Update in Nephrology and Hypertension

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This year’s Update in Nephrology and Hypertension incorporates articles on a range of topics: clinical hypertension; proteinuria, lipids, and renal disease; blood pressure, angiotensin II antagonists, and renal disease; smoking and renal disease; hypertension and coronary artery disease; and chronic kidney disease detection.

Clinical Hypertension

Guidelines Advised Physicians on the Care of Patients with High Blood Pressure


The Joint National Committee (JNC) 7 report aimed to provide a current and succinct guide to improving awareness, prevention, treatment, and control of hypertension. In particular, the JNC 7 report offered 2 major changes from the JNC 6 report. First, the committee reclassified blood pressure, and second, it revised the risk stratification treatment recommendations.

The committee defined a normal blood pressure as less than 120/80 mm Hg, a level that previous committees called “optimal.” The committee classified levels that earlier committees called normal and high-normal as prehypertension. They selected the term prehypertension as a wake-up call for physicians and patients to recognize that cardiovascular risk increases continuously with increasing blood pressure. The report also folded stage 3 hypertension into stage 2 hypertension because the committee recognized that patients with blood pressure greater than 160/100 mm Hg required at least 2 medications for control. The committee wanted to encourage physicians to give patients with stage 2 hypertension combination therapy rather than single-drug therapy and then slowly increase the doses.

For patients with prehypertension, every 20/10 mm Hg increase in blood pressure over the entire range of blood pressure doubles the risk for cardiovascular events. Among patients older than 50 years of age, a systolic blood pressure greater than 140 mm Hg increases the risk for cardiovascular disease, and patients greater than 80 years of age may benefit from lowering a systolic blood pressure to 120 mm Hg. Office measurement of blood pressure is likely more accurate than home values for patients at high risk for cardiovascular disease.

Tension is one of the hardest conditions for physicians to treat, partly because success requires precious time in the office to talk with patients about the disease and the goals of treatment.

For patients with stage 1 hypertension (systolic blood pressure, 120 to 139 mm Hg; diastolic blood pressure, 90 to 99 mm Hg) and no other complications, the JNC 7 recommended lifestyle modification to prevent progression to sustained hypertension. Good evidence has shown that weight reduction, sodium restriction, aerobic physical activity, and moderate alcohol consumption reduce blood pressure. The Dietary Approaches to Stop Hypertension (DASH) diet, which is low in saturated fats and high in fruits and vegetables and restricts calories, reduces blood pressure. For patients with prehypertension and diabetes or chronic kidney disease, the JNC 7 recommended aggressive pharmacologic management to reduce blood pressure less than 130/80 mm Hg.

For patients with stage 2 hypertension (systolic blood pressure >160 mm Hg; diastolic blood pressure >100 mm Hg) hypertension, the JNC 7 recommended initial treatment with a diuretic combined with another class of agents, such as those that are now available in fixed combinations. As with stage 1 hypertension, other agents may be as appropriate or more appropriate for initial, as well as subsequent, therapy because of compelling indications in individual patients.

Diabetes, chronic kidney disease, and recurrent stroke are some compelling indications for individualized drug choices. In the diabetic patient, diuretics combined with 1 or several other classes of agents are useful. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin-receptor blockers (ARBs) now have proven benefits beyond reducing blood pressure in patients with diabetes, and they should be part of every regimen in the diabetic patient. These 2 classes of agents preserve kidney function in patients with chronic kidney disease. β-Blockers may be useful in the patient with a history of coronary heart disease.

Most patients will require at least 2 medications for control, but 65% of physicians still try to control blood pressure with 1 drug. Attempting this goal is no longer considered optimal care. Combination therapy is needed to achieve acceptable rates of control. Optimal adherence requires motivation, trust, and physician empathy. Hypertension is one of the hardest conditions for physicians to treat, partly because success requires precious time in the office to talk with patients about the disease and the goals of treatment.
Hypokalemia Was Associated with Increased Risk for Stroke among Patients

Smith and colleagues wanted to determine the risk for ischemic and hemorrhagic stroke associated with serum potassium levels obtained within 1 year before the stroke. They used data from an ongoing population-based, case-control study of stroke among patients in a large health cooperative. The study involved more than 3000 patients 30 to 79 years of age. Of these patients, 718 had a stroke (593 ischemic strokes and 125 hemorrhagic strokes) between July 1989 and December 2000. The controls were 2397 individuals without a history of stroke who otherwise met the same inclusion criteria as those who had strokes.

