

Hypertension Management in Diabetic Kidney Disease

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IN BRIEF Hypertension is prevalent in most individuals with diabetic kidney disease (DKD). Failure to treat hypertension appropriately in this subgroup of patients results in an increased risk of cardiovascular morbidity and mortality, as well as a faster progression of kidney disease. The current guidance for appropriate treatment of hypertension in this high-risk population provides an opportunity to improve both kidney and cardiovascular outcomes. This review discusses the current state of evidence-based hypertension management in patients with DKD.

The global diabetes epidemic is growing and is largely attributable to the rising incidence of obesity. Moreover, the rising incidence of obesity is driving the higher prevalence of hypertension and kidney disease that contributes to a growing risk of cardiovascular morbidity and mortality among those with diabetes. Although incident rates for end-stage renal disease (ESRD) may have stabilized over the past few years (1,2), prevalence rates for cardiovascular mortality attributable to diabetic kidney disease (DKD) have not (2). In this regard, management of hypertension in this high-risk population contributes significantly to the reduction of the cardiovascular disease (CVD) burden in DKD (3,4).

Hypertension is highly prevalent in individuals with DKD and occurs twice as often as in the general population (3). Notably, the prevalence of hypertension increases from ~36% in CKD stage 1 to ~84% in more advanced CKD stages 4 and 5 (5). There is a strong, continuous relationship between reductions in glomerular filtration rate (GFR) and subsequent cardiovascular event rates after events such as an acute myocar-

dial infarction (MI) (6). It is not only the mortality that is of concern, but also the morbidity and high overall costs of care related to DKD. This is in large part the result of the strong association of DKD with CVD outcomes such as heart failure, stroke, MI, and ESRD (7).

Pathophysiology of Hypertension in DKD

In patients with type 1 diabetes, albuminuria or overt nephropathy generally precedes the appearance of hypertension (8). However, in type 2 diabetes, hypertension in most cases antedates development of albuminuria and reductions in estimated GFR (eGFR) because of shared risk factors, including the presence of obesity, dyslipidemia, and cardiorenal metabolic syndrome.

There are multiple mechanisms in the development of hypertension in patients with DKD, including inappropriate activation of the renin angiotensin aldosterone system (RAAS) and the sympathetic nervous system, volume expansion due to increased sodium reabsorption, peripheral vasoconstriction, upregulation of endothelin 1, inflammation

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and generation of reactive oxygen species, and downregulation of nitric oxide (9). Many of these factors accelerate the development of kidney disease and increase the risk for CVD among people with diabetes and hypertension (8). Thus, they serve as targets for risk reduction by managing hypertension.

Target Blood Pressure for People With DKD

The data are clear that elevations in blood pressure (BP), especially >150 mmHg systolic, are linearly related to increases in kidney disease progression and a higher incidence of cardiovascular events in patients with diabetes. However, the target BP for the management of hypertension is not as clear; few randomized trials have assessed different BP levels in people with diabetic nephropathy, and one failed to demonstrate a benefit of lower BP on cardiovascular risk reduction (10–13).

There is some controversy regarding the 2014 Expert Panel report (JNC-8) (11) for the management of hypertension in those with diabetes, as well as those with kidney disease. The report stated that those with hypertension and diabetes should strive for a BP target of <140/90 mmHg. This recommendation was based on expert opinion, as there were only two trials in patients with diabetes randomizing BP to different levels and evaluating cardiovascular outcomes. This is a shift from previous workgroups that suggested a systolic target of <130 mmHg in this population (10,13).

