

Inhibitors of the Renin–Angiotensin System: Proven Benefits, Unproven Safety

Drugs that affect the renin–angiotensin–aldosterone system are effective in several important diseases. Using them safely and effectively is a basic clinical skill for physicians who treat chronic disease in adults. Activation of the renin–angiotensin–aldosterone system occurs in essential and renal hypertension and predisposes patients to progressive chronic kidney disease. The main effector peptide of the renin–angiotensin system is angiotensin II, which has neural, renal, cardiovascular, and adrenal effects. Two classes of drugs affect angiotensin II: Inhibitors of angiotensin-converting enzyme (ACE) inhibit its formation, and angiotensin-receptor blockers (ARBs) affect its action on cells. Neither of these classes is 100% effective in achieving its biochemical goal (1). Therefore, which drug class is more effective and what the effect is when the 2 classes are used together are important questions for clinicians.

Angiotensin-converting enzyme inhibitors and ARBs are used for hypertension and in patients with kidney disease. Although both drug classes are highly effective in lowering blood pressure in patients with essential hypertension, their comparative antihypertensive effectiveness and their relative advantages and disadvantages are uncertain. Inhibition of the renin–angiotensin system reduces proteinuria—a risk factor for progression of chronic kidney disease—in part independently of its effect on blood pressure (2). However, whether ARBs are as effective antiproteinuric agents as ACE inhibitors, and whether the combination of both is preferable to either agent alone, is also uncertain.

Two articles in this issue (3, 4) attempt to answer these questions. Through systematic review and meta-analysis, they examine the antihypertensive and antiproteinuric effectiveness of ACE inhibitors and ARBs. Although both of these outcomes are surrogate markers for clinical outcomes, such as end-stage renal disease or heart failure, they also fulfill many of the criteria for reliably predicting adverse outcomes. Both reviews were methodologically strong. They used standardized protocols with predefined criteria; extracted data on study design, interventions, population characteristics, and outcomes; evaluated study quality and applicability; and assessed the strength of the body of evidence for key outcomes, according to the QUOROM (Quality of Reporting of Meta-analyses) guidelines (5).

Matchar and colleagues (3) reviewed the comparative effectiveness of ACE inhibitors and ARBs for treating essential hypertension. They identified 61 clinical studies that directly compared ACE inhibitors with ARBs in adults with essential hypertension, reported an outcome of interest, lasted at least 12 weeks, and enrolled at least 20 patients. Forty-seven were randomized, controlled trials (RCTs); 1 was

a nonrandomized, controlled trial; 9 were retrospective cohort studies; 2 were prospective cohort studies; 1 was a cross-sectional cohort study; and 1 was a case–control study. Not surprisingly, ACE inhibitors and ARBs had similar long-term effects on blood pressure. Rates of use as monotherapy were similar for the 2 drug classes, and they had similar effects on mortality and cardiovascular events, quality of life, lipid levels, progression to diabetes, measures of left ventricular mass and function, and measures of kidney disease. However, these outcomes were studied infrequently over the long term, and the studies did not report important outcomes or results in patient subgroups.

The 2 drug classes did not differ in specific adverse effects, except for cough, a well-recognized complication of ACE inhibitors. In the clinical trials, the absolute rate difference for cough was 6.7%, and the number needed to treat to cause 1 case of chronic cough was 15. Cohort studies probably better reflect clinical practice, but investigators are less likely to systematically question patients about specific symptoms. The incidence of cough was much lower in the cohort studies of ACE inhibitors than in RCTs.

Kunz and associates (4) did a systematic review of the effect of monotherapy and combination therapy on proteinuria. Forty-nine RCTs involving 6181 participants reported results of short-term (1 to 4 months) and longer-term (5 to 12 months) comparisons. Of the 49 RCTs, 12 compared ARBs with placebo, 9 compared them with calcium-channel blockers; 23 compared them with ACE inhibitors and 16 compared them with the combination of ARBs plus ACE inhibitors. Twenty-three trials compared combination therapy with ARBs and ACE inhibitors versus treatment with an ACE inhibitor alone.