Smith and colleagues found a greater than 2-fold increase in the odds of ischemic stroke (odds ratio, 2.04 [95% CI, 1.14 to 3.64]) and hemorrhagic stroke (odds ratio, 3.29 [CI, 1.45 to 7.48]) in individuals with hypokalemia. They defined hypokalemia as serum potassium levels of 3.4 mmol/L or greater (normal serum potassium level, 3.5 to 5.0 mmol/L). Few participants were hypokalemic: 3% of those who had ischemic stroke, 6% of those who had hemorrhagic stroke, and 2% of the control group. Stroke risk was not associated with diuretic use.

Since diuretic use was not responsible for the high risk for stroke, serum potassium levels may contribute to disease. Restricted intake of potassium could be responsible for the hypokalemia in study participants. High serum potassium levels are reported to have cardioprotective effects by inhibiting several processes, including free radical formation, proliferation of vascular smooth-muscle cells, platelet aggregation, and arteriolar thrombosis.

Aggressive Education and Treatment Efforts Improved Blood Pressure

This multicenter, double-blind, randomized, active-control, parallel-group trial compared the effects of treatment based on valsartan or amlodipine on blood pressure and cardiovascular end points in hypertension. Follow-up lasted 4 to 6 years or until 1450 patients experienced a primary cardiovascular event. Physicians could add other antihypertensive medications (except for the primary treatment classes) as needed to reach a target blood pressure of less than 140/90 mm Hg. This report was preliminary; final outcomes data are scheduled for later publication.

Julius and colleagues used aggressive educational efforts coupled with a 6-step algorithm to guide drug use. Of 13,449 patients, 92% were taking antihypertensive therapy at entry with a baseline blood pressure of 154/87 mm Hg. In 1051 untreated patients, the baseline blood pressure was 168/95 mm Hg. After 6 months, both groups had indistinguishable blood pressure values, and at 12 months, the mean blood pressure had decreased to 141/83 mm Hg. Subsequent blood pressure for the entire group was 139/80 mm Hg at 24 months and 138/79 mm Hg at 30 months. Achieved blood pressure control exceeded the values that most published large-scale trials have reported, implying that when an explicit blood pressure goal is set and a treatment algorithm is provided, physicians can achieve better control rates than in their regular practice.

Combination therapy was required to achieve these lower goals. By the end of the trial, 85% of patients were receiving at least 2 drugs to achieve blood pressure less than 140/95 mm Hg. Since two thirds of physicians today try to control blood pressure with monotherapy, this study has an important lesson: Physicians need to be willing to increase doses, add medications, and treat patients to achieve a specific goal blood pressure.

Proteinuria, Lipids, and Renal Disease

Microalbuminuria in Patients with Type 1 Diabetes Did Not Imply Inexorably Progressive Nephropathy

Perkins and colleagues aimed to determine the frequency and predictors of a substantial reduction or regression in urinary albumin excretion in patients with type 1 diabetes and microalbuminuria. The study site was the Joslin Clinic, which has a large ongoing cohort study of the natural history of microalbuminuria in patients with type 1 diabetes.

The study involved 386 patients with persistent microalbuminuria, defined as urinary albumin excretion between 30 to 299 μg/min on repeated measurement over a 2-year period. (The investigators estimated urinary albumin excretion by using the albumin-to-creatinine ratio). Perkins and colleagues took subsequent measurements during the next 6 years and grouped the measurements into 2-year periods. They defined regression as a 50% or greater reduction from one 2-year period to the next.