The 2014 Expert Panel relied on moderate-quality evidence from two trials: the U.K. Prospective Diabetes Study (UKPDS) and the Action to Control Cardiovascular Risk in Diabetes blood pressure trial (ACCORD-BP). In the UKPDS, a systolic BP goal of <150 mmHg improved cardiovascular and cerebrovascular outcomes (14). The ACCORD-BP, which was specifically designed to investigate BP

targets in the range of 120 mmHg systolic, failed to demonstrate any cardiovascular risk reduction compared to a standard 140-mmHg target (15). The 2014 Expert Panel recommended a diastolic BP goal of <90 mmHg in patients with diabetes and hypertension, citing lack of any evidence to support a lower diastolic goal of <80 mmHg (11). Only one trial provides evidence for benefit of a diastolic BP target of 80 mmHg. This benefit is derived from a post hoc analysis of the diabetes subgroup of the Hypertension Optimal Treatment (HOT) trial, in which the subgroup of those with diabetes randomized to 80 mmHg had a reduction in composite CVD outcomes (16). It is notable that, in the HOT trial, there were no patients with DKD.

A recent report from the American Diabetes Association (ADA) consensus conference in DKD (17) pointed out the importance of considering the adverse safety signal in clinical trials when diastolic BP is treated to <70 mmHg, and particularly to <60 mmHg in older populations (18). The ADA consensus panel also noted findings from the Kidney Early Evaluation Program that suggest higher incident rates of ESRD in patients with CKD stage 3 and a diastolic BP of <60 mmHg (19).

The JNC-8 report recommends a target BP of <140/90 mmHg in patients of all ages with CKD, with or without diabetes (11). The Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guideline for management of BP in CKD also recommends a BP target \leq 140/90 mmHg in patients with diabetes and CKD with urine albumin excretion <30 mg/day (12). The KDIGO guidelines further state that adults with diabetes and CKD with urine albumin excretion >30 mg/day may be treated to a BP that is <130/80 mmHg, but the evidence grade is 2C, which is very low (12). Hence, although this BP level can be a goal,

the evidence supporting its benefit on CKD progression is very weak.

Data from cohorts of patients with diabetes that support a lower BP goal come from only one randomized, single-center study and multiple observational studies (12). The randomized trial was the Steno-2 Study, a multiple risk factor intervention trial in type 2 diabetes (20). Steno-2 investigators observed reduced risks of cardiovascular events, and progression to ESRD, retinopathy, and autonomic neuropathy in the intensive treatment arm, in which BP averaged \sim 135/72 mmHg over a 13-year period compared to the conventional treatment arm, which averaged \sim 145/78 mmHg (20).

Because there are no randomized, multicenter, controlled trials available to address appropriate BP targets in patients with DKD, the target BP for patients with diabetes is commonly used as an alternate. In addition, the ADA consensus panel (17) pointed out the relevance of 24-hour ambulatory BP measurement to identify at-risk subgroups of patients with diabetes, such as those with masked hypertension and nocturnal non-dipping status, as possible confounders of the relationship between office-measured BP and DKD progression (21).

Approach to Therapy

The emphasis on treatment of hypertension in patients with DKD should include strategies that address multifactorial risk factor reduction and include pharmacotherapy, lifestyle modification, and patient education to improve self-management of these complex risk factors. Such strategies often require innovative team-based approaches involving primary care providers, endocrinologists, nephrologists, nutritionists, pharmacists, nurse educators, mid-level providers, and mental health professionals.

Integrated health care delivery systems, patient-centered medical homes, and accountable care organizations may provide the organizational struc-

ture to provide such multidisciplinary team-based care. A small study from the United Kingdom suggests that self-management techniques such as understanding, and subsequently adhering to, the prescribed BP medication regimen may contribute to a reduction in BP, which in turn will reduce cardiovascular risk (22).

Risk Factor Reduction and Lifestyle Modification

Strategies should target smoking cessation, diet modification, exercise, and weight loss, with the ultimate aim of reducing both CVD risk and DKD progression. The recent double-blind, placebo-controlled, randomized crossover trial called LowSALT CKD Phase 1 assessed the effect of sodium restriction on ambulatory BP and other cardiovascular risk factors (23). Investigators observed that dietary sodium restriction significantly decreased ambulatory BP by 10/4 mmHg over the 24-hour period (23). In addition, considerable reductions in extracellular volume and albuminuria occurred, and albuminuria reduction occurred independent of BP changes. The level to which sodium intake should be restricted is of considerable debate. A recent Institute of Medicine report (24) indicated insufficient evidence for lowering sodium intake to <2.3 g/day with respect to reducing CVD. The possibility of hyperkalemia secondary to high potassium intake in DASH (Dietary Approaches to Stop Hypertension)-type diets in patients with late-stage CKD is also a consideration in people with diabetes.

