Diabetes and Hypertension: Clinical Update

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The presence of hypertension in individuals with type 2 diabetes augments the risk for cardiovascular morbidity and mortality. In this regard, data support that management of hypertension in this high-risk population is a critical risk reduction strategy. In recent years, a number of work groups have redefined hypertension, management strategies, and targets. In this context, there is still considerable discussion on an appropriate target for blood pressure in the diabetic population. However, despite this discussion on target blood pressure, it is widely recognized that there is considerable residual risk for heightened cardiovascular events in the hypertensive, diabetic population despite widespread awareness and treatment. There has been increasing interest in management strategies for blood pressure reduction in this high-risk population that complement traditional antihypertensive agents. Large-scale clinical trials have shown that hypoglycemic agents can complement blood pressure reduction and have a favorable effect on cardiovascular outcomes such as the sodium-glucose cotransporter 2 inhibitors and glucagon-like peptide-1 receptor agonists. In the diabetic population, consideration should be given to the blood pressure lowering effects of the newer hypoglycemic agents when working toward additional glycemic control in patients with hypertension.

Keywords: blood pressure; diabetes; hypertension; cardiovascular outcome trials.

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Our understanding of the prevalence, incidence, and management of hypertension (HTN) in diabetic individuals is evolving in recent years. A number of work groups have redefined HTN and goals for management in the general population that have implications for those with diabetes. Recent work suggests the prevalence of HTN in the United States using a definition of 140/90 mm Hg is approximately 29% in adults greater than 18 years of age, increases with age and has been stable over the past decade.1 However, work released by the American Heart Association/American College of Cardiology for guidance on high blood pressure (BP) suggests the prevalence is as high as 46% in the general population using a new definition of HTN at 130/80 mm Hg.2 The impact of this new guidance on the diabetic population is not yet known; however, previous work supports that in those with diabetes mellitus (DM) approximately 74% have HTN, 62% are obese, and 41% are physically inactive.3 In this context, both DM and HTN are significant risk factors for atherosclerotic cardiovascular (CV) disease (ASCVD) compounded by the presence of other metabolic risk factors. Furthermore, a clinical estimation of 10-year risk for ASCVD can be calculated using DM status in conjunction with age, sex, total cholesterol, high-density lipoprotein cholesterol, systolic BP, BP-lowering medication use, and smoking status. This objective risk assessment can be a helpful clinical tool for risk factor modification and treatment.4 Recent guidelines on lipids and HTN have taken ASCVD risk into consideration for treatment decisions.2,5 Individuals with both HTN and DM are at a 4-fold higher risk of cardiovascular disease (CVD) when compared to age-matched normotensive non-diabetic controls.6 In those with DM, the major cause of morbidity, mortality, and the largest contributor to health care costs is associated CVD.7 As a result, the newest developments in DM and HTN have centered on the debate to determine the BP target for persons with diabetes. Additionally, all new diabetic medications are scrutinized for their effect on CVD outcomes.