The lowest blood pressure levels were associated with a higher hazard ratio for regression (higher hazard ratios indicate greater regression of microalbuminuria). This finding was not surprising since physicians already knew that reducing blood pressure lowered proteinuria in diabetic patients. Lower levels of hemoglobin A1c (particularly levels < 8%) were also associated with higher hazard ratios for regression. The highest hazard ratio for regression occurred...
when cholesterol levels were less than 5.13 mmol/L (198 mg/dL) and triglyceride levels were less than 1.64 mmol/L (145 mg/dL).

Patients with type 1 diabetes who develop microalbuminuria do not inevitably develop progressive diabetic nephropathy. In more than 50% of patients with new-onset type 1 diabetes, microalbuminuria may regress. Microalbuminuria of short duration is especially likely to regress. Early, aggressive pharmacologic therapy and lifestyle modification are the key to suppressing microalbuminuria into the normal range. This study suggests that indicated therapy may include lipid-lowering drugs, even among patients who do not have overt dyslipidemia.

Pravastatin Prevented Cardiovascular Events in Persons with Mild Chronic Renal Insufficiency

Tonelli and colleagues wanted to determine the safety and effectiveness of pravastatin for secondary prevention of cardiovascular disease in people with mild chronic renal insufficiency. Cardiovascular disease is a common cause of morbidity and death in patients with chronic kidney disease. This study was the first to examine the effects of statins specifically in chronic renal insufficiency.

The post hoc subgroup analysis of the Cholesterol and Recurrent Events (CARE) study, a large randomized trial, involved 1711 people with chronic renal insufficiency (defined as creatinine clearance ≤ 1.25 mL/s, measured by using the Cockcroft–Gault equation), previous myocardial infarction, and total plasma cholesterol levels less than 6.21 mmol/L (<240 mg/dL). Participants received either 40 mg of pravastatin (n = 711) or placebo (n = 1000).

After 59 months, compared with the placebo group, the pravastatin group experienced a 28% reduced risk for major coronary events (hazard ratio, 0.72), a 27% reduced risk in fatal myocardial infarction or confirmed nonfatal myocardial infarction (hazard ratio, 0.72), a 35% reduced need for coronary artery bypass graft surgery or other interventions (hazard ratio, 0.65), and a 38% reduced risk for stroke (hazard ratio, 0.62). The benefit seemed to be independent of the severity of renal insufficiency. Patients with mild to moderate renal insufficiency (defined as having a glomerular filtration rate of ≥0.19 mL·s⁻¹·m⁻²) experienced no statistically significant increase in the plasma concentrations of the statin at this pravastatin dose. The incidence of side effects was similar in the 2 groups.

Tonelli and colleagues’ study, in contrast to other research, did not find mild renal insufficiency to be an independent risk factor for cardiovascular disease. Nonetheless, individuals with renal insufficiency are a large, readily identifiable group that seems to be at increased risk for cardiovascular events. Physicians do not frequently use statins in these individuals, presumably because of concerns about medication-related adverse events. The lower rate of adverse events associated with pravastatin in this group of patients with mild renal insufficiency supports using statins more frequently in mild chronic renal disease.

Atorvastatin Added to a Regimen with ACE Inhibitors or ARBs Reduced Proteinuria and the Progression of Kidney Disease

Various mechanisms seem to contribute to the progression of chronic kidney disease. In addition to control of blood pressure, glucose level, and the amount of proteinuria, dyslipidemia may also contribute to the progression of renal disease. Experimental studies and limited clinical trials have indicated that 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors may reduce the rate of progression of kidney disease. These agents can reduce proliferation of mesangial and vascular smooth-muscle cells, inhibit the production of cytokines and macrophage-stimulating factor, and upregulate nitric oxide in the vascular endothelium. These and other mechanisms may be important in the modulation of inflammatory damage in the kidney.

This small study examined the effects of atorvastatin on proteinuria and progressive kidney disease. Bianchi and colleagues selected 56 nondiabetic patients with moderate renal insufficiency (a mean glomerular filtration rate of about 0.48 mL·s⁻¹·m⁻², estimated from the Cockcroft–Gault formula) and an average proteinuria excretion of 2.2 g/d.

