Guiding Lights for Antihypertensive Treatment in Patients with Nondiabetic Chronic Renal Disease: Proteinuria and Blood Pressure Levels?

In the United States, about 20 million adults have chronic kidney disease (1). Many also have hypertension, either as a cause or complication of the kidney disease. Recently released guidelines from the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7) recommended aggressive treatment of hypertension to target blood pressure values less than 130/80 mm Hg in patients with chronic kidney disease (2). The guidelines defined chronic kidney disease as either reduced excretory function (estimated glomerular filtration rate < 60 mL/min per 1.73 m^2, corresponding approximately to a creatinine level > 132.6 μmol/L [>1.5 mg/dL] in men or >114.9 μmol/L [>1.3 mg/dL] in women) or the presence of urinary findings, such as albuminuria (>300 mg/d or 200 mg of albumin per g of creatinine). Stated goals of aggressive blood pressure management were to slow deterioration of renal function and prevent cardiovascular disease. Angiotensin-converting enzyme (ACE) inhibitors or angiotensin-receptor blockers were listed as first-line agents of choice for patients with either diabetic or nondiabetic renal disease. The guidelines did not address whether the target blood pressure should vary depending on severity of renal disease.

In this issue, an important and carefully conducted meta-analysis from Jafar and colleagues brings to the forefront three points relevant to the management of patients with nondiabetic kidney disease and hypertension (3). Does urinary protein excretion level affect outcomes? Are blood pressure targets less than 130/80 mm Hg too high? Should clinicians use both urinary protein and blood pressure levels during follow-up to guide management?

In the individual-patient meta-analysis, Jafar and colleagues summarized renal function outcomes from 11 randomized trials that had compared effects of antihypertensive regimens with or without ACE inhibitors. Patients in the trials had high blood pressure, decreased kidney function, or both. They were usually followed for 2 to 3 years. Blood pressure, urine protein levels, and worsening kidney disease (defined as either kidney failure requiring dialysis or a doubling of serum creatinine levels) were monitored regularly. Greater protein excretion and higher systolic, but not diastolic, blood pressure levels were independently related to increased risk for worsening kidney disease. The lowest risks for worsening renal disease were seen in patients with follow-up urine protein levels less than 2.0 g/d and systolic blood pressure levels of 110 to 129 mm Hg. Disease worsened in approximately 5% and 10% of patients with follow-up protein levels less than 2 g/d and 2 g/d or greater, respectively. Disease worsened in approximately 3% and 6% of patients with follow-up systolic blood pressure of less than 130 mm Hg and 130 mm Hg or greater, respectively.

PROTEIN EXCRETION LEVELS

Jafar and colleagues found that the relationship between higher systolic blood pressure and increased risk for kidney disease progression differed in patients with higher and lower levels of protein excretion. In patients who excreted higher levels, the risks for renal disease progression increased markedly in a graded manner when systolic blood pressure levels exceeded 120 mm Hg. In patients who excreted small amounts of protein (<1 g of protein/d), the risks associated with higher systolic blood pressure were not as great and were relatively constant across systolic blood pressures of 110 to 159 mm Hg.

We were not surprised that higher levels of proteinuria portended worse outcomes. Earlier research shows that proteinuria is associated with increased risk for cardiovascular disease and that it is the most important risk factor for progression of chronic kidney disease to end-stage renal disease (4–6). Whether or not hypertension causes the initial renal insult, both proteinuria and hypertension contribute to ongoing maladaptive intrarenal processes that lead to progressive kidney disease. Proteinuria, specifically albuminuria, is linked to both glomerular hyperfiltration and glomerular and tubulointerstitial scarring that are mediated largely through the renin–angiotensin cascade (7). Micropuncture studies in rats show that agents that block the renin–angiotensin system reduce glomerular injury and tubulointerstitial damage (8, 9). Several trials in humans confirm that antihypertensive agents that block the renin cascade processes and reduce proteinuria improve clinical outcomes (10, 11).

BLOOD PRESSURE TARGETS

Jafar and colleagues found that the systolic blood pressure target of less than 130 mm Hg suggested by the JNC-7 may be too high for patients with nondiabetic renal disease who excrete moderate or greater amounts of protein. Trials in patients with chronic renal disease that actually randomly assigned patients to different target levels of blood pressure control provide some, albeit limited, evidence supporting these findings (12, 13). In these trials, lower blood pressure targets were mean arterial pressures of 92 mm Hg or less (equivalent to a blood pressure ≤ 125/75 mm Hg). Subgroup analyses from the Modification of Diet in Renal Disease Study trials showed that only

patients whose urinary protein exceeded 1 g/d had slowed declines in glomerular filtration rates with the lower versus "usual" blood pressure level target (12). A recent trial in African-American patients with hypertensive renal disease showed no slowing of renal disease progression with the lower target (13). However, the investigators noted interactions based on proteinuria level that tended to favor the lower blood pressure target in participants with higher baseline proteinuria levels.