DEFINITION OF HTN AND BP TARGETS IN DIabetics

Historically, our definition of HTN has been somewhat arbitrary at 140/90 mm Hg and thought to represent the minimum threshold at which vascular damage begins to occur. In their report, JNC7 first recognized the
heightened awareness for an ASCVD risk beginning at a BP of 120/80 mm Hg that was significantly increased at a threshold of >130/85 mm Hg and identified for the first time “prehypertension”. The importance of JNC7 to the management of HTN in diabetes was identifying special populations such as diabetes and suggesting a lower target for treatment (e.g., 130/80 mm Hg). Subsequent efforts to define a target BP in those with diabetes remains controversial as there are disparate data for a number of different target thresholds. Increasing trial data relative to population-based cohorts have yielded varying results and it is becoming clear that one goal for the entire DM population is not likely to be sufficient. The JNC guidelines have varied in their targeted BP goals in the DM population from 130/80 to 140/90 mm Hg in the last 2 editions; 7 vs. 8. The newest guidance comes from the 2017 High Blood Pressure Clinical Practice Guideline from the American College of Cardiology/American Heart Association Task Force. Importantly, this work group redefined HTN and eliminated prehypertension. In this regard, the new definition includes 2 stages of HTN; Stage 1 is defined as a systolic BP of 130–139 mm Hg or a diastolic BP of 80–89 mm Hg and Stage 2 is defined as a BP greater than or equal to 140/90 mm Hg. Normal BP is defined as less than 120/80 mm Hg; elevated BP is a systolic BP of 120–129 with a diastolic BP of less than 80 mm Hg. The rationale for this change was based on observational and randomized control trials, which have reported a gradient of progressively higher CVD risk as BP increases from normal to elevated to Stage 1 HTN. Each set of guidelines emphasize proper technique and accurate in-office measurement of BP. Each also recognizes that there is growing evidence supporting the use of automated office BP measurement, which inflates automated amplitude algorithms that involve population-based data. It is expected this new definition of HTN will increase incident and prevalent HTN as it is applied to the diabetic population. However, it is important to note that there is a distinction made regarding who should be treated with pharmacologic BP-lowering agents. The guidelines recommend DM population patients with an average BP greater than 130/80 mm Hg be treated pharmacologically, assuming that for convenience the vast majority of diabetics will have an ASCVD risk of greater than 10%.

Alternatively, the American Diabetes Association (ADA) recently recommended a target of <140/90 mm Hg for the majority of patients with DM. This work group does not advocate for the more aggressive target of <130/80 mm Hg, except for in certain high-risk individuals and has been updating those who belong to this category as new evidence is produced. Randomized control trials treating patients with DM have shown reductions in CV events and diabetic kidney disease with lowering of BP to less than 140/90 mm Hg. However, results of a number of meta-analysis and randomized control trials for more aggressive targets are more ambiguous. In this regard, in the Action to Control Cardiovascular Risk in Diabetes-Blood Pressure (ACCORD-BP) trial, there were 4,733 participants with DM2 with previous evidence of CVD or 2 additional risk factors for CVD. They were randomized into an intensive-BP group with a goal of systolic BP < 120 mm Hg or a standard-BP group with a goal of systolic BP < 140 mm Hg. The primary outcome was the first occurrence of a major CVD event, which was the composite of nonfatal myocardial infarction (MI), nonfatal stroke, or CVD death. Investigators achieved the targets in both groups (mean BP of 119.3 and 133.5 mm Hg) but did not see any difference in the primary end point. They did see a small but significant difference in the rate of total and nonfatal strokes. They also observed a significant difference in adverse events between the groups with the intensive-BP group having more instances of elevated creatinine levels and hypokalemia. The Systolic Pressure Interventional (SPRINT) trial had 9,361 participants who were at high risk for CV events but did not have DM. They randomized to an intensive-treatment group and a standard-treatment group with the same goals as in the ACCORD-BP trial. The primary end point was the composite of MI, acute coronary syndrome not resulting in MI, stroke, acute decompensated heart failure, or death from CV causes. The mean BP in the groups was 121.4 mm Hg for the intensive group and 136.2 mm Hg in the standard group. They did find a significant decrease in the primary end point for the intensive group, as well as the rate of heart failure, death from CV causes, and death from any cause as secondary outcomes. Like the ACCORD-BP trial, they did see more adverse events in the intensive group with more hypokalemia, sodium abnormalities, acute kidney injury, hypotension, and syncope. Some have hypothesized that the ACCORD-BP trial was underpowered to detect a significant CV outcome difference with the lower BP target goal. To this point, a recent post hoc analysis of the ACCORD-BP trial extracted the patients that would have met the criteria for inclusion in the SPRINT trial. There were 2,592 patients (54.8%) and patients with a hemoglobin A1c of <6.0% were excluded at this level, which is not recommended as standard of care and was thought to have confounded the results. Thus, 652 patients remained with baseline mean ASCVD scores of greater than 14%. In these patients, there was a significant reduction in the composite of CV death, nonfatal MI, nonfatal stroke, any revascularization, or heart failure in the intensive-BP group compared to the standard-BP group (3.48 vs. 4.22% per year, hazard ratio [HR] = 0.19, 95% confidence interval [CI] = 0.65–0.96). There was also a significant decrease in the ACCORD-BP primary end point in the intensive-BP group compared to the standard-BP group (1.26 vs. 1.79% per year, HR = 0.69, 95% CI = 0.51–0.93). This analysis also suggests that CVD risk factors, other than dysglycemia, may be important to confer CV benefit with lower BP targets both in the DM and in the non-DM populations with HTN. Pooled analysis has been done with individual patient data from ACCORD-BP and SPRINT studies both of which randomized hypertensive patients to a systolic BP target of less than 120 mm Hg or less than 140 mm Hg. There were 14,094 patients and 33.6% had DM. The composite primary end point was to look at unstable angina, MI, acute heart failure, and death due to CV causes. This analysis showed that intensive-BP control reduces CV events in patients with and without diabetes.
a diabetic population increased mortality. They evaluated 3,159 diabetic patients with no history of HTN from a total of 101,510 individuals. Although this is a relatively small sample size, it was uniform and thus did not need adjusting for clinical confounders. Normal BP was defined as BP of 120–139/80–89 mm Hg. They found that compared to patients that remained normotensive, those that had a persistent BP below 120/80 mm Hg and those who had a pattern that decreased from normotensive to a BP of less than 120/80 mm Hg had an increased risk of all-cause mortality. Those who were normotensive and developed a BP > 140/90 mm Hg also had increased risk of CVD. This study suggests that changes in BP over time may be used as an important tool in studying HTN and adverse CVD outcomes, rather than simply relying on baseline and final BP readings alone. These data and the results of ACCORD-BP and SPRINT trials suggest that there may be an ideal range to target somewhere between a systolic BP of 120 and 135 mm Hg, with the exception of diabetics who are at high risk of stroke where a systolic BP of less than 120 mm Hg may be of benefit.17,18

