Overview of hypertension in acute and chronic kidney disease

Author: Johannes FE Mann, MD
Section Editors: George L Bakris, MD, William J Elliott, MD, PhD
Deputy Editor: John P Forman, MD, MSc

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INTRODUCTION

Hypertension is a frequent finding in both acute and chronic kidney disease, particularly with glomerular or vascular disorders [1]. The pathogenesis and preferred treatment of hypertension vary with the type of renal disease and its duration. This topic will summarize the pathogenesis and treatment of hypertension in patients with acute and chronic kidney disease and then direct the reader, when necessary, to more detailed discussions in other topics.

PATHOGENESIS OF HYPERTENSION IN KIDNEY DISEASE

The pathogenesis of hypertension varies with the type of disease (eg, glomerular versus vascular) and with the duration of disease (acute versus chronic).

Acute glomerular disease — Patients with acute glomerular disease, such as poststreptococcal glomerulonephritis, tend to be volume expanded and edematous due to sodium retention [2]. As a result, the elevation in blood pressure is primarily due to fluid overload, as evidenced by suppression of the renin-angiotensin-aldosterone system and enhanced release of atrial natriuretic peptide [3]. Although these changes are most prominent with severe disease, the incidence of hypertension is increased even in patients with a normal serum creatinine concentration [4]. Both a familial predisposition to hypertension and subclinical volume expansion are thought to be important in this setting.

Experimental studies of the nephrotic syndrome or glomerulonephritis suggest that sodium retention in these disorders is due to increased reabsorption in the collecting tubules [5]. Two different abnormalities in collecting tubule function have been identified in glomerular disease, both of which could increase sodium reabsorption:

- Relative resistance to atrial natriuretic peptide due at least in part to more rapid degradation of the second messenger cyclic guanosine monophosphate (GMP) by the enzyme phosphodiesterase [4]. In an animal model of nephrotic syndrome, infusion of a phosphodiesterase inhibitor largely reverses this defect and restores the normal natriuretic response to volume expansion.

- Increased activity of the Na-K-ATPase pump in the cortical collecting tubule but not in other nephron segments [6]. This pump provides the energy for active sodium transport by pumping reabsorbed sodium out the cell into the peritubular capillary.

How these changes might be induced by the nephrotic syndrome or glomerulonephritis is not clear. They are not likely to be mediated by aldosterone, the secretion of which is reduced by volume expansion-mediated reductions in plasma renin activity [3].

Acute vascular disease — Hypertension is also common in acute vascular diseases, such as vasculitis or scleroderma renal crisis. In these settings, the elevation in blood pressure results from ischemia-induced activation of the renin-angiotensin system rather than volume expansion [2]. This difference in mechanism between glomerular and vascular disease may be of therapeutic importance. (See 'Treatment of hypertension in acute glomerular or vascular disease' below.)

Chronic kidney disease — Hypertension is present in approximately 80 to 85 percent of patients with CKD [7]. The prevalence of hypertension is elevated in patients with kidney damage and a normal glomerular filtration rate (GFR) and increases further as the GFR falls. Data from the Modification of Diet in Renal Disease Study, for example, showed that the prevalence of hypertension rose progressively from 65 to 95 percent as the GFR fell from 85 to 15 mL/min per 1.73 m^2 [8]. As in patients without renal disease, the prevalence of hypertension is also higher in patients with higher body weight and in black patients. (See "Overweight, obesity, and weight reduction in hypertension", section on 'Effects of adiposity on blood pressure' and "Hypertensive complications in Black individuals".)

A variety of factors can contribute to the increased prevalence of hypertension in patients with CKD:

