm (< 120 mmHg) [14••]. By contrast, in those participants assigned to the more-intensive glycemic arm, the risk of the primary composite outcome (CV events and mortality) did not differ depending on the BP target (< 120 vs. < 140 mmHg; HR, 1.04; 95% CI, 0.83–1.29) [14••]. This indicated that a more-stringent BP goal had no further effect on reducing CV outcomes when the HbA1c was targeted below 6.0%.

Along these lines, a re-analysis of ACCORD participants restricted to those in the less-intensive glycemic arm who would have met eligibility criteria for SPRINT (other than the exclusion for DM) also found a beneficial association between strict SBP control and CV outcomes (HR, 0.79; 95% CI, 0.65–0.96) [15]. These secondary analyses suggest that the effects of intensive SBP control on CV disease events were similar in patients without T2DM and in those with T2DM who are assigned to receive less-intensive glycemic therapy. The primary ACCORD analyses did not reflect this effect, likely because the study design required pooling the results of both the intensive and the standard glycemic control arms [14••].

In addition to concerns about the exclusion of patients with T2DM from the SPRINT trial, critics have also noted that SPRINT used unattended automatic BP measurements for many participants, a method not used in other randomized controlled BP trials [8]. It has been suggested that this method

may underestimate BP values in standard trial protocols and may even underestimate conventional office SBP readings by as much as 16 mmHg [8]. However, an analysis of SBP values in SPRINT participants stratified by those participants who were either alone during the entire BP measurement process ($n = 4082$), never alone ($n = 2247$), alone for pre-measurement resting ($n = 1746$), and alone only for BP measurement ($n = 570$), found no difference between groups. This provides some assurance that BP values in SPRINT were similar whether BP measurements were attended or unattended, and therefore the BP findings are comparable to other randomized controlled BP trials [16]. An additional concern has also been raised regarding the perceived additional medications which would be needed to achieve the lower SBP target in SPRINT. However, an important frequently overlooked aspect of SPRINT is that even the lower SBP goal was actually attained with fewer medications (2.8 for achieved SBP of 121 mmHg) than were used in many other hypertension trials with a higher BP target (< 140/90 mmHg) and an achieved SBP of 130–140 mmHg (~ 3 medications) [17]. This suggests that additional non-pharmacologic factors such as behavioral changes to re-inforce medication adherence and lifestyle changes, as well as pharmacologic measures such as the use of the less commonly prescribed diuretic chlorthalidone contributed to achieving the lower BP target with avoidance of excessive medications use among SPRINT participants.

The case for a SBP target < 130 mmHg in persons with T2DM is further underscored in a secondary analysis of nearly 11,000 persons with T2DM at moderate-to-high risk for CV disease in the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial which found that the fixed-dose combination of perindopril-indapamide (vs. placebo) reduced mortality and major vascular (macro- or microvascular) events even when administered to T2DM patients whose baseline BP were already < 120/70 mmHg [18]. This supports the recommendation that adults with T2DM can benefit from more-intensive BP lowering and a target SBP < 130 mmHg levels [18].

Long-term follow-up of UK Prospective Diabetes Study Group participants randomized to tight BP control (< 150/85 mmHg) or less-tight BP control (< 180/105 mmHg) found those in the tight BP control arm (achieved BP = 144/82 mmHg) compared with less-tight BP control (achieved BP = 154/87 mmHg) had a 24% reduction in risk of developing any micro- or macrovascular complications related to T2DM ($p = 0.0046$). Although the achieved mean SBP in the tight control group did not reach levels below 130 mmHg, the diastolic BP approached 80 mmHg [19], which is the usual diastolic level targeted concurrently with a SBP target < 130 mmHg (BP goal < 130/80 mmHg). These findings suggest this more-aggressive diastolic BP lowering has positive effects on reducing adverse CV events in persons with T2DM. Finally, a meta-analysis by Ettehad et al. identified 123 studies with 613,815 participants and found BP lowering < 130 mmHg significantly reduced the risk of major CV disease events and mortality [20].