A multicenter, open-label, randomized, parallel-group trial was done at 81 clinical sites in Japan to evaluate the effect of intensified multifactorial intervention on CV outcomes and mortality in type 2 diabetes. In this study, 2,542 type 2 diabetics aged 46–69 with an A1c over 6.9% were randomly assigned to conventional therapy for blood glucose (A1c less than 6.9%), BP (less than 130/80), and lipid control (LDL less than 120 mg/dl or less than 100 mg/dl in patients with a history of coronary artery disease [CAD]) or intensive therapy with A1c less than 6.2%, BP less than 120/75, and LDL cholesterol less than 80 mg/dl (or less than 70 mg/dl in patients with a history of CAD). Occurrence of a MI, stroke, revascularization (coronary artery bypass surgery, percutaneous transluminal coronary angioplasty, percutaneous transluminal cerebral angioplasty, carotid endarterectomy, and carotid artery stenting) and all-cause mortality were considered the primary outcomes. Post hoc analysis showed that there was no significant difference between all-cause mortality and coronary events in the 2 groups. Cerebrovascular events were significantly less in the intensive-treatment group.19

### NEW DIABETES MEDICATIONS, CVD, AND BP

The first data that surfaced regarding negative CVD associations appeared in the 1970s from the University Group Diabetes Program (UGDP). In that study, it was observed that phenformin (biguanide) and tolbutamide (sulfonylurea) were associated with increased CVD mortality. In 2007, 2 meta-analyses were published that showed rosiglitazone (a thiazolidinedione) was associated with an increase in the occurrence of MI. The United States Food and Drug Administration (FDA) then implemented new regulations to ensure that newer anti hyperglycemic agents (AHA) did not increase risk of major adverse cardiac events including CV death, MI, and stroke. In the 1990s, metformin was associated with a CVD benefit and remains the first-line agent in DM2.20 Due to this history and the recent upsurge in new AHAs, there have been a significant number of large-scale clinical trials whose results have been published in the last 3 years and are shown in Table 1.