Moderation of alcohol intake, weight loss, and increased physical activity as recommended by the current ADA standards of care are all beneficial for management of hypertension in patients with DKD (25).

Pharmacotherapy

This section integrates recommendations from the JNC-7, KDIGO, and 2014 Expert Panel report, as well as the ADA guidelines.

If a patient has end-organ injury such as left ventricular hypertrophy and albuminuria, then lifestyle modification and antihypertensive pharmacotherapy should be initiated at the initial visit. In the absence of end-organ injury, a trial of 1–2 months of lifestyle modification alone, especially focusing on sodium intake reduction, should be tried. If goal BP is not reached through nonpharmacological approaches, then pharmacotherapy should be considered. An updated algorithm from the original National Kidney Foundation consensus report is provided in Figure 1.

Interruption of the RAAS

The use of ACE inhibitors or angiotensin II receptor blockers (ARBs) for RAAS inhibition to reduce albuminuria, cardiovascular risk, and the progression of DKD is well supported by a number of clinical trials

(26–28). Hence, the 2014 Expert Panel, ADA, and KDIGO guidelines recommend ACE inhibitors or ARBs at maximally tolerated doses as first-line therapy for the treatment of hypertension in patients with DKD (11–13).

Historically, there have been concerns about the residual risk for progression of DKD and cardiovascular outcomes despite maximally dosed ACE inhibitors or ARBs. In the past decade, a number of investigators have sought to explore whether the combined use of an ACE inhibitor and an ARB may slow CKD progression further than either agent used alone. The trial data clearly demonstrate a lack of benefit and an increased risk of harm, manifested by increased risk for hyperkalemia and acute kidney injury using the combined RAAS approach. The VA NEPHRON-D (Veterans Affairs

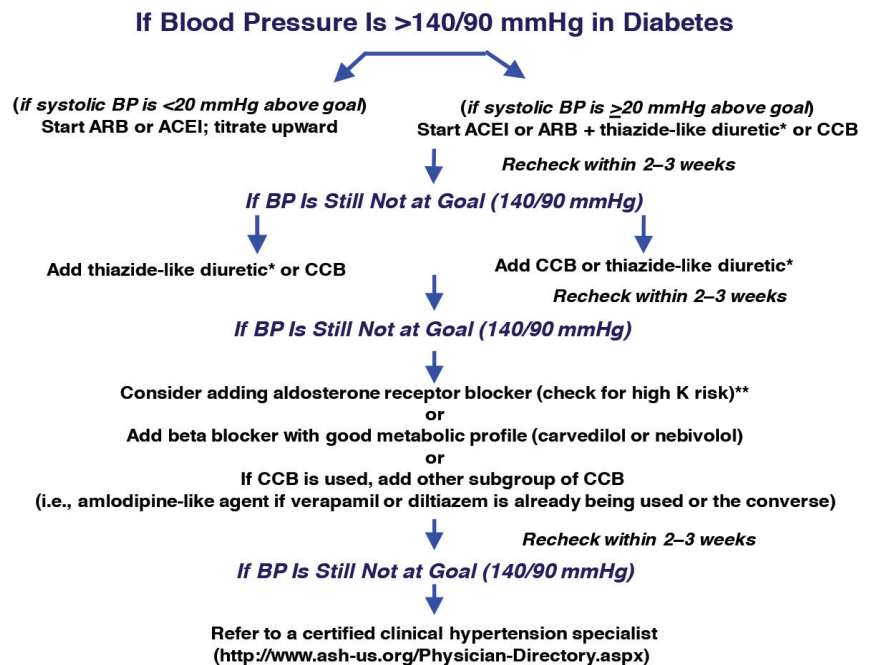


FIGURE 1. An updated general approach for achieving BP goals in people with diabetes. This integrated approach summarizes the National Kidney Foundation consensus report and American Society of Hypertension guidelines (49,50). ACEI, ACE inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; K, potassium. *Diuretics such as chlorthalidone and indapamide. **Risk factors for hyperkalemia; note hyperkalemia is defined as serum potassium >5.5 mEq/L.