Varying interpretations of the available evidence have led to multiple guidelines from several organizations recommending a target SBP below 130 mmHg. Among these, the ACC/AHA retains the position that the target BP for patients with T2DM should be < 130/80 mmHg. Similarly, Canada's 2018 Guidelines for Diagnosis, Risk Assessment, Prevention, and Treatment of Hypertension recommend that persons with T2DM to be treated to a BP target of < 130/80 mmHg [21]. Along these same lines, the 2018 European Society of Cardiology/European Society of Hypertension (ESC/ESH) guidelines while advocating for a BP treatment goal of < 140/90 mmHg in persons with T2DM, does provide clinicians the option to target values to or below 130/80 mmHg if such treatment is well tolerated [22, 23].

The Case Against a Systolic Blood Pressure Target < 130 mmHg in Persons with T2DM

The evidence for benefit of a SBP target < 130 mmHg is derived mainly from studies which excluded participants with T2DM (SPRINT) or from secondary analyses of other studies which did include participants with T2DM. This limited evidence has led some organizations to recommend higher SBP targets for patient with T2DM. Thus, in contrast to the ACC/AHA 2017 guideline and other similar guidelines that support a SBP target < 130 mmHg in T2DM, the Academy of Family Physicians [24] recommends a somewhat higher target BP of < 140/90 mmHg in all persons with T2DM. The 2019 American Diabetes Association's Standards of Medical Care in Diabetes recommends treatment to a target BP < 140/90 mmHg for individuals with T2DM and hypertension and a low CV disease risk (10-year atherosclerotic CV disease risk < 15%) [4]. The American Diabetes Association also recommends a lower BP target of < 130 mmHg, only if the 10-year CV disease risk is >15%, provided it can be safely attained [4]. Similarly, the Australian National Heart Foundation 2016 guidelines suggest a primary target SBP of < 140 mmHg, and to only consider a secondary SBP target < 120 mmHg in selected high-risk populations (with > 15% 5-year CV disease risk) [25]. Finally, after their review of the existing evidence, the National Institute for Health and Clinical Excellence (NICE) in their 2019 draft report also recommended a BP target of < 140/90 mmHg for adults with T2DM (under 80 years old), in contrast to their earlier 2011 report which similarly recommended a BP target of < 140/90 mmHg but with an even lower BP target (< 130/80 mmHg) for those adults with T2DM presenting with end organ damage [26, 27].

These guidelines advocating a target BP of < 140/90 mmHg in adults with T2DM are largely based on the primary findings of the ACCORD trial. This study, with a mean follow-up of 4.7 years, found no difference among the 4733 participants in the primary composite outcome of non-fatal myocardial infarction, non-fatal stroke, or death from CV causes whether the target BP was < 140/90 mmHg or whether it was < 120/80 mmHg [11]. In addition to ACCORD, further evidence supporting a SBP target < 140 mmHg comes from a secondary analysis by Bohm et al. of over 30,000 enrollees in the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) and Telmisartan Randomized Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease (TRANSCEND) studies (11,487 participants with T2DM), which revealed that compared with an achieved in-trial SBP of 120 to < 140 mmHg, either a higher SBP of ≥ 160 mmHg or a lower SBP < 120 mmHg was associated with a significantly increased composite outcome of CV death, myocardial infarction, stroke and hospitalization for congestive heart failure, as well as all-cause death [28]. Thus, the findings support an intermediate SBP < 140 mmHg (range 120–140 mmHg) to be optimal [28].

Several meta-analyses have drawn similar conclusions. A systematic review and meta-analysis of over 100,000 study participants by Emdin et al. reported that for a baseline SBP ≥ 140 mmHg, each 10-mmHg lower SBP was associated with a significantly lower relative risk of mortality (13%), CV events (11%), coronary heart disease (12%), stroke (27%), albuminuria (17%), and retinopathy (13%) [29]. By contrast, when the baseline SBP was < 140 mmHg, additional SBP lowering was not associated with a lower risk of CV disease or coronary heart disease events although there was an observed lower risk of stroke, retinopathy, and progression of albuminuria [29]. Further, Brunström and Carlberg analyzed 49 trials that included 73,738 participants, most with T2DM, and found that anti-hypertensive treatment in those participants with a baseline SBP of 140–150 mmHg led to a 13% reduction in the risk of all-cause mortality, 16% reduction in myocardial infarction, and 20% reduction in heart failure. However, in participants who started with a baseline SBP < 140 mmHg, further anti-hypertensive treatment resulted in an unexpected 15% increase in CV mortality risk and 12% increase in risk of myocardial infarction, suggesting that a lower SBP target of < 130 mmHg may be associated with worse outcomes [10•]. Two additional meta-analyses found that the overall benefit of lowering BP in patients with T2DM dissipated as BP fell below 130/80 mmHg [29–31], except for a continuing incremental benefit on stroke.