Before randomization, Bianchi and colleagues treated all patients for a 12-month run-in with an ACE inhibitor or ARB, titrated to maximal effective dosage, plus other antihypertensive agents as needed. They then added atorvastatin (10 to 40 mg/d) or placebo. After 12 more months, the patients in the atorvastatin group experienced a continued decrease in urinary protein excretion (from 2.2 g/d to 1.2 g/d; P < 0.01) compared with patients in the placebo group. Creatinine clearance stabilized in the atorvastatin group, while it continued to decrease in the placebo group (from 0.84 to 0.74 mL/s; P < 0.01). The benefits seemed to be an additive effect of ACE inhibitors or ARBs. Renal protective therapy in patients with diabetic and nondiabetic chronic kidney disease should include treatment of dyslipidemia in addition to control of blood pressure and blood glucose.
Systolic Blood Pressure Was a Key Predictor of Renal Outcome in Diabetic Patients


The Reduction of Endpoints in NIDDM [non–insulin-dependent diabetes mellitus] with the Angiotensin II Antagonist Losartan (RENAAL) study, first published a few years ago, involved 1513 patients with type 2 diabetes and established nephropathy assigned to take the ARB losartan. The investigators assigned patients to either losartan or placebo, with other agents added to achieve the goal of a trough blood pressure less than 140/90 mm Hg (trough blood pressure is the measurement taken immediately before the next dosing). The average follow-up was 3.4 years. Losartan decreased the rate of doubling of creatinine levels and decreased the rate of progression to end-stage renal disease.

Bakris and colleagues’ subgroup analysis of the RENAAAL trial focused on the effects of blood pressure on the progression of diabetic nephropathy. It evaluated the effect of baseline and post-treatment systolic blood pressure and diastolic blood pressure and pulse pressure on doubling of serum creatinine levels, incidence of end-stage renal disease, or death. It also explored the implications of dihydropriydine calcium-channel blockers as add-on drugs to control blood pressure in these patients.

Using a Cox proportional hazards regression model, Bakris and colleagues measured the hazard ratio for these outcomes for baseline systolic blood pressure, baseline diastolic blood pressure, and pulse pressure, as well as blood pressure immediately preceding the outcome event. Baseline systolic blood pressure greater than 140 mm Hg increased the risk for end-stage renal disease or mortality by 38% (P = 0.05) compared with baseline systolic blood pressure less than 130 mm Hg. Baseline diastolic blood pressure and pulse pressure less than 60 mm Hg did not predict increased risk for any end point. However, as the pulse pressure increased with systolic blood pressure, risk progressively increased. Patients in the losartan group with a baseline pulse pressure greater than 90 mm Hg had a 53.5% lower risk for end-stage renal disease (P = 0.003) and a 35.5% lower risk for end-stage renal disease or death (P = 0.02) than the placebo group.

Bakris and colleagues’ study showed that baseline systolic blood pressure was a key indicator of renal outcomes in patients with type 2 diabetes. It was the first study to establish a meaningful systolic blood pressure goal for patients with progressive diabetic nephropathy. Consistent with other studies in this Update, achieving systolic blood pressure less than 140 mm Hg will probably require using 3 or more drugs at doses titrated as needed.

Systolic Blood Pressure Goal between 110 and 129 mm Hg May Reduce Kidney Disease Progression


Angiotensin-converting enzyme inhibitors are known to reduce blood pressure and urine protein excretion and slow the progression of chronic kidney disease. Jafar and colleagues wanted to determine the blood pressure and urine protein excretion levels associated with the lowest risk for progression of chronic kidney disease during antihypertensive therapy with and without ACE inhibitors. They pooled data from 11 randomized, controlled trials that compared the effects of any hypertensive regimens with or without ACE inhibitors on 1860 mostly nondiabetic patients with kidney disease. They defined the progression of kidney disease as a doubling of baseline creatinine level or onset of kidney failure.