Nephropathy in Diabetes) study, which involved ACE inhibitor + ARB therapy in patients with established DKD, found an increased risk of hyperkalemia and acute kidney injury and did not show any benefit on mortality and cardiovascular events (29). The ONTARGET (Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial) was a multicenter double-blind, randomized, controlled trial that found combination therapy to be associated with more adverse events without a further reduction in cardiovascular or renal events (30). Finally, ALTITUDE (Aliskiren Trial in Type 2 Diabetes Using Cardiovascular and Renal Disease Endpoints), in which patients took a direct renin inhibitor + an ACE inhibitor, ended prematurely because of higher renal and cardiovascular event rates in the combination arm (29–31). Therefore, the use of combination RAAS therapy should not be used in people with advanced CKD.

Mineralocorticoid receptor (MR) blockers such as spironolactone or eplerenone offer an additional opportunity for RAAS intervention in the treatment of resistant hypertension by counteracting the “aldosterone breakthrough” that occurs in a subset of patients on RAAS-inhibiting therapy (32–34). Studies also demonstrate consistently greater reductions in BP and albuminuria when MR blockers are added to an ACE inhibitor or ARB. However, the use of this combination comes with the risk of hyperkalemia and, hence, should be done with frequent monitoring. A recent review of clinical trials nicely demonstrated that those at highest risk for hyperkalemia have an eGFR <45 mL/min/1.73 m² and a baseline serum potassium level on appropriate diuretics of >4.5 mEq/L. These individuals are at a three- to eightfold increased risk of developing hyperkalemia if an ACE inhibitor or ARB is started. Moreover, if an RAAS blocker is already being used and a mineralocorticoid inhibitor is added

with the aforementioned eGFR and potassium values, such patients are at a more than sevenfold higher risk of developing hyperkalemia (35,36).

The ADA consensus conference work group highlighted the remaining gap in our understanding of combination RAAS strategies and the incorporation of MR blockade (17). There has been great interest in the combination of MR blockade with an ACE inhibitor or ARB. However, in small studies, there has been a signal for increased hyperkalemia risk, and larger trials are needed (37). In this regard, there are novel nonsteroidal MR blockers in development that may provide some insight in the future. Moreover, potassium binding agents such as patiromer and ZS-9 may reduce the risk of hyperkalemia and allow for future investigation of the various RAAS combinations (38,39).

Calcium Channel Blockers

Nondihydropyridine calcium channel blockers (CCBs), including diltiazem and verapamil, are useful for the treatment of hypertensive patients with DKD. They may be used as first-line therapy in patients intolerant of ACE inhibitors and ARBs or as second-line agents in combination with an ACE inhibitor or ARB (40). These agents may reduce higher-level albuminuria without an RAAS blocker, but in combination with an ACE inhibitor or ARB, they help to reduce blood pressure while preserving kidney function in people with diabetes (41). Dihydropyridine CCBs such as amlodipine and nifedipine are effective antihypertensive agents but do not reduce proteinuria and cause dose-dependent peripheral edema as a side effect. They should only be used in conjunction with an RAAS blocker because they do provide benefit in this setting (42). The incidence of peripheral edema may be reduced by using dihydropyridine CCBs in combination with an ACE inhibitor (43).

