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Management of Hypertension in Diabetic Patients With Chronic Kidney Disease

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An estimated 26 million individuals in the United States have chronic kidney disease (CKD),\(^1\) and no less than 11 million have diabetes; an unknown proportion has the metabolic syndrome. The preponderance of those with diabetic kidney disease (DKD) will not progress to kidney failure, but rather will succumb to cardiovascular disease (CVD).\(^2\) DKD occurs with frequencies of 30% and 40%, in patients with type 1 and type 2 diabetes, respectively. Blood pressure reduction is the most potent CVD risk reducer in type 2 diabetes, as delineated in the U.K. Prospective Diabetes Study (UKPDS), in which better blood pressure control decreased the onset or degree of albuminuria and micro- and macrovascular complications.\(^3\) In addition, blood pressure control is synergized in the context of multiple risk factor intervention. In the Steno 2 study, a small and carefully conducted study of type 2 diabetic patients, impressive CVD risk reductions occurred within 8 years of multidisciplinary interventions including 1) smoking cessation, 2) aspirin use, 3) exercise, 4) tight glycemic control, 5) dietary intervention, 6) lipid treatment, and 7) vitamin and chromium administration.\(^4\)

Pathophysiology of Hypertension
Hypertension in CKD is marked by extracellular fluid volume expansion, sympathetic nervous system activation, and vasoconstrictor accumulations of endothelin and asymmetric dimethylarginine, an endogenous nitric oxide inhibitor.\(^5\) Salt sensitivity is common. The prevalence of “non-dipping,” the absence of the naturally occurring blood pressure decline during sleep, increases as CKD worsens from 15% in normal subjects to 75% in those with kidney failure (CKD Stage 5).\(^6\) In CKD, a linear correlation exists between hypertension and progressive kidney damage; blood pressure control is crucial to slowing the progression of CKD.\(^7\) Diabetes is also associated with increased arterial stiffness from accelerated atherosclerosis, in part the consequence of increased protein glycation attributable to suboptimal glycemic control.\(^8,9\)

Evaluation of Hypertensive Patients
A careful patient history includes the following:

- Duration of hypertension
- Previously used medications
- Review of adverse drug side effects, allergies, or intolerances
- Identification of social/support networks (isolation decreases medication adherence)
- Smoking, alcohol, or drug history
- Current medication reconciliation (reviewing pill bottles and counts to confirm that the patient is taking medications as directed) that includes use of complementary and over-the-counter drugs that may increase blood pressure (Table 1)
- Menstrual history (i.e., oligomenorrhea from polycystic ovary syndrome)
• Exercise and dietary history, including sodium, calcium, and potassium intake
• Screening for obstructive sleep apnea (Epworth scale)
• Assessment of medication-taking behavior (i.e., adherence)

Systematic review must include symptoms of CVD and secondary forms of hypertension (dyspnea, palpitations, chest pain, and spells). The physical examination should focus on signs of target organ damage, including retinal changes, arterial bruits of renal or other large artery origin, left ventricular hypertrophy (LVH), and signs of secondary hypertension, such as thyromegaly and tremor (thyrotoxicosis) and pink striae (Cushing’s disease).

An initial laboratory evaluation includes measurement of electrolytes, blood urea nitrogen (BUN), serum creatinine with estimation of the glomerular filtration rate (GFR), complete blood count, uric acid, fasting lipid levels of cholesterol and triglycerides, hemoglobin A1c, urinary albumin excretion, and an electrocardiogram. In the future, central aortic pressure and pulse wave velocity measurements will likely complement the tests listed above.10

### Blood pressure measurement modalities

**Office-based blood pressure measurement (OBP).** Most randomized, controlled trials continue to rely on OBP readings to monitor the response to treatment and outcomes. However, small differences in OBP readings correlate with greater differences in non-OBP readings, as documented in the Heart Outcomes Prevention Evaluation trial.11

The current seventh Joint National Committee (JNC 7)12 and National Kidney Foundation (NKF) and American Diabetes Association guidelines13,14 base blood pressure monitoring (ABPM) on signs of target organ damage and untreated hypertensive patients. Interestingly, in treated hypertensive patients, outcomes and prognosis were more closely linked to nocturnal blood pressure.19

Some automated blood pressure devices have been validated for OBP and record, average, and report data from multiple readings.17 In obese patients whose upper arm measurements preclude appropriate cuff size, wrist monitors, if held at the level of the heart, offer an alternative.