They performed a multivariate regression analysis to assess the association of blood pressure and urine protein excretion level with kidney disease progression. Among this cohort of patients who were followed for an average of 2.2 years, the measurements associated with the lowest risk for kidney disease progression were systolic blood pressure between 110 and 129 mm Hg and urine protein excretion less than 2.0 g/d. Angiotensin-converting enzyme inhibitors reduced blood pressure and urine excretion to desired levels (relative risk for kidney disease progression, 0.67). Kidney disease was more likely to progress at systolic blood pressure levels greater than 130 mm Hg and urine protein excretion levels greater than 1.0 g/d (P < 0.006). Jafar and colleagues also found that a systolic blood pressure less than 110 mm Hg might be associated with a higher risk for kidney disease progression.

The relationship of higher systolic blood pressure and urine protein excretion as independent risk factors for kidney disease progression was highly statistically significant. Treating systolic blood pressure to less than 130 mm Hg and suppressing urinary protein excretion to less than 1 g/d may be appropriate targets. These findings clearly apply to patients with nondiabetic kidney disease, in whom the risk for progression of kidney disease is greater than the risk for cardiovascular disease.

Dual Blockade of the Renin–Angiotensin System Was Superior to Maximal Recommended ACE Inhibitor Doses for Treating Diabetic Nephropathy


Jacobsen and colleagues wanted to determine whether adding a maximal recommended dose of ARBs offered a more thorough blockade of the renin–angiotensin system in patients with type 1 diabetes and diabetic nephropathy who were already receiving a maximal dose of ACE inhibitors. The randomized, double-blind, crossover trial involved 24 patients with type 1 diabetes and diabetic nephropathy. The patients received either 300 mg of irbesartan once daily or placebo in addition to 40 mg of enalapril once daily for 8 weeks.

At the end of each treatment period, Jacobsen and colleagues measured albuminuria, 24-hour blood pressure, and glomerular filtration rate. They found that adding irbesartan to enalapril resulted in an additional 25% reduction in proteinuria level ($P < 0.001$), an 8 mm Hg reduction in systolic blood pressure ($P = 0.002$), and a 4 mm Hg reduction in diastolic blood pressure ($P = 0.003$). The addition of irbesartan to enalapril did not adversely affect glomerular filtration rate or plasma potassium level. The dual blockade seemed to be safe and well tolerated.

This short-term, 8-week study supported the hypothesis that treatment with both ACE inhibitors and ARBs in maximal dosages offered a synergistic renal and cardiovascular protection that is not obtainable with ACE inhibitors alone in patients with type 1 diabetes and nephropathy. Long-term trials are needed to further establish the role of dual blockade of the renin–angiotensin system and renal and cardiovascular protection.

Jacobsen and colleagues’ study is the first to demonstrate that dual blockade of the renin–angiotensin system achieves better control of albuminuria level and 24-hour blood pressure than maximal recommended doses of an ACE inhibitor alone in patients with diabetic nephropathy. Many small studies have reported additive effects when using suboptimal dosages of both classes of agents. Although this trial used maximal recommended doses of enalapril and irbesartan, the doses of both agents may have been too low. However, dose-ranging studies of the antiproteinuric and antihypertensive effects of these agents at dosages beyond their recommended daily dosages have not been performed. Further studies are needed to determine whether much higher doses of these agents would further reduce proteinuria level beyond optimal blood pressure–lowering effects.

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**Smoking and Renal Disease**

**Smoking Was Associated with Renal Impairment and Proteinuria in a Healthy Population**


Smoking has been associated with renal impairment among patients with diabetes or hypertension, but the effects on a healthy population have been unclear. Briganti and colleagues studied the relationship between cigarette smoking and indicators of kidney damage in a healthy sample of participants who were not diabetic, did not have impaired fasting glucose levels or impaired glucose tolerance, and did not have hypertension. The population-based, cross-sectional study involved 11 247 randomly selected Australian adults. Briganti and colleagues tested the participants for kidney damage (glomerular filtration rate $< 0.58$ mL·s$^{-2}$·m$^{-2}$, determined by using the Cockcroft–Gault equation), and proteinuria (urine protein–creatinine ratio $\geq 0.20$ mg/mg) and measured smoking status with a questionnaire.