Diuretics

Thiazide or thiazide-like diuretics (e.g., chlorthalidone and indapamide) have an important role in the management of hypertension in patients with diabetes (11,17). Although diuretics once were considered initial therapy, recent guidelines now include them with three other drug classes (i.e., ACE inhibitors, ARBs, and CCBs), any of which may be used to initiate BP-lowering therapy. The important point is to understand volume status in individuals with DKD; because not all patients have volume issues, using these agents as initial therapy may be of limited value in this population. Moreover, in advanced CKD (eGFR >30 mL/min/1.73 m²), chlorthalidone and indapamide have the most significant BP-lowering effect (44). Although these agents have multiple side effects, including hyperglycemia, dyslipidemia, hyperuricemia, and electrolyte abnormalities, their long-term use with management of these side effects does not adversely affect outcomes (45). Combination preparations containing thiazide diuretics with an ACE inhibitor or ARB may be beneficial in reducing the risk of hyperkalemia, as well as patients' pill burden. Long-acting loop diuretics (e.g., torsemide) are effective at an eGFR <30 mL/min/1.73 m² and helpful in volume management (34).

Emerging Antihypertensive Therapies

Endothelin-1 is a potent vasoconstrictor that exerts its effect via the endothelin receptor type A (ET_A) and type B (ET_B). ET_A and ET_B are expressed on the renal vascular smooth muscle, whereas ET_B predominates in tubular epithelial cells. Recent clinical studies suggest that selective blockade of the ET_A receptor may be beneficial in the treatment of hypertension, diabetes, and proteinuria (46). ET_A receptor activation is thought to mediate vasoconstriction, as well as increases in albuminuria and glomerular filtration barrier injury. Conversely, ET_B receptor acti-

vation promotes vasodilatation and clearance of endothelin (46). A recent trial evaluating the benefits of the ET_A receptor antagonist avosentan in diabetic nephropathy had to be terminated prematurely because of safety concerns related to fluid overload. However, avosentan did show some beneficial effect in reducing proteinuria (47).

The DORADO trial studied the use of darusentan (a selective ET_A receptor antagonist) and found a dose-dependent reduction of systolic BP (47). Atrasentan is another selective ET_A receptor antagonist that has shown significant BP reduction in a recent randomized, controlled trial (47). However, none of these drugs has been approved by the U.S. Food and Drug Administration for the treatment of hypertension. Further study may be needed to resolve issues with side effects, including fluid overload, as well as hepatotoxicity with some of the drugs.

Device therapy targeting the sympathetic nervous system for the treatment of hypertension is another novel approach. Renal denervation involves ablating sympathetic nerves in renal arteries by using a catheter to deliver radiofrequency energy of low power to the endothelial layer. Initial studies of sympathetic denervation in patients with resistant hypertension, including the SYMPPLICITY HTN-1 and HTN-2 trials, demonstrated a clinically significant, sustained decrease in BP. However, the SYMPPLICITY HTN-3 trial studied renal denervation in patients with resistant hypertension. Unfortunately, its results did not demonstrate a significant reduction of BP in these patients at 6 months. Subsequent discussions have focused attention on the lack of a standardized technique, as well as the inability to assess for adequacy of ablation as possible reasons that SYMPPLICITY HTN-3 did not show benefit (48). An updated technique and other changes

will lead to future clinical trials using this procedure.

Baroreflex activation therapy is also being studied as a device-based, nonpharmacological treatment in patients with resistant hypertension. The activation of these stretch baroreceptors leads to inhibition of sympathetic output, which then leads to decreased heart rate, cardiac contractility, reduced secretion of antidiuretic hormone, and thus decreased intravascular volume and tone (48). Unlike renal denervation, the effectiveness of baroreflex activation can be assessed immediately after device implantation (48). These devices show promising early results but require further study regarding efficacy and safety before being approved for use in the treatment of hypertension.

In summary, there have been many improvements in the understanding and treatment of diabetic nephropathy over the past 30 years. It is clear that, in advanced nephropathy with very high albuminuria, RAAS blockade has been a key factor in slowing disease progression along with attaining better blood pressure control. The rate of decline in CKD has slowed from an average annual rate of 8 mL/min/1.73 m² to ~2 mL/min/1.73 m² in clinical trials. Newer medications and approaches continue to be investigated as well. Hence, there is great hope that earlier intervention, along with greater knowledge of the disease's natural history, will advance toward normalizing CKD progression in diabetes.

Duality of Interest

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