Need to Revisit Step Therapy for ARBs

To the Editor:

We read with interest the article by Yokoyama et al. (April 2007 issue of JMCP) on the effects of a step-therapy program for angiotensin receptor blockers (ARBs) on antihypertensive medication utilization patterns and the cost of drug therapy. The authors reported a saving of $0.03 per member per month with step-therapy intervention that required the use of an angiotensin-converting enzyme inhibitor (ACEI) prior to an ARB in a health plan population of approximately 1 million. However, we have found the conclusions in the study, as well as the editorial, unbalanced and troubling for several reasons.

First, there were several limitations of the study design that would clearly impact the cost-saving results. The authors did outline the limitations. These included the potential costs of member and provider dissatisfaction, pharmacy and prescriber costs associated with requesting a prior authorization or changing to an ARB antihypertensive alternative, costs incurred in visits to the physician to switch therapy, and administrative and resource costs required to run the intervention program. In addition, there were pharmacy costs associated with explaining claim rejections to patients. However, not enough emphasis in the manuscript or accompanying editorial was placed on the fact that rebate contracts on drug costs were not factored into the cost analysis. These significant rebates would neutralize the apparent cost savings for a step-therapy managed care intervention program outlined in this manuscript. This analysis would have helped to present a more balanced case for your readers.

Another factor not addressed satisfactorily in the article was the finding that, of the 1,296 patients who attempted to obtain an ARB under the step-therapy intervention, 6.6% did not receive any antihypertensive therapy within 12 months of the index date. Not taking therapy certainly will save money in the short term, but was stopping antihypertensive medication medically and ethically appropriate for these patients? What was their clinical outcome, and were costs incurred for later cardiovascular medications/interventions? Only pharmacy claims data were considered in the article, and the effects of step-therapy intervention on clinical outcomes, including effective blood pressure (BP) control and/or attainment of the JNC 7 (Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure) BP goal were excluded.

Perhaps more alarming was the accompanying editorial to this article. We have identified several troubling statements and examples of selective literature citing; we have listed a sample below:

- The editorial downplays the limitations of the analysis. Despite the manuscript noting many factors that would negatively impact the apparent cost savings, the editorial claims that the savings are “underestimated.”
- The editorial incorrectly cites a draft report from the Agency for Health Research and Quality (AHRQ), “Comparative long-term benefits and harms of ACEIs versus ARBs for treating hypertension,” ignoring reported differences in BP efficacy and medication persistence between ACEI and ARBs. The report states that there are significant differences in several assessments, including BP lowering, frequency of cough, and persistence. This is perhaps an irrelevant point, since this report is only at the draft stage and has serious limitations that still need to be addressed before it is finalized.
- The editorial questions the long-term safety of ARBs, citing the AHRQ report. However, the report conclusions regarding long-term differences between ACEIs and ARBs are severely limited by the duration and quality of the studies included, with nearly 70% being 6 months’ duration or less.
- The report analyses assume that agents within a class are equivalent (i.e., a class effect) and, therefore, minimize differences among the individual agents and disregard evidence-based medicine. For example, both candesartan and irbesartan have demonstrated greater BP-lowering efficacy over losartan in 2 well-controlled clinical studies at maximum doses, meeting stringent U.S. Food and Drug Administration requirements for superiority claims.
- The editorial selectively cites literature on medication adherence for patients receiving ACEIs. Several studies that were not cited in the editorial demonstrate significantly higher compliance and lower discontinuation rates with ARBs compared with ACEIs. Compliance and adherence are recognized cost drivers for managed health care.

An important point that should be taken into account is that clinical studies with ARBs are more recent than studies with ACEIs, which were conducted in the 1990s, when the prevalence of metabolic syndrome and type 2 diabetes mellitus was considerably less in the United States. There are now data with ARBs in “difficult-to-treat” hypertensive patients that cannot be extrapolated to the older studies with ACEIs in a less severe hypertensive population. In addition, the change in population risk, with higher failure rates with monotherapy and differences in compliance, make the cost estimates unrealistic.

Hypertension control continues to be a tremendous unmet medical need in the United States, with approximately two thirds of the 72 million Americans with high blood pressure not meeting recommended target blood pressure goals. ARBs and ACEIs are integral medications in the antihypertensive armamentarium. Although both drug classes inhibit the renin-angiotensin aldosterone system, important clinical differences exist between the classes as well as within each class that are important for physicians to consider when trying to optimize care for individual patients. In light of the asymptomatic nature of hypertension and often lifelong duration of therapy for individuals who have high blood pressure, artificially limiting the important treatment choices for physicians and patients...
should not be encouraged; decisions as critical as these deserve responsible, well-balanced analyses and careful, thorough review of the available evidence.

