THE EFFECTIVE PHYSICIAN

Three False Truths?

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Since it is often said that half of what one learns in medical school is not true, it should be useful to review common assumptions that we employ in daily practice. Recent publications have prompted serious discussion about some widely accepted concepts in patient management.

β-Blockers for Hypertension

In England, the National Institute for Health and Clinical Excellence (NICE), in collaboration with the British Hypertension Society, issued new guidelines this summer that discourage the use of β-blockers for the treatment of hypertension in patients without angina.

Clinical researchers examined the results of several large clinical trials to come to new recommendations about treatment strategies for hypertension. Thiazides were more cost effective than β-blockers and, more importantly, β-blockers were found to be inferior to calcium channel blockers and angiotensin-system agents in reducing major cardiovascular events, especially stroke. Most of the studies relied on work with atenolol, and there are some who question whether the data on atenolol should be applied across the entire class of β-blockers.

The new guidelines recommend angiotensin-system agents as first-line treatment for patients under the age of 55 years with noncomorbid hypertension. For patients over age 55 years, the guidelines recommended a diuretic or calcium channel blocker as the first-line agent.

For patients requiring additional agents, an angiotensin-converting enzyme (ACE) inhibitor with either a calcium channel blocker or a diuretic was recommended for all age categories. If three agents are needed, the step therapy called for using all three agents.

ACE Inhibitors, ARBs Offer Renoprotection

The use of ACE inhibitors or angiotensin II receptor blockers (ARBs) as first-line agents for hypertension in patients with diabetes has been incorporated into international practice guidelines and some pay-for-performance programs. This recommendation is based on renoprotective effects that are independent of hypertension control, as demonstrated in clinical studies in the last decade. A recently published metaanalysis has challenged this belief and attributed their effectiveness to hypertension control alone.

The investigators selected 127 studies for the review, 77 of which compared ACE inhibitors/ARB agents with active interventions. When blood pressure differences were reduced by antihypertensive agents in control groups, there was no evidence of additional renoprotective effects. Small benefits were seen in patients with nondiabetic nephropathy, but treatment groups were small. Neither agent affected glomerular filtration rate when compared with other antihypertensive agents. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) in particular stratified data by renal impairment and did not show added benefit of ACE inhibitors or ARBs in subjects with renal insufficiency.

Trials of these agents versus another class of medication did not show differences in progression to end-stage disease or other indicators of function. There was evidence of small benefit on urinary excretion of albumin.

The investigators concluded that ACE inhibitors and ARB agents are effective in protecting diabetic patients from nephropathy by virtue of their antihypertensive effects alone but do not offer intrinsic added value compared with other agents beyond their effectiveness in lowering blood pressure, which should be the most important element in the therapeutic plan for these patients.

Glucose Monitoring for Type 2 Diabetes

Despite widespread use, evidence supporting the home monitoring of glucose for type 2 diabetes is lacking. The 2006 Standards of Care from the American Diabetes Association recommend self-monitoring several times a day for patients who are on intensive insulin regimens, but they also recommend self-monitoring as appropriate to achieve glucose control goals in other patients, despite the lack of evidence guiding frequency or timing of such measurement.

The Fremantle Diabetes Study recently published data related to the effect of glucose self-monitoring in its study population. Nearly 400 patients did not monitor their blood glucose level, while 900 performed self-monitoring at least four times a week. Longitudinal and cross-sectional data did not show significant hemoglobin A_{1c} control differences between the two groups. Patients who attended education classes were five times more likely to self-monitor.

Given the economic impact of self-monitoring and its limited effect, the authors suggest that resources be deployed in other areas designed to improve glycemic control in type 2 diabetes.

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Novel Renin Blocker Effective in Diabetics

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MADRID — Aliskiren, the novel renin-blocking drug, improved 24-hour blood pressure control and showed greater systolic pressure reductions, compared with ramipril, in diabetics with uncontrolled hypertension, according to data presented at the annual meeting of the European Society of Hypertension.

Aliskiren also can be safely combined with the ACE inhibitor in this population, the combination giving the greatest degree of pressure reduction.

Aliskiren works by blocking the renin-regulated conversion of circulating angiotensinogen to angiotensin-1. The new drug (brand name Rasilez) is the first of what may soon be a burgeoning class of renin blockers. It is being considered for approval by regulatory authorities in Europe and the United States.

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Dr. Yagiz Uresin, professor of clinical pharmacology at Istanbul (Turkey) University, presented a multicenter international study of 837 patients with diabetes and hypertension. At baseline, the patients had blood pressures of over 155 mm Hg systolic and 98 mm Hg diastolic.

After a washout period and a 2- to 4-week placebo run-in, the patients were randomized to aliskiren monotherapy, 150 mg/day; ramipril monotherapy, 5 mg/day; or a combination of 150-mg aliskiren plus 5-mg ramipril per day. After 4 weeks, the investigators doubled the doses in all study groups.

After 8 weeks, aliskiren gave mean pressure reductions of 14.7 mm Hg systolic and 11.3 mm Hg diastolic. This was significantly better than the 12.0 and 10.7 mm Hg reductions obtained with ramipril alone. In combination, the two drugs gave mean pressure reductions of 16.6 mm Hg systolic and 12.8 mm Hg diastolic.

Using a target pressure of 130/80 mm Hg, slightly over 8% of the patients in the monotherapy arms could be considered well controlled by the end of the study. Combination therapy bumped this up to 13%. The low number of patients who were able to reach target pressures reflects the difficulty of treating longstanding hypertension in diabetic patients, said Dr. Uresin.

A separate subgroup analysis drawn from the same international cohort showed that aliskiren alone and in combination with ramipril gave significantly better round-the-clock diastolic pressure control than did ramipril alone.

A total of 173 patients—55 on ramipril alone, 57 on aliskiren alone, and 61 on the combination—underwent 24-hour ambulatory monitoring. Using the smoothness index, a scale that measures the consistency of pressure control over a 24-hour period, the investigators found that aliskiren alone and in combination with ramipril provides significantly greater consistency over the course of a day. Smoothness index scores correlate with reversal of left ventricular hypertrophy and carotid artery wall thickening.

The difference between renin blockade and ACE inhibition was greatest in the early morning hours. At 21-24 hours post dose, the renin blocker alone and in combination with ramipril gave significantly better pressure control than did ramipril alone. Systolic pressures remained between 4 and 12 mm Hg below baseline in patients on aliskiren or aliskiren plus ramipril. In the ramipril group, systolic pressure rose to near baseline levels at the end of the 24-hour dosing cycle.

Adverse effects in the new study were similar to those found in earlier trials showing aliskiren as having a low side-effect profile. The impact of side effects was low in all treatment groups, said Dr. Uresin.

About one-third of the patients in each monotherapy group had some untoward effects, the most common being headache, cough, nasopharyngitis, and diarrhea. These were mild and self-limiting in the vast majority. Just over 2% of the ramipril monotherapy group and just under 3% of the aliskiren group had serious side effects; the incidence was reduced to 1.4% for the combination.

The addition of aliskiren to ramipril can cut the incidence of coughing, which is the most common reason patients quit ACE inhibitor therapy. Dr. Uresin pointed out that incidence of cough was just under 5% in the ramipril-alone group, and just over 2% for aliskiren. The rate was 1.8% among those taking the combination. The difference was statistically significant. "This was definitely not expected," said Dr. Uresin. Though the mechanism underlying the cough attenuation is not clear, it may have to do with reduced bradykinin levels following renin blockade, he said. ■