**ABPM.** The lack of decline of nocturnal blood pressure, or “non-dipping,” is abnormal but common in patients with CKD and/or proteinuria. This deficit has been linked to cardiovascular events, development of microalbuminuria, progression of CKD, and development of LVH. Yet there are no published trials of renal or cardiovascular outcomes that determine whether blood pressure control, titrated by ABPM, is efficacious.

Profuse epidemiological data in diabetes, with or without CKD, underscores ABPM’s utility, although normal ABPM pressures are lower than OBP readings, i.e., a 24-hour mean blood pressure that mildly exceeds 130/80 mmHg is associated with target organ damage and excessive cardiovascular risk in patients without diabetes. However, standards have not yet been developed for diabetes or CKD.

In a small but carefully designed study of CKD patients that included patients with diabetes, ABPM more strongly predicted death and progression to kidney failure than OBP.18 The presence of non-dipping predicted mortality and progression to kidney failure. More recently, day- and night-time blood pressure readings predicted prognosis in treated and untreated hypertensive patients. Furthermore, a growing body of literature documents the importance of non-OBP measurements by patients or by 24-hour ambulatory blood pressure monitoring (ABPM) in diabetes and CKD. Recently, the European Society of Hypertension recommended 24-hour ABPM and home-based readings as an integral part of hypertension evaluation.15 Readers are directed to guidelines that detail appropriate measurement methodology.12,16

### Table 1. Agents and Factors That May Increase Blood Pressure

| Alcohol |
| Calcineurin inhibitors (e.g., cyclosporine and tacrolimus) |
| Cocaine |
| Cyclooxygenase type 2 inhibitors |
| Erythropoiesis stimulating agents (e.g., epoetin alfa and darbepoetin alfa) |
| Gamma aminobutyric acid |
| Herbal preparations including those containing European black licorice |
| High-dose glucocorticoid steroids |
| Monoamine oxidase inhibitors |
| Metoclopramide (rarely) |
| Nonsteroidal anti-inflammatory agents |
| Oral contraceptives |
| Sodium intake (> 100 mmol sodium per day) |
| Selective serotonin reuptake inhibitors |
| Sympathomimetics (e.g., amphetamines, including drugs for treatment of attention deficit hyperactivity disorder and narcolepsy) |
| Tobacco |
| Vascular endothelial growth factor inhibitors (e.g., bevacizumab) |
| Withdrawal from beta blockers or clonidine |

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tion, known as “masked hypertension,” bears increased cardiovascular risk, and the extent of this phenomenon in CKD and DKD is unknown. Finally, ABPM is indicated in resistant hypertension for prognosis and as a guide to therapy, as well as for hypertensive symptoms out of office, white-coat hypertension, and autonomic failure (Table 2).

**Self- and home-based blood pressure measurement (HBP).** HBP is more easily conducted than ABPM but excludes nocturnal blood pressure readings. HBP coincides more closely with 24-hour ABPM than OBP. An initial HBP target of < 130/80 mmHg for CKD has proven salutary, with no patients progressing to CKD Stage 5 at the 2-year follow-up in a recent trial.21

Equally important is the notation that those who engage in HBP adhere to their antihypertensive regimens more fully. HBP more accurately predicts future adverse events than OBP measurement. Based on the Ohasama Study, blood pressure measurements taken in the morning and evening yield additional prognostic information in this regard.23

American Association of Instrumentation (AAMI)-validated blood pressure cuffs from a variety of manufacturers range in price from ~$30 to $100. To most closely simulate ABPM, obtain blood pressure readings twice weekly during initial drug titration, before breakfast, and after the evening meal. After blood pressure has stabilized, obtain readings every 1–2 weeks. Finally, blood pressure cuffs should be calibrated with an accurate, physician-approved oscillometric or, if available, mercury-based blood pressure–measuring device, which are still used in the United States, albeit less frequently due to restrictions governing the use of elemental mercury.

**Pharmacological Treatment of Hypertension in DKD**

**Initial considerations**

Hypertensive DKD patients, especially African Americans, harbor tremendous risk for kidney failure,2 and intensive therapy is unequivocally protective. Thus, attaining and maintaining recommended blood pressure goals is a clinical mandate. However, DKD patients frequently require three to four agents to achieve blood pressure goals.24–26

Two agents are advised when the initial blood pressure exceeds the JNC 7 target by > 20/10 mMm. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin 2 receptor blocker (ARB) combinations, especially with diuretics or calcium channel blockers (CCBs), make financial and prescriptive sense (i.e., result in lower daily pill counts and promote medication adherence), particularly given that the DKD "drug load" is extensive.