- Sodium retention is generally of primary importance, even though the degree of extracellular volume expansion may be insufficient to induce edema.
- Increased activity of the renin-angiotensin system is often responsible for at least part of the hypertension that persists after the restoration of normovolemia, particularly in patients with vascular disease since renal ischemia is a potent stimulus of renin secretion. Regional ischemia induced by scarring may also play a role.
- Hypertension can be a causative (eg, hypertensive nephrosclerosis) or contributory factor in the development of kidney disease.
- Hypertension may result from enhanced activity of the sympathetic nervous system [9]. The afferent signal may arise in part within the failing kidneys since it is not seen in patients who have undergone bilateral nephrectomy.
- Secondary hyperparathyroidism raises the intracellular calcium concentration, which can lead to vasoconstriction and hypertension [10]. Lowering parathyroid hormone secretion by the chronic administration of an active vitamin D analog can reduce both intracellular calcium and the systemic blood pressure.
- Treatment with erythropoietin may increase blood pressure, an effect that is in part related to the degree of elevation in the hematocrit. (See "Hypertension following erythropoiesis-stimulating agents (ESAs) in chronic kidney disease", section on 'Pathogenesis'.)
- Impaired nitric oxide synthesis and endothelium-mediated vasodilatation has been demonstrated in patients with uremia [11]. Although the mechanisms are unclear, potential explanations include reduced nitric oxide availability due to a state of increased oxidative stress or cofactor deficiency-induced uncoupling of nitric oxide synthase.

In addition to the factors that can raise the mean arterial pressure, two other factors may be important:

- Patients with end-stage kidney disease (ESKD) are more likely to have an increase in central pulse pressure and isolated systolic hypertension [12]. Why this occurs is incompletely understood, but increased aortic stiffness probably plays an important role.
- Patients with CKD may not demonstrate the normal nocturnal decline in blood pressure (such patients are called "nondippers"), a possible risk factor for hypertensive complications [13]. (See "Out-of-office blood pressure measurement: Ambulatory and self-measured blood pressure monitoring".)

TREATMENT OF HYPERTENSION IN ACUTE GLOMERULAR OR VASCULAR DISEASE

In view of the differences in pathogenesis, the mechanism and treatment of hypertension vary in patients with acute glomerular and vascular disease.

We prefer initial therapy with diuretics (particularly loop diuretics in patients with reduced glomerular filtration rates [GFRs]) to treat hypertension in patients with acute glomerular disease and edema since diuretics will also treat the hypervolemia and associated edema. If the hypertension persists, angiotensin-converting enzyme (ACE) inhibitors may be effective, even in the low-renin hypertension often associated with acute glomerulonephritis [14]. This response may reflect activation of tissue renin-angiotensin systems, such as that in the kidney, vascular endothelium, and adrenal gland. (See "Renin-angiotensin system inhibition in the treatment of hypertension".)

In comparison with acute glomerulonephritis, we prefer ACE inhibitors as initial antihypertensive therapy in patients with acute vascular diseases since renal ischemia leads to activation of the renin-angiotensin system. Strong data support this approach in patients with scleroderma renal crisis, and we prefer angiotensin inhibition in polyarteritis nodosa and other vasculitides, as well. (See "Renal disease in systemic sclerosis (scleroderma), including scleroderma renal crisis", section on 'Treatment' and "Treatment and prognosis of polyarteritis nodosa", section on 'Hypertension'.)

TREATMENT OF HYPERTENSION IN CHRONIC KIDNEY DISEASE

Treatment of even mild or stage 1 hypertension is important in patients with CKD to protect against both progressive renal function loss and cardiovascular disease, the incidence of which is increased with mild to moderate stages 1 to 3 CKD. (See "Antihypertensive therapy and progression of nondiabetic chronic kidney disease in adults" and "Chronic kidney disease and coronary heart disease", section on 'Blood pressure control'.)

Goal blood pressure — Goal blood pressure in patients with diabetic and nondiabetic CKD is presented in detail elsewhere:

- (See "Antihypertensive therapy and progression of nondiabetic chronic kidney disease in adults", section on 'Blood pressure goal'.)
- (See "Treatment of hypertension in patients with diabetes mellitus".)

In addition to blood pressure control, specific goals related to a reduction in urinary protein excretion have been formulated to slow the rate of progression of proteinuric CKD:

- We suggest a proteinuria goal of less than 1000 mg/day (or less than 1000 mg protein/g of creatinine in a spot urine specimen).
- In patients who are initially nephrotic and in whom this goal is unobtainable, we attempt to achieve a minimum reduction in proteinuria of at least 50 to 60 percent from baseline values **plus** protein excretion less than 3.5 g/day (or less than 3500 mg protein/g of creatinine in a spot urine specimen).

The evidence supporting our recommendations for proteinuria reduction in patients with diabetic and nondiabetic CKD is discussed separately:

- (See "Antihypertensive therapy and progression of nondiabetic chronic kidney disease in adults", section on 'Proteinuria goal'.)
- (See "Treatment of diabetic kidney disease".)