The newest group of AHAs is the sodium-glucose cotransporter 2 inhibitors (SGLT2-I). The approved medications in this class are empagliflozin, canagliflozin, and dapagliflozin. They improve glucose levels by increasing urinary glucose excretion by selectively decreasing urinary glucose reabsorption in the renal proximal tubule. The first large-scale multicenter trial results were published in September 2015 from the Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes (EMPA-REG OUTCOME) trial. The study included 7,028 patients with DM2 that were at high risk for CV events. High risk included history of MI, evidence of significant CAD, unstable angina, stroke (ischemic or hemorrhagic), or occlusive peripheral artery stenosis occurring greater than 2 months prior to informed consent. The primary outcome was the composite of death from CV causes, nonfatal MI, or nonfatal stroke and occurred in 10.5% of patients in the pooled empagliflozin group compared with 12.1% in the placebo group. The HR in the empagliflozin group was 0.86, 95.02% confidence interval (CI) 0.74–0.99, \( P = 0.04 \) for superiority. There was a significant difference in death from any cause with a relative risk reduction (RRR) of 32% (5.7 vs. 8.3%), RRR of 35% for hospitalization for heart failure (2.7 vs. 4.1%), and RRR of 38% for death from CV causes (3.7 vs. 5.9%) in the empagliflozin group vs. placebo.

### Table 1. Result of large-scale clinical trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Medication</th>
<th>N</th>
<th>Years followed (median)</th>
<th>CV results (primary outcome – HR)</th>
<th>BP change (systolic/diastolic in mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CANVAS</td>
<td>Canagliflozin</td>
<td>9,734</td>
<td>1.5</td>
<td>Superior 0.86</td>
<td>−3.93/−1.39</td>
</tr>
<tr>
<td>EMPA-REG OUTCOME</td>
<td>Empagliflozin</td>
<td>7,028</td>
<td>3.1</td>
<td>Superior 0.86</td>
<td>−4/−1.5</td>
</tr>
<tr>
<td>LEADER</td>
<td>Liraglutide</td>
<td>9,340</td>
<td>3.8</td>
<td>Superior 0.87</td>
<td>−1.2/0</td>
</tr>
<tr>
<td>SUSTAIN6</td>
<td>Semaglutide</td>
<td>3,297</td>
<td>2.1</td>
<td>Superior 0.74</td>
<td>−1.3/0</td>
</tr>
<tr>
<td>EXCSEL</td>
<td>Exanlitide</td>
<td>14,752</td>
<td>3.2</td>
<td>Noninferior</td>
<td>−1.57/+0.25</td>
</tr>
<tr>
<td>ELIXA</td>
<td>Lixisenatide</td>
<td>6,068</td>
<td>2.1</td>
<td>Noninferior</td>
<td>−0.8/0</td>
</tr>
<tr>
<td>SAVOR-TIMI</td>
<td>Saxagliptin</td>
<td>16,492</td>
<td>2.1</td>
<td>Noninferior</td>
<td>N/A</td>
</tr>
<tr>
<td>EXAMINE</td>
<td>Alogliptin</td>
<td>5,380</td>
<td>1.5</td>
<td>Noninferior</td>
<td>N/A</td>
</tr>
<tr>
<td>TECOS</td>
<td>Sitagliptin</td>
<td>14,671</td>
<td>3.0</td>
<td>Noninferior</td>
<td>N/A</td>
</tr>
</tbody>
</table>