After adjustment for potential confounding factors, smoking was statistically significantly associated with renal impairment in men (odds ratio, 3.59) but not in women. Among participants with high-normal systolic blood pressure, smoking was statistically significantly associated with proteinuria (odds ratio ranging from 3.64 to 5.76 for blood pressures of 131.5 mm Hg and 139.5 mm Hg, respectively). Smoking was also associated with high-normal 2-hour glucose levels (odds ratio ranging from 1.76 to 10.84 for glucose levels of 7.0 mmol/L [126.13 mg/dL] and 7.7 mmol/L [138.74 mg/dL], respectively). In addition, for every 10 pack-years of cigarette smoking among current smokers, individuals had a 0.031 mL·s$^{-2}$·m$^{-2}$ decrease in estimated glomerular filtration rate. People with glomerular filtration rates less than 0.58 mL·s$^{-2}$·m$^{-2}$ had almost double the number of pack-years than those with rates greater than 0.58 mL·s$^{-2}$·m$^{-2}$.

In summary, the findings provided strong evidence linking smoking with renal impairment in the healthy population. Discouraging smoking is especially important in those with high-normal systolic blood pressure and 2-hour glucose levels.

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**Hypertension and Coronary Artery Disease**

**Calcium Antagonists Were as Effective as Non–Calcium Antagonists for Treating Hypertensive Patients with Coronary Artery Disease**


Until the International Verapamil-Trandolapril Study (INVEST) trial, the only evidence of benefit from using...
hypertensive agents for patients for coronary artery disease was from subgroup analyses of existing clinical trials. The INVEST trial was the first major trial primarily designed to study hypertensive patients with established coronary artery disease. The multicenter, multicountry, randomized, open-label, blinded, end point study involved 22,576 hypertensive patients with coronary artery disease 50 years of age or older. The patients received either a calcium antagonist strategy (verapamil sustained-release) or a non–calcium antagonist strategy (atenolol). (β-Blockers are the only class of agents approved for secondary cardioprotection, although ACE inhibitors may soon gain approval.) Concomitant therapies—trandolapril or hydrochlorothiazide—were added as needed to reduce blood pressure to 140/90 mm Hg. If diabetes or renal impairment were present, the target blood pressure was 130/85 mm Hg. Also, trandolapril was recommended for patients with heart failure, diabetes, or renal impairment. The primary outcome of the study was a composite end point of death from any cause, nonfatal myocardial infarction, or nonfatal stroke.

After 5 years (mean, 2.7 years per patient), the investigators found no difference in the primary end point between the 2 treatment groups. A total of 2,269 patients had experienced a primary outcome event (9.93% in the calcium antagonist strategy group and 10.17% in non–calcium antagonist strategy group [relative risk, 0.98 (CI, 0.90 to 1.06)]). In addition, 2-year blood pressure control was similar between the groups—65.0% (systolic) and 88.5% (diastolic) of patients in the calcium antagonist strategy group achieved goal blood pressure, and 64.0% (systolic) and 88.1% (diastolic) of patients in the non–calcium antagonist strategy group achieved goal blood pressure. The findings indicated that a β-blocker strategy and a calcium antagonist strategy gave similar cardioprotection.

Patients receiving the verapamil–trandolapril strategy were less likely to develop diabetes than those receiving the atenolol–diuretic strategy. Other major clinical trials in hypertension have demonstrated that patients treated with diuretics or β-blockers experienced an increased incidence of new-onset diabetes during the trial compared with patients receiving ACE inhibitors, ARBs, or calcium antagonists. The question now arises whether physicians should look to treatment strategies that do not carry increased risk for new-onset diabetes. Longer trials are needed to determine whether selected treatment strategies are just delaying the new onset of diabetes or whether they actually prevent diabetes.

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