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ACE Inhibitors or ARBs in Hypertension? In Chronic Kidney Disease? CME

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Learning Objectives

Upon completion of this activity, participants will be able to:

1. Compare the efficacy and adverse effect profile of angiotensin-converting enzyme inhibitors vs angiotensin-receptor blockers in the treatment of essential hypertension.
2. Compare angiotensin-converting enzyme inhibitors vs angiotensin-receptor blockers alone or in combination for the treatment of proteinuria in patients with chronic renal disease.

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from Heart*wire* — a professional news service of WebMD

January 17, 2008 — A pair of articles in the January 1, 2008 *Annals of Internal Medicine* brings together the existing literature to address issues that have persisted since the introduction of angiotensin-receptor blockers (ARBs): namely, when and how these drugs might be advantageous in conditions long served by angiotensin-converting enzyme (ACE) inhibitors.

A meticulous survey of studies found that the two drug classes are about equally safe and effective at managing high blood pressure and have similar effects on other risk factors and clinical outcomes in patients with essential hypertension [1]. It also confirmed that ARBs are less likely to cause coughing, but suggested that the side effect might be less common with ACE inhibitors than randomized trials indicate.

In the setting of chronic kidney disease (CKD), concludes the other study, which is a meta-analysis, ACE inhibitor and ARB monotherapy are similarly effective at reducing proteinuria, but a combination of the two angiotensin-2-suppressing drugs works better than either agent individually [2]. But a blanket recommendation to combine them would be premature, according to the authors, because there is little evidence that the combination would improve clinical outcomes over monotherapy, and the safety of such combination therapy is largely undefined.

The authors of both analyses acknowledge that they have major limitations, particularly the heterogeneity of the combined studies, their limited follow-up times, and spotty data on adverse effects.

"The most important contribution of these systematic reviews is that they tell us what we do not know," notes an accompanying editorial [3]. They suggest that the two drug classes are comparably effective as antihypertensive and antiproteinuric agents, writes **Dr Patrick S Parfrey** (Memorial University of Newfoundland, St John's), but "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."

No "clinically meaningful difference" in hypertension

"With the exception of rates of cough, the available evidence does not strongly support the hypothesis that ACE inhibitors and ARBs have clinically meaningful differences in benefits or harms for individuals with essential hypertension," according to the report's authors, led by **Dr David B Matchar** (Duke Center for Clinical Health Policy Research, Durham, NC).

He and his colleagues analyzed 69 reports based on 61 randomized and observational studies that lasted at least three months and directly compared an ACE inhibitor and an ARB in adults with essential hypertension and evaluated meaningful end points like blood pressure control, treatment compliance, and adverse events.

The strength of evidence was considered high for the observation that the two drug classes are similarly effective at controlling blood pressure. They were comparable in 37 of the 50 studies evaluated for that outcome; 47 of those 50 studies were randomized controlled trials (RCTs).

Also similar were the associated rates of death and cardiovascular (CV) events, quality-of-life measures, successful use of the ACE inhibitor or ARB as the only antihypertensive agent, effects on lipid levels and left ventricular (LV) mass, and risk of dysglycemia or renal dysfunction.

Mortality and CV-event outcomes were available for only nine studies, most of which excluded patients with clinically significant CV disease or comorbidities, the group

reported. Few of the studies followed patients for even as long as a year, and "there were really very limited data about major events, such as heart attack and stroke," Matchar told **heart*wire***.

The two drug classes showed similar risks of headache and dizziness, but ACE inhibitors were about three times more likely to have cough as a side effect, regardless of whether the study was cohort-based or an RCT. But the rates of cough were "dramatically higher" in the RCTs, probably because in RCTs, in contrast to cohort-based studies, patients are more likely to be queried specifically for that side effect, Matchar said.

Rate of cough as a side effect of ACE inhibitor and ARB therapy

Research setting	ACE inhibitor (%)	ARB (%)
Randomized controlled trials	9.9	3.2
Cohort-based studies	1.7	0.6

ARB = angiotensin receptor blocker

Other evidence suggested that patients are more likely to stick with ARBs than with ACE inhibitors when each were given as initial therapy, but "the magnitude of this difference is difficult to quantify," according to the report.