CCBs are divided into dihydropyridine and nondihydropyridine classes. Nifedipine and felodipine are examples of the former, and diltiazem and verapamil are examples of the latter.

**ACE inhibitors and ARBs**

Blockade of the renin-angiotensin-aldosterone system (RAAS) in CKD of any type is beneficial. ACE inhibitors are the cornerstone of antihypertensive, renoprotective, cardiovascular, risk-modifying therapy in diabetes; they retard progression of DKD and reduce proteinuria in type 1 and type 2 diabetes.2,12,13,25,27,28 Side effects include hyperkalemia, acute renal failure, and ACE inhibitor–induced cough. Angioedema occurs rarely, but it is essential to inform patients of this rare life-threatening condition, which occurs primarily in African Americans (< 1 episode per 1,000 drug-years for Caucasians; 4/1,000 drug-years in African Americans).29 ACE inhibitors are lipid neutral and may augment insulin sensitivity, yet they are rarely associated with hypoglycemia. Some posit that ACE inhibitors confer special cardiovascular protective and antiproteinuric effects, whereas others contend that attainment of blood pressure targets is the key to success for any antihypertensive class of drugs.

ARBS have the largest data set for slowing progression of renal disease in type 2 diabetes. The Irbesartan Diabetic Nephropathy Trial (IDNT)27 and Reduction in End Points in Type 2 Diabetes With the Angiotensin II Antagonist Losartan study trial28 demonstrated renoprotection in established type 2 diabetes with DKD. ARBs in both trials reduced development of heart failure but not of cardiovascular mortality. An IDNT post hoc analysis revealed improved cardiovascular outcomes by achieving systolic blood pressure readings near 120 mmHg.29 In the Losartan for Endpoint Reduction trial, cardiovascular and total mortality benefit in DKD occurred in losartan-treated, but not atenolol-treated, subjects, and this effect coincided with LVH regression.30 An additional benefit of improved glycemic control was found in the ARB-treated group compared to beta blocker therapy with or without concurrent diuretic use.30 ARBs have a much lower incidence of cough and angioedema than ACE inhibitors. To date, no direct, large-scale comparative superiority studies regarding DKD or CKD comparing ACE inhibition to ARB therapy are available.

A maximally tolerated dose of either an ACE inhibitor or an ARB is always indicated in DKD unless absolutely contravened by side effect or hypersensitivity, even in more advanced stages of CKD. Therefore, maximally tolerated doses of anti-RAAS drugs are the rule, not the exception. Combination therapy composed of an ACE inhibitor and an ARB generally offers a small

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**Table 2. Blood Pressure Thresholds for Definition of Hypertension in People Without Diabetes**

<table>
<thead>
<tr>
<th>Category</th>
<th>Threshold</th>
</tr>
</thead>
<tbody>
<tr>
<td>OBP:</td>
<td>140/90 mmHg</td>
</tr>
<tr>
<td>24-hour ABPM:</td>
<td>125–130/80 mmHg</td>
</tr>
<tr>
<td>Daytime:</td>
<td>130–135/85 mmHg</td>
</tr>
<tr>
<td>Nighttime:</td>
<td>120/70 mmHg</td>
</tr>
<tr>
<td>HBP:</td>
<td>~130–135/85 mmHg</td>
</tr>
</tbody>
</table>

*In CKD, the blood pressure target is < 130/< 80 mmHg by ABPM.19 Systolic blood pressure should be > 115 mmHg by HBP monitoring.

Adapted from Ref. 15.
additive blood pressure–reducing effect of 2–4 mmHg and a synergistic proteinuria-reducing effect.\textsuperscript{31}

\section*{Diuretic agents}

Most DKD patients are volume expanded, necessitating sodium restriction and diuretic treatment. Ideally, these high-risk hypertensive patients are treated with ACE inhibitor-diuretic or ARB-diuretic combinations. The importance of the diuretic component is underscored by the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), in which equivalent protection against coronary heart disease death and nonfatal myocardial infarction was shown in comparisons among mildly hypertensive diabetic subjects and non-diabetic subjects treated with ACE inhibitor, amlodipine, or the diuretic chlorthalidone.\textsuperscript{24} Chlorthalidone was superior to amlodipine and lisinopril for prevention of heart failure and stroke, perhaps attributable to superior blood pressure control in this treatment arm. African Americans had significantly lower blood pressure and superior outcomes with diuretic monotherapy at the expense of worsened glycemic control, hyperuricemia with or without gout, hypokalemia, and hyponatremia.