Technique of blood pressure measurement — There are multiple techniques available to measure blood pressure in patients with (and without) CKD. These techniques are discussed in detail elsewhere. (See "Blood pressure measurement in the diagnosis and management of hypertension in adults".)

Several observational studies have found that 24-hour ambulatory blood pressure is a stronger predictor of end-stage kidney disease (ESKD), cardiovascular disease, and death than office-based measurements [15,16]. In 436 patients with CKD who underwent both ambulatory and office-based blood pressure measurements, for example, a daytime ambulatory systolic pressure greater than 145 mmHg was associated with a threefold increased risk of developing cardiovascular disease and a nearly twofold increased risk of ESKD or death compared with patients whose daytime systolic pressure was 126 to 135 mmHg. The prognostic value of nighttime ambulatory blood pressure was even stronger. By contrast, the mean of six office-based measurements taken over two days was not associated with cardiovascular disease, ESKD, or death.

Ambulatory blood pressure monitoring and home blood pressure monitoring, which is less expensive than ambulatory blood pressure monitoring, are presented in detail separately. (See "Out-of-office blood pressure measurement: Ambulatory and self-measured blood pressure monitoring".)

Benefits of sodium restriction — Sodium restriction enhances the effect of many antihypertensive drugs. This is also true in patients with CKD [17,18], most of whom, as discussed below, are treated with angiotensin inhibitors to slow disease progression. The potential benefits of sodium restriction were demonstrated in a crossover trial of 52 patients with proteinuric CKD (mean protein excretion of 1.6 g/day and mean creatinine clearance of 70 mL/min), all of whom were taking lisinopril [17]. Four treatments were given in random order, each for six weeks: a low-sodium diet with placebo, a low-sodium diet with valsartan, a regular-sodium diet with placebo, and a regular-sodium diet with valsartan. Compared with a regular-sodium diet (mean urinary sodium excretion 184 mmol/day), a low-sodium diet (mean 106 mmol/day) decreased blood pressure to a greater degree than addition of valsartan (11 versus 3 mmHg). Addition of valsartan had a minimal additional effect (2 mmHg) on blood pressure beyond a low-sodium diet.

Use of diuretics and goal of therapy — Because of the reduction in renal function, higher doses of diuretics are typically required in patients with CKD who are usually volume expanded even in the absence of edema. Thiazide diuretics become less effective when the glomerular filtration rate (GFR) is less than 30 mL/min [19]. In such patients, loop diuretics are preferred as initial therapy. Torsemide, which has a longer duration of action than furosemide, may be preferred. (See "Treatment of resistant hypertension".)

If edema persists, a thiazide diuretic can be added to the loop diuretic. The rationale for combined therapy is that most of the fluid leaving the loop of Henle after the administration of a loop diuretic is reabsorbed in the distal tubule, the site of action of thiazide diuretics. Thus, thiazides have an enhanced diuretic effect in patients treated with a loop diuretic. (See "Causes and treatment of refractory edema in adults".)

The efficacy of combined diuretic therapy has been illustrated in a report of five patients with CKD (serum creatinine 2.3 to 4.9 mg/dL [203 to 433 micromol/L]) who had an inadequate response to 160 to 240 mg/day of furosemide in divided doses [20]. Increasing the furosemide dose had only limited efficacy. By contrast, the addition of 25 to 50 mg twice daily of hydrochlorothiazide produced a marked diuresis. Chlorthalidone is generally preferred to hydrochlorothiazide because it is more potent and has a longer duration of action [21]. (See "Treatment of resistant hypertension".)

In edematous patients with CKD, the initial goal is removal of edema. However, if hypertension persists once edema has been removed, plasma volume expansion may still be present and contribute to the hypertension. Thus, when diuretics are used to treat hypertension in patients with CKD without overt edema, the dose and/or frequency of diuretic should be increased when the antihypertensive response is inadequate.

Diuretic therapy should be increased until one of two endpoints is reached: the blood pressure goal is achieved or the patient has attained "dry weight," which, in the presence of persistent hypertension, is defined as the weight at which further fluid loss leads to symptoms (cramps, fatigue, orthostatic hypotension) or leads to decreased tissue perfusion as evidenced by an otherwise unexplained elevation in the serum creatinine concentration.