Although any differences in efficacy between the two drug classes are likely to be small, according to Matchar et al, pinning down such small differences might be worth the challenge of mounting a large long-term randomized study, given that small changes in blood pressure are known to have a substantial outcomes effect.

To **heart*wire***
Matchar said, "if there really is a marginal benefit to be had from, say, greater tolerability of ARBs compared with ACE inhibitors, then we really do need some [more definitive] head-to-head studies to show it."

"Encouraging" support for combination therapy in CKD

The other reported study provided "high-quality evidence" that monotherapy with ACE inhibitors or ARBs reduces proteinuria to comparable degrees in patients with CKD, regardless of the underlying cause of renal dysfunction. And, write the authors, led by **Dr Regina Kunz** (University Hospital, Basel, Switzerland), "evidence is encouraging that the combination of the two drugs is more effective, at usual doses, than either drug alone."

The group analyzed 49 RCTs that compared ARBs with ACE inhibitors, a combination of the two drug classes, placebo, or calcium-channel blockers and tracked microalbuminuria and proteinuria over at least four weeks in patients with CKD.

ARBs and ACE inhibitors were similarly effective at lowering proteinuria, ARBs were more effective than calcium-channel blockers, and a combination of ARBs and ACE inhibitors was more effective than either agent alone.

Ratio of means (95% CI)* for change in proteinuria, by randomized therapy, over two follow-up intervals

Randomized therapy	Over 1 - 4 mo	Over 5 - 12 mo
ARBs vs placebo	0.57 (0.47 - 0.68)	0.66 (0.63 - 0.69)
ARBs vs ACE-I	0.99 (0.92 - 1.05)	1.08 (0.96 - 1.22)
ARBs vs CCBs	0.69 (0.62 - 0.77)	0.62 (0.55 - 0.70)
ARB+ACE-I vs ARBs	0.76 (0.68 - 0.85)	0.75 (0.61 - 0.92)

ARB+ACE-I vs ACE-I	0.78 (0.72 - 0.84)	0.82 (0.67 - 1.01)

ACE-I = angiotensin-converting-enzyme inhibitor; ARB = angiotensin-receptor blocker; CCB = calcium-channel blocker
*Ratio of means = ratio of the average treatment effect in the intervention group (either ARBs alone or in combination with ACE inhibitors) relative to the control group (placebo or single-drug comparator), with 95% CI

Only one-third of the reports included details on how adverse drug effects were assessed in the studies; according to the authors, few "presented adverse drug reactions in a structured manner that allowed us to make causal inferences," and 45 of the 49 studies "lacked quantitative data even on more common but less severe adverse drug reactions, prohibiting a reliable estimate of their incidence."

According to Parfrey, the editorialist, the findings from Kunz et al, along with those of the recent Irbesartan in the Management of PROteinuric patients at high risk for Vascular Events (**IMPROVE**) trial [4], suggest 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." However, he cautions, "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. . . . We need a large-scale, long-term, head-to-head, three-group RCT comparing monotherapy with ARBs or ACE inhibitors and with combination therapy involving both ARBs and ACE inhibitors."

The report by Matchar et al notes that coauthor **Dr Douglas C McCrory**
(Duke Center for Clinical Health Policy Research) has received honoraria from AstraZeneca and coauthor **Dr Gregory P Samsa** (Duke Center for Clinical Health Policy Research) holds Pfizer stock or stock options. The article by Kunz et al says that "meetings, literature search, and statistical analysis were supported in part by Novartis" and that coauthor **Dr Johannes F E Mann**
(Munich General Hospital, Germany) has received honoraria from Boehringer-Ingelheim, Novartis, and Aventis and grants from Aventis and Novartis.

Sources

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4. Bakris GL, Ruilope L, Locatelli F, et al. Treatment of microalbuminuria in hypertensive subjects with elevated cardiovascular risk: results of the IMPROVE trial. *Kidney Int*. 2007;72:879-885.

The complete contents of **Heart*wire***, a professional news service of WebMD, can be found at www.theheart.org, a Web site for cardiovascular healthcare professionals.

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Clinical Context

More than 65 million Americans have hypertension, and it is the leading attributable risk factor for death throughout the world. According to the editorialist of the 2 studies reviewed, drugs affecting the rennin-angiotensin system are effective in several important diseases including essential hypertension and chronic renal disease,

and ACE inhibitors and ARBs both affect angiotensin II, with potential for efficacy alone or in combination in both diseases.