HR, hazard ratio; N/A, not applicable.
In this trial, empagliflozin showed an average decrease in systolic BP of 4 mm Hg and decrease in diastolic BP of 1.5 mm Hg compared with placebo by measuring seated-in-office BP measurement. Similar results were found in a cohort of 825 patients with empagliflozin vs. placebo when using 24-hour ambulatory BP monitoring for 12 weeks. This double-blinded placebo-controlled trial showed a significant difference in adjusted mean systolic BP of −3.44 mm Hg (95% CI = −4.78 to −2.09) for 10 mg of empagliflozin (P < 0.001) and −4.16 mm Hg (95% CI = −5.50 to −2.83) for 25 mg of empagliflozin (P < 0.001) when compared to placebo. There was also a significant difference in adjusted mean diastolic BP of −1.36 mm Hg (95% CI = −2.15 to −0.56) for 10 mg of empagliflozin (P < 0.001) and −1.72 mm Hg (95% CI = −2.51 to −0.93) for 25 mg of empagliflozin (P < 0.001) when compared to placebo.

Empagliflozin-treated patients had a significantly lower risk of progression to macroalbuminuria or other renal outcomes such as doubling of serum creatinine and initiation of renal replacement therapy compared to placebo. This study showed when empagliflozin was added to standard care in type 2 diabetics who are at high risk for CV events, it was associated with slower progression of kidney disease and significantly lower risk of clinically relevant renal events.

In June of 2017, the results of the Canagliflozin Cardiovascular Assessment Study (CANVAS) Program and CANVAS-Renal were published. Data were pooled from these 2 trials, which included a total of 9,734 patients of which 65.6% had CVD at baseline. The primary outcome was the same composite as in the EMPA-REG OUTCOMES trial and occurred in 26.9 vs. 31.5 participants with events per 1,000 patient-years (HR = 0.86, 95% CI = 0.75–0.97) comparing the canagliflozin group to placebo with a P < 0.02 for superiority. There was no difference observed for the secondary outcomes such as death from any cause or death from CV causes, but fewer hospitalizations for heart failure were seen in the canagliflozin group. There was also a substantial effect on renal outcomes. Progression of albuminuria occurred less frequently in the canagliflozin group compared to placebo, 89.4 vs. 128.7 participants with an event per 1,000 patient-years (HR = 0.73, 95% CI = 0.67–0.79). Progression of albuminuria, the composite of sustained 40% reduction in estimated glomerular filtration rate, the need for renal-replacement therapy, or death from renal causes occurred less frequently among patients in the canagliflozin group as well. The canagliflozin group saw a mean difference in systolic BP of −3.93 mm Hg (95% CI = −4.30 to −3.56) and a mean difference of diastolic BP of −1.39 mm Hg (95% CI = −1.61 to −1.17) with a P < 0.001. A new concern was raised with this study, as the canagliflozin group saw an increased risk of amputation of the toes, feet, or legs, occurring in 6.3 vs. 2.4 participants per 1,000 patient-years (HR = 1.97, 95% CI = 1.41–2.75). An ongoing clinical trial is being conducted with dapagliflozin and its effect on CVD outcome.

There have been 4 major clinical trials evaluating glucagon-like peptide-1 receptor agonist (GLP-1 RA) effect on CV outcomes in patients with DM2. Two of these major trials have shown CV benefit, and 2 trials have shown non-inferiority. The Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial included 9,340 patients of whom 81.3% had established CVD. The primary outcome was the composite of first occurrence of death from CV causes, nonfatal MI, or nonfatal stroke. The primary outcome occurred in 13% of the liraglutide group compared to 14.9% in the placebo group (HR = 0.87, 95% CI = 0.78–0.97) with a P = 0.01 for superiority. There was also a significant difference in death from CVD causes and death from any cause with fewer deaths occurring in the liraglutide group. There was no significant difference in the frequencies of nonfatal MI or nonfatal stroke. Liraglutide showed a decrease in systolic BP of 1.2 mm Hg (95% CI = −1.9 to −0.5) and no significant change in diastolic BP.

The Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes (SUSTAIN-6) was published in 2016. There were 3,297 patients that underwent randomization to semaglutide or placebo and 83% of patients had established CVD. The primary outcome was the same as in the LEADER trial and occurred in 6.6% of the semaglutide group compared to 8.9% in the placebo group (HR = 0.74, 95% CI = 0.58–0.95) with a P = 0.02 for superiority. There was no significant difference in frequency of nonfatal MI or risk of CV death. However, there were fewer nonfatal strokes in the semaglutide group, 1.6 vs. 2.7% (HR = 0.61, 95% CI = 0.38–0.99) with a P = 0.04. The mean systolic BP was 1.3 mm Hg lower in the 0.5-mg dose group and 2.6 mm Hg lower in the 1.0-mg dose group compared to placebo. There was no significant difference in diastolic BP between groups.

Semaglutide is a once-weekly injection as opposed to liraglutide which is a daily injection. Exenatide is another GLP-1 RA that has a once-weekly preparation. The Exenatide Study of Cardiovascular Event Lowering (EXCEL) Study Group evaluated this medication in 14,752 patients of whom 73.1% of patients had pre-existing CVD. The results were published in September 2017, and the primary outcome studied was the same as LEADER and SUSTAIN-6 trials. There was no significant difference between exenatide and placebo for the primary outcome or any of the secondary outcomes. There was a decrease in systolic BP of 1.57 mm Hg and a slight increase in diastolic BP of 0.25 mm Hg. The first trial of this class was the Evaluation of Lixisenatide in Acute Coronary Syndrome (ELIXA) trial. This trial differed in that the study population consisted of patients with DM2 who had suffered an acute coronary event within 180 days prior to screening. The primary end point, in addition to the above trials, included hospitalization for unstable angina in the composite. There was no significant difference between groups for the primary or secondary outcomes. There was a significant difference between the groups in regard to systolic BP with an average difference across all visits of −0.8 mm Hg (95% CI = 0.13 to −0.3) in the lixisenatide group compared to placebo with a P = 0.001.

Three dipeptidyl peptidase 4 inhibitors (DPP-4 I) have been studied for CV safety, and although the trials varied slightly, they all showed noninferiority for the primary end points and did not include BP data. The investigators in the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus (SAVOR)-Thrombolysis in Myocardial Infarction (TMI) 53 study randomized 16,492 patients with DM with an increased risk for CV events to...
receive saxagliptin or placebo. Patients were deemed to have increased risk if they were at least 40 years old and had a history of a clinical event of the coronary, cerebrovascular, or peripheral vascular system associated with atherosclerosis. Alternatively, men 55 years of age or older or women 60 years of age or older with at least one additional risk factor such as dyslipidemia, HTN, or active smoking were included as high risk. The primary end point was the composite of CV death, nonfatal MI, and nonfatal ischemic stroke, and these occurred in 7.3% of patients in the saxagliptin group vs. 7.2% in the placebo group (HR = 1.00, 95% CI = 0.89–1.12). More patients in the saxagliptin group (3.5%) were hospitalized for heart failure than the placebo group (2.8%) with a \( P = 0.007 \) (HR = 1.27, 95% CI = 1.07–1.51) and no difference in the rates of pancreatitis.

In the Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care (EXAMINE) study investigators evaluated patients with DM2 with a history of MI or unstable angina requiring hospitalization within the previous 15–90 days. This study included 5,380 patients who underwent randomization to receive alogliptin or placebo, and the primary end point was the same as the SAVOR-TIMI 53 trial. The primary end point occurred in 11.3% of patients in the alogliptin group vs. 11.8% in the placebo group (HR = 0.96, upper boundary of one-sided repeated CI of 1.16). There were no differences in adverse events or other outcomes between the 2 groups.