Jafar and colleagues also found that follow-up systolic blood pressure levels less than 110 mm Hg were associated with increased risks for worsening renal disease. No trials in patients with chronic renal disease intentionally test potential harmful effects of "excessive" lowering of blood pressure (systolic blood pressure $<$ 110 mm Hg). More thorough evidence in other patient populations focused mainly on diastolic blood pressure and did not definitively establish whether lowering blood pressures "too much" increased the risk for death or cardiovascular events (14–16). The magnitude of any such risk is probably small and is, at least partially, explained by factors independent of treatment, such as underlying poorer health in patients with the lowest blood pressures (17). Regardless, in our experience, aggressive lowering of blood pressure has some downsides. Some patients say that they feel poorly when their blood pressure is "too low." Others find it difficult to tolerate or pay for the many drugs that are often needed to achieve very low blood pressure targets.

Relying on Levels of Proteinuria and Blood Pressure To Guide Management

Findings of Jafar and colleagues' meta-analysis confirm that both higher systolic blood pressure and protein excretion level reflect pathophysiologic forces that lead to adverse outcomes. The findings suggest that hypertensive patients with chronic renal disease and higher levels of protein excretion merit more aggressive management than do those with lower levels of protein excretion. However, neither blood pressure nor protein excretion level is a perfect marker for effects of interventions on clinical outcomes.

Antihypertensive agents have actions other than lowering blood pressure and reducing proteinuria, and these actions probably have clinical effects independent of both blood pressure and proteinuria reduction (11). Some antihypertensive agents might lower blood pressure but increase proteinuria, and some have varying effects on cardiovascular and renal outcomes. Many antihypertensive agents have proven clinical benefits (18), but certain agents, such as ACE inhibitors and angiotensin-receptor blockers, probably have specific effects on causal pathways and maladaptive processes particularly salient to patients with nondiabetic chronic renal disease. Regardless, pathways that lead people to particular clinical outcomes (for example, end-stage renal disease, coronary heart disease, and strokes) probably differ, even among people who share common risk factors, such as proteinuria and high systolic blood pressure. In the end, reliable estimates of the overall benefits and harms derived from targeting specific threshold protein excretion or blood pressure levels can be made only with very large trials that are designed to test effects of different follow-up targets on various clinical outcomes.

Beholders with skeptically tinted glasses will probably find additional reasons to cautiously translate the findings of Jafar and colleagues into practice. The outcome that was examined was a composite measure that included a laboratory value—doubling of creatinine levels. Numbers of study participants were too small and studies were too short in duration to reliably assess effects on end-stage renal disease and other important outcomes, such as heart attacks, strokes, and death. Confidence intervals for risks associated with particular levels of protein excretion and blood pressure were wide, which limited the ability to precisely determine gradations of risk associated with the various levels. Although sensitivity analyses showed that kidney disease progression was more strongly related to earlier rather than later values of blood pressure, reverse causality was not excluded, and bidirectional effects between blood pressure levels and renal outcomes were likely. The study retrospectively examined data from trials that were designed to test effects of ACE inhibitors on renal outcomes rather than establish target levels of protein excretion and blood pressure. Achieving low protein excretion and blood pressure targets is difficult and expensive, may not be feasible in many patients, and may cause adverse effects. Blood pressure levels and urine creatinine excretion are variable measures; a few measurements at follow-up visits do not give reliable pictures for individual patients.

So, then, what is the significance for clinicians of this meta-analysis? We believe that it adds to accumulating evidence in three areas. First, proteinuria has earned a seat at the table of modifiable cardiovascular risk factors and should not be viewed as only a domain of nephrologists. Second, reducing proteinuria is an important factor for preserving renal function, not only in diabetic patients but also in nondiabetic patients with hypertension. Third, the findings add credence to the following reasonable, although not yet proved beneficial, approach.

Perform dipstick urine testing periodically to detect proteinuria in all patients with hypertension. Measure spot urinary albumin–creatinine ratios in patients with positive dipstick test results. In patients with proteinuria, aim to reduce excretion levels to less than 1 to 2 g/d (that is, a spot urinary albumin–creatinine ratio $\leq$ 1). In patients with chronic renal disease and proteinuria, target systolic blood pressures of 110 to 130 mm Hg. Aim for lower levels within this range, when possible and if tolerated, in patients with protein excretion greater than 2 g/d. Target systolic and not diastolic blood pressures. Although the level to which diastolic blood pressure can be safely reduced while concentrating on systolic blood pressure con-

trol is not clear, achieving target systolic levels of 110 to 130 mm Hg usually decreases diastolic pressure to levels (approximately 60 to 70 mm Hg) that current evidence suggests are reasonably safe. Recognize that some patients have only a partial reduction in proteinuria when they are treated with an ACE inhibitor (19) and that a recent trial suggests added clinical benefits of combining an angiotensin-receptor blocker with an ACE inhibitor, even when systolic blood pressure is controlled to less than 130 mm Hg (20). For patients with hypertension and chronic renal disease, advocate for more, larger, and longer trials that test alternative management approaches and measure diverse clinical outcomes.

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