Choice of antihypertensive therapy — Attainment of goal blood pressure in patients with CKD typically requires multidrug therapy [22]. As with goal blood pressure discussed above, the choice of agent depends in part upon whether or not the patients have proteinuria.

Sequence of antihypertensive therapy in proteinuric CKD

First-line therapy in proteinuric CKD — High-quality evidence favors the use of an angiotensin-converting enzyme (ACE) inhibitor or angiotensin II receptor blocker (ARB) as first-line therapy in patients with proteinuric CKD (ie, protein excretion greater than 500 mg/day) because, in addition to lowering the blood pressure, these drugs slow the rate of progression of CKD. The supportive data are presented elsewhere:

- (See "Antihypertensive therapy and progression of nondiabetic chronic kidney disease in adults", section on 'Effect of renin-angiotensin system inhibitors on progression of CKD'.)
- (See "Treatment of hypertension in patients with diabetes mellitus".)

Common side effects of angiotensin inhibition in patients with CKD include an acute reduction in GFR and hyperkalemia. In addition, both ACE inhibitors and ARBs are contraindicated in pregnancy. These issues are discussed in detail separately. (See "Major side effects of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers".)

The use of ACE inhibitors or ARBs to manage hypertension in children with CKD is discussed in detail elsewhere. (See "Chronic kidney disease in children: Complications", section on 'Hypertension'.)

Second- and third-line therapy in proteinuric CKD — Our suggestions for second- and third-line antihypertensive therapy in patients with proteinuric CKD depend upon whether overt volume overload is present:

- In patients with CKD who have proteinuria and **edema**, initial therapy usually consists of both an angiotensin inhibitor for renal protection and a loop diuretic for edema, which, by increasing renin release, may also enhance the antihypertensive effect of the angiotensin inhibitor. The use of a diuretic may also restore the antiproteinuric effect of ACE inhibitor therapy in patients without an adequate antiproteinuric response since volume expansion

reduces angiotensin II release and makes the blood pressure less dependent upon angiotensin II [23,24]. (See "Renin-angiotensin system inhibition in the treatment of hypertension", section on 'Antihypertensive response'.)

If further antihypertensive therapy is required, we suggest a non-dihydropyridine calcium channel blocker (eg, diltiazem or verapamil) since these drugs also lower proteinuria. By contrast, dihydropyridines (eg, amlodipine) have little or no effect on protein excretion [25]. (See "Antihypertensive therapy and progression of nondiabetic chronic kidney disease in adults", section on 'Calcium channel blockers'.)

- In patients with CKD who have proteinuria but **not edema**, we suggest either a diuretic or a non-dihydropyridine calcium channel blocker as second-line and then third-line therapy. Volume expansion, even in the absence of edema, often plays a major role in hypertension associated with CKD. (See 'Use of diuretics and goal of therapy' above.)

Issues related to diuretic use and the goal and limitations of diuretic therapy are discussed above. (See 'Use of diuretics and goal of therapy' above.)

Sequence of antihypertensive therapy in nonproteinuric CKD — In contrast to their renoprotective effects in proteinuric CKD, angiotensin inhibitors do **not** appear to be more beneficial than other antihypertensive agents in patients with nonproteinuric CKD [26]. These data are discussed in detail elsewhere. (See "Antihypertensive therapy and progression of nondiabetic chronic kidney disease in adults", section on 'Lack of benefit in nonproteinuric CKD'.)

In patients with nonproteinuric CKD, we suggest the following sequence, which depends upon the presence or absence of edema:

- In patients **with edema**, we prefer initial therapy with a loop diuretic. Once the edema is controlled, an angiotensin inhibitor or a dihydropyridine calcium channel blocker (eg, amlodipine) can be added in either order if hypertension persists.

- In patients **without edema**, we start with an angiotensin inhibitor and then add a dihydropyridine calcium channel blocker (eg, amlodipine) as second-line therapy. This approach has not been studied specifically in patients with nonproteinuric CKD. Rather, it is extrapolated from our recommendations for hypertensive patients in general, which are guided by the findings of the Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trial. If needed, we suggest adding a diuretic as third-line therapy. (See "Choice of drug therapy in primary (essential) hypertension", section on 'ACCOMPLISH trial'.)