The most recently published trial in the DPP-4 I class is the Trial Evaluating Cardiovascular Outcomes with Sitagliptin
(TECOS). This trial included 14,671 patients with DM2 with a history of major CAD, ischemic cerebrovascular disease, or atherosclerotic peripheral arterial disease randomized to receive sitagliptin or placebo. The primary outcome composite also included hospitalization for unstable angina in addition to the composite in the TECOS and SAVOR-TIMI 53 trials. The primary end point occurred in 11.4% per 100 person-years in the sitagliptin group and 11.6% per 100 person-years in the placebo group. There was no difference between groups for any of the CVD events and no difference in hospitalizations for heart failure. Although BP change was not investigated during these CVD outcome trials, systemic review and meta-analysis have indicated that DPP-4 I decreases BP. Data from 15 trials including 5,636 participants showed that DPP-4 I were associated with a mean difference in systolic BP of −3.04 mm Hg (95% CI = −4.37 to −1.72) with a P < 0.00001 and −1.47 mm Hg (95% CI = −1.79 to −1.15) with a P < 0.00001 for diastolic BP compared to placebo or no treatment.31

**APPROACH TO BP TREATMENT IN PATIENTS WITH DIABETES**

Lifestyle management remains an important aspect of BP treatment regardless of the use of pharmacologic therapy. The ADA recommends lifestyle management for patients with DM if they have a BP of greater than 120/80 mm Hg. Lifestyle management includes moderate physical activity, dietary/lifestyle changes, and weight loss. These changes include moderation of alcohol intake and increased potassium and fruit/vegetable intake.15 In patients without ischemic heart disease or heart failure, the algorithm in Figure 1 is an excellent approach. Renin–angiotensin–aldosterone system (RAAS) blocking agents should remain the first-line agent especially in patients with albuminuria. They have been shown to reduce progression of diabetic kidney disease, reduce CVD events, and target the underlying pathophysiology of inappropriate activation of RAAS that is present in diabetes with concomitant obesity and HTN. The RAAS blocking agents, angiotensin-converting enzyme inhibitors, or angiotensin receptor blockers should not be used together due to increased risk of adverse events. Diuretics, chlorothalidone, and indapamide, in particular, have been shown to reduce CVD events and are important BP-lowering agents in patients with diabetes. Dihydropyridine calcium channel blockers can be appropriately added to RAAS blockade therapy. Beta blockers should be used selectively to treat HTN in diabetic patients. They are useful in patients with ischemic heart disease or heart failure but can mask hypoglycemia symptoms, impair insulin sensitivity, and cause lipid derangements and weight gain. Mineralocorticoid receptor antagonists should be added in diabetic patients with resistant HTN as they reduce sympathetic nerve activity, reduce albuminuria, and have additional CVD benefits. Referral to a HTN specialist should be considered in patients that have complex issues with HTN and related complications.33,34

**CONCLUSION**

DM and HTN are associated with an increased risk of ASCVD and attendant morbidity and mortality. Although we do not have consensus on a treatment BP goal in diabetic patients, there has been an increased effort to research the topic in the last few years. We have learned that there is an increased signal for CVD events with BP greater than 140/90 mm Hg and there appears to be an increase in adverse events if systolic BP is less than 120 mm Hg. Diabetic patients with increased CVD risk, in particular patients with high risk of stroke, would likely benefit from a more aggressive target. The studies discussed above suggest a target range rather than a specific single number for BP in diabetic individuals and an individualized approach should be implemented in this population. There have been some additions to our armamentarium for treating DM in recent years. Large-scale clinical trials have shown that members of the SGLT2-Is and GLP-1 RA have a favorable effect on CVD outcomes. In the DM population, consideration should be given to the BP-lowering effects of the newer AHAs when adding additional therapy of glycemic control in patients with HTN.

**DISCLOSURES**

The authors declare no conflict of interest.

**REFERENCES**