Finally, further data advocating caution regarding intensive lowering of SBP comes from secondary analyses of study participants with T2DM (ACCORD, $n = 4311$) or without T2DM (SPRINT, $n = 6715$), which found that a SBP target of < 120 mmHg led to a greater incidence of newly diagnosed chronic kidney disease [32]. Based on this evidence, many experts recommending a higher SBP target in T2DM may point to the fact that virtually the only consistently demonstrated benefit of lowering SBP < 130 mmHg is a lower risk of stroke, which is outweighed by evidence suggesting an increased risk of incident chronic kidney disease and the potential of worsened CV outcomes with proposed lower systolic BP targets.

Conclusion and Areas of Uncertainty

There remains ongoing controversy regarding the optimal BP goal in patients with T2DM and hypertension. It is still unclear whether the ideal BP goal for patients with T2DM should be a SBP < 130 or < 140 mmHg (Table 1). Primary analysis of the ACCORD trial found no benefit in composite CV outcomes and mortality with a BP target < 120 mmHg compared with < 140 mmHg [11]. However, secondary analyses of ACCORD data suggest that the optimal BP target in T2DM varies by the state of glycemic control, with better outcomes in the intensive BP arm only seen among those randomized to less intensively controlled blood glucose (HbA1c target 7.0–7.9%), but not among those with much lower HbA1c targets (< 6.0%). Moreover, intense glucose lowering was found in the ACCORD, ADVANCE, and Veterans Affairs Diabetes Trial to not significantly reduce major CV events [35] and was actually associated with an increased risk of mortality in ACCORD [35, 36]. These data suggest that in instances when a less-stringent HbA1c goal is targeted for patients with T2DM (e.g., advanced age, multiple comorbidities, hypoglycemic unawareness), a lower BP goal may be appropriate [37]. The ACC/AHA advocates a target BP of < 130/80 mmHg for adults with T2DM since the majority this population has a 10-year risk for atherosclerotic CV disease that is equal to or exceeds 10%, and are therefore categorized as high-risk for CV events [5••].

Most of the aforementioned trials utilized more traditional diabetes medications such as insulin, metformin, sulfonylurea, and/or thiazolidinediones [14••]. It is currently uncertain whether newer diabetic medications such as the glucagon-like peptide-1 (GLP1) receptor agonists and the sodium-glucose co-transporter 2 (SGLT2) inhibitors, which have cardioprotective and renoprotective effects [38–40] may be associated with different outcomes based on the degree of BP control. Two of the major trials that have provided insight into the potential CV impact of these newer glycemic agents are the Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes (EMPA-REG) and The Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER). EMPA-REG assigned participants to receive SGLT2 inhibitors or placebo

Table 1 National clinical guideline comparisons of blood pressure targets in adults with type 2 diabetes mellitus and hypertension

Guideline group	Target BP (mmHg)	Qualifications for BP (mmHg) targets
Ok to leave panel members appointed to the - technically that is how it was released Eighth Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (2014) [6]	< 140/90	
American Diabetes Association 2015 Standards of Medical Care [33]	< 140/90	
National Institute for Health and Clinical Excellence (2011) [34]	< 140/90	<130/80 for adults with T2DM and end organ damage
National Institute for Health and Clinical Excellence Draft (2019) [27]	< 140/90	exclusive of persons over 80 years old
American Academy of Family Physicians (2014) [24]	< 140/90	
American Diabetes Association Standards of Medical Care (2019) [4]	< 140/90	< 140/90 If low CV disease risk (10-year risk < 15%) < 130/80 if CV disease risk > 15% and BP target can be safely attained
European Society of Cardiology and the European Society of Hypertension (2018) [22]	< 140/90	< 130/80 if treatment is well tolerated
Australian National Heart Foundation (2016) [25]	< 140	< 120 in selected high-risk populations (> 15% 5-year CV disease risk)
Hypertension Canada (2018) [21]	< 130/80	
American College of Cardiology/American Heart Association (2017) [5••]	< 130/80	