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DISCLOSURES
C. Venkata S. Ram and Thomas Giles attest to having no conflicts of interest, including consulting work or receipt of research grants or compensation from pharmaceutical manufacturers.

REFERENCES

The Authors Respond:
Ram and Giles raised concern about the impact of rebates on net drug cost and program savings. While there would be a loss in manufacturer rebates for the formulary angiotensin receptor blockers (ARBs), these offsets were considered before the step-therapy program was implemented. Rebates would only apply to select ARBs, and at the time of the study, net costs of these agents, including rebates, were higher than the cost of generic angiotensin-converting enzyme inhibitors (ACEIs). Regarding Ram and Giles comment on the 6.6% of patients who did not receive any antihypertensive therapy within 12 months of the index date, this finding is consistent with analyses of other step-therapy programs as discussed in the article. More recently, evaluation of an ARB step-therapy program at BlueCross BlueShield of Texas by Gleason et al., presented at the Academy of Managed Care 19th Annual Meeting & Showcase, found that 8.8% of members had no antihypertensive claim in at least 4 months of follow-up.

Although we acknowledge there are limitations in the analysis that were properly addressed, we believe the findings are credible and useful for decision making.

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DISCLOSURES
The author discloses that she completed a fellowship with Novartis Pharmaceuticals Corporation, sponsor of the research discussed in her JMCP article.

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The Editors Respond:
We welcome the opinions of Ram and Giles regarding angiotensin receptor blocker (ARB) step-therapy interventions. In general, step-therapy interventions are becoming increasingly common in administration of pharmacy benefits in the United States. The proportion of large employers with step-therapy edits doubled from 22% in 2000 to 44% in 2004. For the 12-month period through September 30, 2004, step-therapy protocols were reported by 85% of health maintenance organizations,
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two thirds of preferred provider organizations, 79% of Medicaid plans, and about one half of Medicare-risk plans. Hence, there is increasing need to measure clinical, service, and cost outcomes of these interventions, the principal point of the editorial by Curtiss in which a categorical system to rate step-therapy interventions by the degree of restrictiveness was proposed. This categorical system would clearly define the step-therapy intervention according to variables such as the number of first-line therapies required and the scope and method of attestation required of the prescribers.

Regarding specific concerns, Ram and Giles claim that insufficient attention was paid to the effects of rebates on drug cost savings associated with the ARB step-therapy intervention evaluated by Yokoyama et al. Presumably this criticism also applies to Gleason, who reported in the same issue of JMCP even larger drug cost savings from a separate ARB step-therapy intervention. Of note, Yokoyama included the limitation that rebate contracts could offset some of the estimated drug cost savings. Curtiss, in his editorial, did not mention drug manufacturer rebates because these contracts with pharmacy benefit managers and health plans for ARBs acknowledge and allow the widespread use of step-therapy interventions that require prior use with an angiotensin-converting enzyme inhibitor (ACEI). Hence, a rebate of 20%, for example, on ARBs with a typical managed care price of $2.00 per day of therapy still leaves a gap of about $1.40 per day compared with a generic ACEI such as generic benazepril that has a managed care price of $0.40 per day or less. This means that 4 to 5 patients can be treated with a generic ACEI for the cost of treating 1 patient with an ARB. And, of course, from the patient viewpoint, these rebate contracts provide no compensation to members forced to pay higher copayments for brand drugs compared with generic drugs.

We do agree with Ram and Giles that not taking a drug will produce drug cost savings in the short term, and while we are also curious about the outcomes for the 6.6% of patients who did not receive any antihypertensive therapy within 12 months of the step-therapy intervention, this proportion seems small in the context of results of antihypertensive medication adherence studies. Fewer than 50% of even high-risk patients are adherent on both antihypertensive and lipid-modifying drugs within 3 months of starting drug therapy and only about one third at 6 months.

Third, Ram and Giles cast doubt on the assertion that savings from the step-therapy intervention were underestimated. However, the possibility of underestimation of savings is quite clear. Since Yokoyama et al.’s study sample was drawn for only a 6-month period, a program run for a full year would likely have been applied to many more patients, producing additional cost savings. Additionally, Yokoyama et al.’s study sample was limited to continuously enrolled members, who represented only 76% of the patient population to which the program was actually applied.

Fourth, the editorial is accused of ignoring differences in blood pressure reduction efficacy. One is hard-pressed to find better evidence than independent, expert systematic review of all of the available evidence, and to quote from page 31 of the Agency for Health Research and Quality (AHRQ) executive summary, “overall, there was no clear difference in the blood pressure lowering efficacy between the two classes of agents, no matter what criteria were used for study inclusion. Because of the heterogeneity in study protocols, quantitative meta-analysis was not performed.” Although no systematic review is flawless, the U.S. government AHRQ evidence reviews are widely respected in most evidence-based medicine circles as one of the least biased, most inclusive, and most accurate reports available. For Ram and Giles to selectively scoop a few studies from the mass of heterogeneous data reflects a narrow approach; in this case, the forest should be appreciated over the trees.