Individuals initiated on diuretics, ACE inhibitors, ARBs, or selective aldosterone receptor antagonists (SARAs) should undergo testing in 1 week for electrolytes and serum creatinine. Chlorthalidone (12.5–25 mg daily) is the preferred thiazide because of its impressive evidence base, yet it is paradoxically prescribed only minimally.\textsuperscript{26} Patients with an estimated GFR < 40 ml/min/1.73 m\textsuperscript{2} should be treated with loop diuretics at least twice daily, with dose titration to achieve normal extracellular fluid status.\textsuperscript{13}

\section*{CCBs}

The nondihydropyridine CCBs dil-tiazem and verapamil are lipid- and glucose-neutral agents and may reduce proteinuria. Dihydropyridine CCBs, such as amlodipine and nifedipine, increase proteinuria when used alone,\textsuperscript{32} but this adverse effect is abrogated during concurrent ACE inhibitor or ARB administration.

Notably, amlodipine increased heart failure compared to chlorthalidone, when used alone in patients with diabetes in the ALLHAT.\textsuperscript{26} The Anglo-Scandinavian Cardiovascular Outcomes Trial (ASCOT), which compared atenolol and a thiazide diuretic to amlodipine and an ACE inhibitor, revealed better outcomes in the latter group, and the best outcomes occurred in the atorvastatin-treated cohort.\textsuperscript{35} Central aortic pressure was lower with the CCB/ACE inhibitor combination despite similar OBPs.

\section*{Beta blockers}

Beta blockers are used with other drugs and are indicated in patients who have had myocardial infarctions. Their track record in primary prevention of cardiovascular events in hypertension is inferior to other agents including diuretics, and this observation prompted the British Health Service to remove them from its list of first-line antihypertensive agents.\textsuperscript{34} Concern has been recently raised regarding therapeutic inferiority of atenolol compared to other available beta blockers.\textsuperscript{35} This author discourages the use of atenolol as antihypertensive therapy, although it was shown to decrease cardiovascular risk and micro- and macrovascular diabetes complications in the UKPDS.\textsuperscript{36} This author recommends the use of carvedilol or the longer-acting beta blocker metoprolol.

The beta blocker carvedilol is a combined nonselective beta- and alpha-1 adrenergic inhibitor and is now available as a generic. This agent is associated with improved survival in heart failure.\textsuperscript{37} In a cohort of hypertensive, type 2 diabetic patients previously treated by ACE inhibitors or ARBs, carvedilol was compared to metoprolol. Carvedilol decreased albumin excretion by 16%, decreased the new onset of microalbuminuria, and increased insulin sensitivity during the course of a 6-month trial.\textsuperscript{38}

\section*{Holistic Treatment of Hypertension in DKD}

After a diagnosis of uncontrolled hypertension (blood pressure > 130/ > 80 mmHg) is established by ABPM, HBP, or OBS, therapy must start or be intensified. Collaborative management by an advanced nurse practitioner, a nurse with expertise in hypertension, and a physician has been shown to improve blood pressure control in diabetic hypertensive patients.\textsuperscript{39} To provide ultimate CVD risk reduction, multiple risk factor modification is mandatory and includes hypolipidemic therapy and smoking cessation. The latter is highly important because DKD, in the presence of ongoing tobacco use, can sound the death knell for the kidneys and obviates the antihypertensive effects of many blood pressure–reducing drugs.\textsuperscript{40} Aerobic physical activity with a minimum of 30–45 minutes of brisk walking, 5 days weekly, is strongly encouraged.\textsuperscript{41} Patients should be counseled to moderate alcohol intake to less than one drink daily for females and two drinks daily for males.

Any use of alternative or over-the-counter medications should be evaluated. Dietary instructions must emphasize the central importance of limiting sodium to 2,000 mg daily to potentiate the action of antihypertensive and antiproteinuric agents.\textsuperscript{42} If hyperkalemia is not an issue, the Dietary Approaches to Stop Hypertension diet is appropriate for CKD Stages 1–3,\textsuperscript{43} and formal dietary consultation for integration of these concepts into the diet of patients with diabetes is crucial. Potassium restriction in CKD Stage 4 is advised, particularly when SARA, ACE inhibitor, or ARB therapy is ongoing. Weight reduction is important, and vigilance for aggravating factors of hypertension is advised.