Fourth-line therapy with other agents — Other antihypertensive drugs can be used as necessary in patients with CKD who have resistant hypertension. A mineralocorticoid receptor antagonist (spironolactone or eplerenone) is an effective fourth-line agent for the treatment of resistant hypertension in general and in patients with CKD. In addition to reducing blood pressure, mineralocorticoid receptor antagonists also have antiproteinuric properties that may be associated with a slower decline in renal function. However, trials with patient-important outcomes are not available yet. (See "Treatment of resistant hypertension".)

The efficacy of mineralocorticoid receptor antagonists was evaluated in a study of 46 patients with a mean estimated GFR (eGFR) of 57 mL/min per 1.73 m^2 and hypertension that was not controlled with three mechanistically complementary drugs, including a diuretic and angiotensin inhibitor [27]. The mean fall in systolic pressure induced by mineralocorticoid receptor antagonists was 14.7 mmHg.

The main adverse effects of mineralocorticoid receptor antagonists in patients with CKD are a reduction in kidney function and hyperkalemia. In the above study, 39 percent had a decline in eGFR of 30 percent or more when goal blood pressure was achieved, and 17 percent developed hyperkalemia [27]. Risk factors for hyperkalemia included a baseline eGFR ≤45 mL/min in patients with a serum potassium above 4.5 mEq/L and a fall in eGFR of more than 30 percent after therapy.

Possible benefit from nocturnal therapy — The average nocturnal blood pressure is approximately 15 percent lower than daytime values. Failure of the blood pressure to fall by at least 10 percent during sleep is called "nondipping" and is one of the strongest predictors of adverse cardiovascular outcomes. (See "Out-of-office blood pressure measurement: Ambulatory and self-measured blood pressure monitoring".)

Many patients with CKD are nondippers [16]. Shifting one antihypertensive medication from the morning to the evening has been proposed as a means to restore the normal nocturnal blood pressure dip in these patients; however, the data are not consistent [28-31].

The effect of shifting at least one antihypertensive medication from the morning to the evening on the incidence of cardiovascular disease was evaluated in an open-label randomized trial of 661 patients with CKD (defined as an eGFR below 60 mL/min per 1.73 m^2 or an albumin-to-creatinine ratio greater than 30 mg/g on two separate occasions) who were randomly assigned to take all medications in the morning or to take at least one at bedtime [31]. At baseline, the two groups had similar mean ambulatory blood pressure (135/77 versus 135/79 mmHg) and proportion of nondippers (68 versus 65 percent). The only medication classes permitted to be taken at bedtime were ACE inhibitors, ARBs, or long-acting calcium channel blockers.

The following findings were noted through 5.4 years follow-up [31]:

- Mean ambulatory blood pressure remained similar between the groups, and there was no change in nocturnal blood pressure or the proportion of nondippers in patients who continued to take all antihypertensive drugs in the morning. By contrast, patients assigned to take at least one medication at bedtime had significant reductions in both nocturnal blood pressure (from 129/73 to 117/65 mmHg) and the proportion of nondippers (from 65 to 41 percent).

- Taking at least one medication at bedtime resulted in significantly fewer major vascular events, defined as myocardial infarction, stroke, or cardiovascular death (2.7 versus 7.8 percent). Most of the benefit was driven by a significant reduction in the incidence of myocardial infarction (1.5 versus 4.8 percent).

Similar observations have been made in hypertensive patients without CKD, including in the Heart Outcomes Prevention Evaluation (HOPE), in which many subjects took ramipril or placebo at bedtime. (See "Overview of hypertension in adults".)

Serious concerns about this trial include its open-label design and small number of events. In addition, the effect size (a 72 percent reduction in the relative risk of myocardial infarction, stroke, or cardiovascular death) is considerably larger than the true effects of most rigorously studied interventions. As an example, treating hypertensive patients with antihypertensive medications reduces the relative risk of cardiovascular events by 20 to 40 percent [32]. However, there seems to be little downside to taking at least one (nondiuretic) antihypertensive medication at night while awaiting additional data to confirm the clinical benefit.

Maintenance dialysis — The major therapeutic goal in hypertensive dialysis patients is gradual fluid removal to attain "dry weight." (See "Hypertension in dialysis patients".)