BP, blood pressure; *CV*, cardiovascular

and found SGLT2 inhibitors led to a better primary outcome (death from CV causes, non-fatal myocardial infarction, or non-fatal stroke) [38]. Among the study participants receiving SGLT2 inhibitors, those who achieved better glycemic control (< 8.5 vs. ≥ 8.5%, *p* value for interaction 0.01) had better primary outcomes, in contrast to primary outcomes by BP, which did not differ (SBP ≥ 140 mmHg (HR, 0.83; CI, 0.66–1.03) vs. SBP < 140 mmHg (HR, 0.89; CI, 0.73–1.08), *p* value for interaction 0.65) [38]. The LEADER trial found that outcomes by level of glycemic control did not differ and outcome differences by BP control were not reported [39]. The existing evidence informing national clinical guidelines for BP control in patients with T2DM was obtained prior to the introduction of these newer glycemic agents. While these newer medications may have established cardio- and renoprotective benefits, how their use will impact future proposed SBP targets in persons with T2DM and hypertension remains to be elucidated.

While there are ethnic differences in the prevalence of DM with racial/ethnic minorities having rates nearly double that of their White peers [41], at present, there are no recommended differences in goal BP targets [5••]. The ACC/AHA 2017 guidelines suggests African American adults with hypertension but without heart failure or CKD, including those with DM, should begin initial anti-hypertensive treatment with a thiazide-type diuretic or calcium channel blocker [5••]. They also note that two or more anti-hypertensive medications are often needed to achieve a BP target of < 130/80 mmHg, especially in African American adults, with hypertension [5••].

One final point to consider is the implication of ambulatory BP and whether targets using office BP measures should be even lower to account for the high prevalence of masked hypertension (discordant in-office normal BP vs. out-of-office hypertension), which has been reported to occur in anywhere from 10 to 40% of patients [42]. In a subsample of 508 participants of the third follow-up cohort of the Australian Diabetes, Obesity, and Lifestyle Study 3, masked hypertension was found in 21% [43], while Zhao et al. [44] reported a prevalence of masked hypertension was approximately 26.5% in a cohort of 266 adults with DM. Masked hypertension is also important to consider as it was recently reported to have a nearly threefold higher risk of all-cause and CV mortality than sustained hypertension [45]. In this study, DM-related mortality was similar to other subgroups. Thus, the prevalence or severity of masked hypertension in persons with DM does not appear to be greater than the general population, suggesting the search for and treatment of masked hypertension in persons with DM should not differ from the general population, but this is yet another reason to consider the lower BP target of < 130/80 mmHg in persons with DM.

What Is Already Known on This Topic Hypertension and T2DM are two of the most common and important worldwide risk factors for premature CV disease and death.

Persons with T2DM commonly have co-existing hypertension.

The optimal BP goal for persons with T2DM remains controversial.

What This Report Adds In people with T2DM and a SBP ≥ 140 mmHg, the data is unequivocal that anti-hypertensive treatment targeting a goal BP < 140 mmHg is associated with

a reduced risk of mortality and CV events. Whether the target SBP should be further lowered to < 130 mmHg is contentious and varies with interpretation of the available data. Most randomized trials support no difference in CV or mortality risk with a more-intensive approach to lowering BP in persons with T2DM, with the exception of those with HbA1C target levels of 7.0–7.9 who may benefit from a lower SBP goal. While some data may be interpreted to suggest a potential extrapolated benefit of a SBP target of < 130 mmHg, this recommendation may need to be balanced with the concurrent costs and potential adverse effects of additional medication. Newer DM agents such as SGLT2 inhibitors and GLP1 receptor agonists have been demonstrated to have cardio-protective effects. What their impact may be on SBP targets in persons with T2DM and hypertension remains to be elucidated.

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Compliance with Ethical Standards

Conflict of Interest Jenny I. Shen, Susanne B. Nicholas, Sandra Williams, and Keith C. Norris declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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