The 2 studies comprise a meta-analysis of 61 studies comparing the effectiveness of ACE inhibitors and ARBs in adults with essential hypertension, and a systematic review of 49 RCTs examining short-term and longer-term outcomes of ACE inhibitors and ARBs for proteinuria in patients with chronic renal disease.

Study Highlights

- **Matchar and colleagues (essential hypertension**)
  - Included were studies that directly compared ACE inhibitors and ARBs of any design (RCTs, controlled trials, nonrandomized trials, cohort and case control studies) lasting at least 12 weeks and enrolling at least 20 patients, which provided direct comparison of ACE inhibitors and ARBs.
  - Outcomes examined were blood pressure control, adherence, quality of life, intermediate outcomes, and harms.
  - Of 61 studies analyzed, 47 were RCTs, 9 were retrospective cohort studies, 1 cross-sectional, 1 case control cohort, and 1 nonrandomized trial.
  - Rates of use as monotherapy were similar for the 2 classes of drugs.
  - ACE inhibitors and ARBs had similar efficacy for blood pressure control, with no significant differences in benefits or harms (strength of evidence: high).
  - Quality-of-life measures and adherence were similar for ACE inhibitors and ARBs.
  - There were no consistent differential effects seen for death and cardiovascular events.
  - Both classes of medication had similar effects on lipid levels, left ventricular mass, and risk for dysglycemia or renal dysfunction.
  - Adverse effects of headache and dizziness were similar for the 2 classes.
  - Cough as an adverse effect was 3 times more common with ACE inhibitors, with overall rates much higher in randomized trials (9.9% vs 3.2%) vs cohort-based studies (1.7% vs 0.6%).
  - The number needed to treat to cause 1 case of chronic cough for ACE inhibitors was 15.
  - The average duration of follow-up exceeded 6 months in only one third of the head-to-head studies, and there was a lack of long-term studies.
  - There was a lack of adequate studies reporting adverse effect profile of both medication classes.
- **Kunz and colleagues (chronic renal disease)**
  - Included were RCTs of short-term (1 to 4 months) and longer-term (5 to 12 months) studies involving a total of 6181 patients with microalbuminuria and proteinuria of diabetic origin and other causes and reported changes in proteinuria during follow-up.
  - Trials were at least 4 weeks in duration with parallel group or crossover designs.
  - Excluded were studies of patients who had renal transplantation and those with less than 10 participants.
  - Of 49 RCTs, 12 compared ARBs with placebo, 9 with calcium-channel blockers, 23 with ACE inhibitors, and 16 with the combination of ACE inhibitors and ARBs.
  - 23 trials compared combination ARBs and ACE inhibitors with an ACE inhibitor alone.
  - Monotherapy with ACE inhibitors or ARBs reduced proteinuria to a similar degree but less than combination therapy.
  - Mean reduction in proteinuria with combination vs ARB monotherapy in 5- to 12-month studies was 0.75 vs 0.82 (ratio of means) with ACE inhibitors.
  - Monotherapy with ARBs reduced proteinuria vs placebo, with a ratio of means of 0.57 in 1 to 4 months and 0.69 in 5 to 12 months.
  - Results were similar for ACE inhibitors and ARBs vs calcium-channel blockers.
  - 92% of studies lacked quantitative data on adverse drug reactions.
  - In the absence of safety data on long-term combination therapy with ACE inhibitors and ARBs, therapy should be limited to those with stage 3 or 4 disease with close monitoring of potassium levels.
  - The editorialist concluded that monotherapy with ACE inhibitors or ARBs was sufficient treatment for early-stage renal disease with relatively low albumin exertion, and combination therapy was effective for patients with heavier proteinuria when monotherapy failed to decrease 24-hour urinary protein excretion to less than 0.5 g.

Pearls for Practice

- ACE inhibitors and ARBs are equivalent in efficacy for the treatment of essential hypertension, and ACE inhibitors are associated with a 3 times higher rate of chronic cough.
- ACE inhibitors and ARBs are similar in efficacy for the treatment of proteinuria of chronic renal disease, with the combination being more effective than monotherapy with either drug, but long-term adverse effects are not well documented.