Monotherapy with ARBs reduced proteinuria compared with placebo (ratio of means in 5- to 12-month comparisons was 0.66 [95% CI, 0.63 to 0.69]); results were similar when ARBs were compared with calcium-channel blockers. Monotherapy with ARBs and ACE inhibitors reduced proteinuria to a similar degree, albeit less than combination therapy with both drug classes. The ratio of the mean reduction with ARB monotherapy to reduction with combination therapy in 5- to 12-month comparisons was 0.75 (CI, 0.61 to 0.92), and the ratio of combination therapy versus ACE inhibitors was 0.82 (CI, 0.67 to 1.01). The effect on proteinuria was consistent across subgroups. However, most studies included in the meta-analysis were small and of variable quality, and they did not provide reliable data about adverse drug reactions.

A recent large randomized trial adds to the body of evidence. The IMPROVE (Irbesartan in the Management of PROteinuric patients at high risk for Vascular Events)

trial enrolled 405 hypertensive patients with elevated cardiovascular risk with early-stage renal disease and relatively low albumin excretion rates (6). The outcome measure was urinary protein excretion. Adjusted week-20 baseline geometric ratios for ramipril plus irbesartan and ramipril plus placebo did not differ significantly. Taken together, the results of the IMPROVE trial and the systematic review by Kunz and associates indicate that monotherapy with inhibitors of the renin–angiotensin system is sufficient for patients with early-stage renal disease and relatively low albumin excretion, and that combination therapy is effective for patients with heavier proteinuria and may be prescribed in those in whom monotherapy fails to decrease 24-hour urinary protein excretion to less than 0.5 g.

Systematic reviews often discover an evidence deficit about clinically important questions. The reviews by Matchar and colleagues and Kunz and associates are no exception. Assuming that both ACE inhibitors and ARBs are equally effective antihypertensive and antiproteinuric agents, what are their comparative long-term outcomes and adverse consequences? The evidence does not answer this question. In Matchar and colleagues' systematic review concerning essential hypertension (3), the average duration of follow-up exceeded 6 months in only 21 of 61 (34%) head-to-head studies. In these studies, mortality and major cardiovascular event rates were available for only 3322 participants, serious adverse event rates were available for 3829 participants, and quality-of-life measurements were available for 1142 participants. This stunningly low number of participants in long-term comparative studies, the corresponding very low numbers of patients with serious events, and the heterogeneity of the study protocols tell us that we need large, long-term, head-to-head studies of ACE inhibitors versus ARBs.

Drug safety—always an important issue—is even more important in patients with chronic kidney disease. These patients are at high risk because of substantial comorbid conditions and susceptibility to hyperkalemia as the glomerular filtration rate decreases. The combination of ACE inhibitors and ARBs in stage 3 or 4 chronic kidney disease could predispose to hyperkalemia-associated admissions and death, as occurred after physicians began to use spironolactone plus ACE inhibitors in routine care of severe heart failure (7). Forty-five of 49 (92%) studies of the antiproteinuric effects of monotherapy and combination therapy, including the large registration clinical trials, lacked quantitative data on adverse drug reactions (4). Rates of stopping a study medication (defined broadly as discontinuation of therapy for reasons directly linked to the drug, indirectly linked to the drug, or not linked to the drug) is an indirect measure of drug safety. The parallel-group randomized trials provided rates of discontinuation of the study drug for 818 patients in studies of ARBs versus ACE inhibitors, 95 patients in studies of combination therapy versus ARBs, and 34 patients in studies of combination therapy versus ACE inhibitors. These trials tell us next to

nothing about the rates of serious adverse effects from combination therapy.

The most important contribution of these systematic reviews is that they tell us what we do not know. For combination therapy, we have no safety data in chronic kidney disease, and we do not know the rates of progression of chronic kidney disease (other than the surrogate outcome of proteinuria). We need a large-scale, long-term, head-to-head, 3-group RCT comparing monotherapy with ARBs or ACE inhibitors, and with combination therapy involving both ARBs and ACE inhibitors. In the interim, physicians should closely monitor patients—and especially their serum potassium levels—who are using combination therapy with ACE inhibitors and ARBs and have stage 3 or 4 chronic kidney disease. The therapeutic objective should be to reduce proteinuria to less than 0.5 g/d.

In conclusion, although ACE inhibitors and ARBs are effective and comparable antihypertensive and antiproteinuric agents—differing only in a higher incidence of cough with ACE inhibitors—we know far too little about their long-term safety, especially with combination therapy of ACE inhibitors plus ARBs in stage 3 or 4 chronic kidney disease.

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