Although clinical differences may exist within each class particularly with respect to U.S. Food and Drug Administration-approved indications (some agents are indicated for hypertension alone while others have additional renal or cardiac indications), the clinical profiles sufficiently overlap for the ARBs and ACEIs to validate step-therapy in the absence of individual medical necessity. As noted in the AHRQ report (page 11), “The hypothesis that ACEIs and ARBs have clinically meaningful differences in long-term outcomes in individuals with essential hypertension is not strongly supported by the available evidence.” Added to the thorough evaluation of evidence presented in the AHRQ report on comparative effectiveness are the results of retrospective analyses such as Winkelmeyer et al. who found multivariate-adjusted 1-year mortality that was not different between ARB and ACEI users among 14,190 Medicare beneficiaries who received either an ACEI or ARB within 90 days of a myocardial infarction (hazard ratio, 1.04; 95% confidence interval (CI), 0.88-1.22). Regarding the complaint by Ram and Giles that the AHRQ report is presently available only in “draft” form, this is the customary procedure for AHRQ, and readers might consider the confirmatory conclusion from the final 2006 version of the NICE (National Institute for Health and Clinical Excellence) guidelines for hypertension treatment (page 18): “the GDG (guideline development group) felt that the benefits from ACEIs and angiotensin-II receptor antagonists were closely correlated and that they should be treated as equal in terms of efficacy (although, because of cost differences, ACEIs should be initiated first).” It is true that adherence and persistence with antihypertensive therapy are necessary to realize the anticipated efficacy as measured by intermediate outcomes such as blood pressure reduction as well as the hard endpoints of myocardial infarction and cardiovascular-related death. Ram and Giles profess 2 studies to support a claim of superior adherence with ARBs, one a study by Koylan et al. conducted in Turkey that was an outlier among the 17 studies evaluated in the AHRQ report on
comparative effectiveness. The AHRQ report at page 43 concluded, “With the possible exception of the study by Koylan et al., adherence with ACEIs and ARBs was similar (Table 7).” In the second study cited by Ram and Giles, the lisinopril (ACEI) group had a higher severity of illness and greater use of concurrent medication such as antihyperlipidemics, antiplatelet agents, and beta-blockers compared with the valsartan (ARB) group, and the adjusted adherence was statistically significant but not practically significant, 89.9% for lisinopril (95% CI, 89.3%-90.6%) versus 90.1% for valsartan (95% CI, 89.0-91.1%).

For those who prefer trees rather than the forest, we recommend reading the 72 studies referenced in the 57-page AHRQ report on comparative effectiveness of ACEIs and ARBs and the 79 studies referenced in the 98-page NICE hypertension guideline; ACEIs and ARBs are clinically sufficiently similar to allow step therapy. Artificially limiting clinicians’ ability to care for patients by selectively citing literature should be roundly condemned by all; likewise, selectively citing contrar Yo utlier literature to support frivolous expenditure on costly medication that fails to provide unique benefits should be also be denounced in the public forum.

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6. Personal communication with an officer of a pharmacy benefits management company.


The Hickory Project Builds on the Asheville Project—An Example of Community-Based Diabetes Care Management

To the Editor:

We read with interest the recent JMCP commentary calling for managed care organizations (MCOs) and community pharmacies to seize the opportunity to work together in chronic care and disease management. Your readers may be interested in the Hickory Project, a disease management partnership developed to demonstrate the value of using community pharmacists and nurse practitioners as care managers to improve quality measures and positively impact patient health outcomes in Hickory, North Carolina, and the surrounding area. This combined effort includes the coordinating services of American Health Care (AHC), a pharmacy benefit manager and disease management company, and brings together Wells Fargo Insurance Services, community pharmacists, nurses, physicians, and support staff. One of the key functions of AHC is to integrate medical and pharmacy data for patients with diabetes who are enrolled in the disease management program. Lessons learned from the Asheville Project, also in North Carolina, are incorporated into the Hickory Project.

Pharmacists and nurse practitioners in the local community are recruited and held responsible for direct patient contact (to coach, encourage, and educate the patients) with a goal of achieving improved patient care and quality measures as outlined by a patient’s physician and national guidelines. This project involves 9 independent community pharmacies, 7 nurse practitioner clinics, and AHC. Trained clinical professionals meet with each patient monthly to provide education and monitor health progress. The patient’s weight and blood pressure are documented at each meeting, and lab values, self-monitoring blood glucose tests, and medications are reviewed. All interactions are recorded on a patient progress summary.