SUMMARY AND RECOMMENDATIONS

- Patients with acute glomerular disease tend to be volume expanded and edematous due to sodium retention. As a result, the elevation in blood pressure is thought to be primarily due to fluid overload, as evidenced by suppression of the renin-angiotensin-aldosterone system and enhanced release of atrial natriuretic peptide. (See 'Acute glomerular disease' above.)

- In acute vascular diseases, such as vasculitis or scleroderma, the elevation in blood pressure results from ischemia-induced activation of the renin-angiotensin system rather than volume expansion. (See 'Acute vascular disease' above.)

- In patients with chronic kidney disease (CKD), hypertension is likely due to a combination of factors including sodium retention, increased activity of the renin-angiotensin system, and enhanced activity of the sympathetic nervous system. (See 'Chronic kidney disease' above.)

- The hypertension in acute glomerular disease with edema typically resolves after fluid removal with diuretics or, if necessary, dialysis. By comparison, lowering angiotensin II formation with an angiotensin-converting enzyme (ACE) inhibitor is effective in many patients with vasculitis or scleroderma. (See 'Treatment of hypertension in acute glomerular or vascular disease' above.)

- Goal blood pressure in patients with diabetic and nondiabetic CKD is presented in detail elsewhere. (See "Antihypertensive therapy and progression of nondiabetic chronic kidney disease in adults", section on 'Blood pressure goal' and "Treatment of hypertension in patients with diabetes mellitus".)

- In patients with **proteinuric** (defined as protein excretion above 500 to 1000 mg/day) CKD, we recommend an ACE inhibitor or angiotensin receptor blocker as first-line therapy for the treatment of hypertension (**Grade 1A**). (See "Antihypertensive therapy and progression of nondiabetic chronic kidney disease in adults", section on 'Effect of renin-angiotensin system inhibitors on progression of CKD' and "Treatment of diabetic kidney disease".)

- In patients with proteinuric CKD who also have edema, initial therapy usually consists of both an angiotensin inhibitor for renal protection and a loop diuretic for edema, which, by increasing renin release, may also enhance the antihypertensive effect of the angiotensin inhibitor. In such patients who require additional antihypertensive therapy, we suggest a non-dihydropyridine calcium channel blocker (eg, diltiazem or verapamil) since these drugs also lower proteinuria (**Grade 2C**). (See 'Second- and third-line therapy in proteinuric CKD' above.)

- In patients with proteinuric CKD who do not have edema, we suggest using a diuretic or a non-dihydropyridine calcium channel blocker as second-line, with the other as third-line, therapy if needed (**Grade 2C**). (See 'Second- and third-line therapy in proteinuric CKD' above.)

- In contrast to their renoprotective effects in proteinuric CKD, angiotensin inhibitors do **not** appear to be more beneficial than other antihypertensive agents in patients with **nonproteinuric** CKD [26] (see "Antihypertensive therapy and progression of nondiabetic chronic kidney disease in adults", section on 'Lack of benefit in nonproteinuric CKD'). We therefore use the following approach in patients with nonproteinuric CKD (see 'Sequence of antihypertensive therapy in nonproteinuric CKD' above):

- In patients with nonproteinuric CKD who have edema, we suggest initiation of a diuretic as first-line therapy (**Grade 2C**). Once the edema is controlled, an ACE inhibitor or angiotensin receptor blocker or dihydropyridine calcium channel blocker (eg, amlodipine) can be added in either order if hypertension persists.

- In patients with nonproteinuric CKD who do not have edema, we suggest an ACE inhibitor or angiotensin receptor blocker as first-line therapy (**Grade 2C**). If needed, a dihydropyridine calcium channel blocker and diuretic can be added as second- and third-line therapy, respectively.

- Other antihypertensive drugs can be used as necessary in patients with CKD who have treatment-resistant hypertension. A mineralocorticoid receptor antagonist (spironolactone or eplerenone) is an effective fourth-line agent for the treatment of resistant hypertension in general and in patients with CKD, although these drugs increase the risk for hyperkalemia. (See 'Fourth-line therapy with other agents' above.)

- In patients with CKD who require antihypertensive therapy, we suggest that at least one medication (but not a diuretic) be taken at bedtime rather than taking all medications in the morning (**Grade 2C**). (See 'Possible benefit from nocturnal therapy' above.)

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