\section*{Resistant Hypertension}

There are minimal data regarding the frequency of additional secondary causes of hypertension in patients with preexistent CKD, with the exception of obstructive sleep apnea.\textsuperscript{44} However, if the attainment of target blood pressure has not occurred within 4–6 months of appropriate therapy despite the application of maximally tolerated doses from three to four different classes of antihypertensive drugs including a diuretic, an evaluation for resistance to therapy should be undertaken.\textsuperscript{45}

This evaluation includes:
- Medication reconciliation
- Evaluation of medications that may aggravate hypertension (Table 1)
- 24-hour urine collection for sodium, potassium, and creatinine
- Reduction of sodium intake to < 100 mEq/day

Evaluations of the following are also recommended:
- Sleep apnea or sleep deprivation\textsuperscript{44}
• Hypothyroidism
• Hyperthyroidism
• Cushing’s syndrome
• Pheochromocytoma
• Polycystic ovary syndrome
• Primary aldosteronism in any of its several forms

The latter disorder, although present in 10–20% of cases of resistant hypertension, is difficult to diagnose in more advanced CKD because plasma aldosterone may be elevated and renin suppressed. Persistent hypokalemia, hypernatremia, or metabolic alkalosis are clues to the diagnosis. Weight loss and exercise are potent blood pressure–reducing activities, if practiced consistently.

The choice of additional antihypertensives is limited by a general lack of evidence base in patients with CKD. Recent recommendations by the NKF espouse the use of ACE inhibitors/ARBs, diuretics, and CCBs as the initial three drug classes to treat high blood pressure while instituting and maintaining lifestyle modifications. Fourth- and fifth-line agents include central alpha agonists, such as clonidine; pure alpha blockers, such as doxazosin; and direct vasodilators, such as hydralazine or minoxidil. Recent data involving long-acting nitrates for the treatment of isolated systolic hypertension is promising, but a well-informed recommendation cannot be proffered.

Unfortunately, none of these medications has a CVD risk reduction database. A careful review of the indications and side effects of these agents before prescribing is necessary, or referral to a hypertension specialist or a physician familiar with these medications is obligatory.

Available SARAs in the United States include spironolactone and eplerenone. These drugs are undergoing study as agents for additional control of proteinuria in CKD Stages 1 and 2. This drug class is associated with OBP reductions of 5–7 mmHg, significant proteinuria reductions, and urinary albumin excretion reductions of 30–50%. Reversible and mild GFR reductions have been documented. Notably, spironolactone has effectively treated resistant hypertension in patients with normal or near-normal kidney function. A significant risk of SARA-induced hyperkalemia is evident during coadministration of another anti-RAAS agent (ACE inhibitor or ARB) in advanced DKD, and caution is advised. At a minimum, frequent and careful follow-up of serum potassium levels must be carried out in such circumstances.

**Direct renin inhibitors**

There currently are no data regarding this class of agents in DKD or even nondiabetic CKD. The Aliskiren Trial in Type 2 Diabetics study of aliskiren as a therapeutic add-on to ACE inhibitor or ARB therapy in reducing proteinuria and CV end points is currently enrolling subjects in the United States and Europe.

**Clinic Follow-up**

Patients should return for follow-up twice monthly until the goal blood pressure is achieved and monthly for 3 months thereafter. Each office visit represents an opportunity for additional intervention. Medication reconciliation, financial considerations, and practices that increase drug adherence should be reviewed. The use of HBP should be reviewed and encouraged, and blood pressure cuff accuracy should be validated with an AAMI-approved device. Referral to a hypertension specialist is encouraged when blood pressure control requires more than 4–6 months because data from several recent trials show decreased cardiovascular events in patients when blood pressure targets are attained within 6 months. If feasible, confirmatory ABPM should be conducted after HBP and OBP recordings consistently register < 130/80 mmHg. Lastly, parameters such as proteinuria should be monitored in conjunction with electrolytes, BUN, and serum creatinine.

**Summary and Conclusions**

Control of hypertension in DKD requires a collaborative network among patients, primary care providers, endocrinologists, and nephrologists. Careful blood pressure measurement, a multiple risk factor modification strategy, and persistent and judicious RAAS blockade in combination with diuretics and add-ons should result in good blood pressure control in a majority of patients. Engaging patients and their families through HBP, lifestyle modification, and collaboration with clinic nurses, advanced practice nurses, and clinical pharmacists will facilitate success, thereby reducing the extraordinarily high CVD risk burden of DKD and retarding progression to kidney failure.

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