Choice of Angiotensin Converting Enzyme Inhibitors versus Angiotensin II Receptor Blockers among Hypertensive Adults: Nationally Representative Estimates, 1997-2004

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ABSTRACT

**Background:** A new report finds little evidence of differences in effectiveness between ARBs and ACEIs in treating hypertension. In this study, we develop the implications of the report by examining trends in ARB and ACEI use and by analyzing the patient level characteristics associated with being prescribed an ARB versus an ACEI.

**Methods:** We use nationally representative data from the 1997-2004 Medical Expenditure Panel Survey. Our sample is comprised of adults (age 35+) who reported treatment for hypertension and used a RAAS-modifier. We begin by estimating the total number of persons who purchased an ACEI or an ARB during the year for each year from 1997-2004. Then, we combine data for the years 2002-04 to estimate a multivariate logistic model to identify socioeconomic and clinical factors associated with an increased, or decreased, probability of ARB use.

**Results:** From 1997-2004 the adult population reporting treatment for hypertension increased from 28.6 to 43.0 million persons. The study group, which consisted of those with any RAAS-modifier use, increased from 10.9 to 25.6 million and the proportion using an ARB increased from 10.1 to 35.4%. Among persons who used a RAAS-modifier from 2002-04, men, the uninsured, persons living in the Midwest or west, and patients with diabetes or coronary artery disease were less likely than others to use an ARB.

**Conclusions:** Use of the newly-introduced ARBs increased rapidly despite little evidence of greater effectiveness compared to ACEIs. Among patients with RAAS-modifier use, the ACEI / ARB choice was influenced by both clinical and non-clinical factors.

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Introduction

For more than a decade following their invention in the late-1970s angiotensin converting enzyme inhibitors (ACEIs) were regarded as an innovative class of antihypertensive drugs that had a unique effect on the renin–angiotensin-aldosterone system (RAAS) (Ondetti et al, 1977; Atkinson and Robinson, 1979). In 1995, the first angiotensin II receptor blocker (ARB) was approved for use in the U.S. ARBs work by blocking angiotensin II receptors, rather than inhibiting the angiotensin converting enzyme (Pitt et al, 1997). Although ACEIs and ARBs have relatively similar mechanisms of action, questions remain regarding potential differences in effectiveness and safety between these two classes of RAAS-modifying medications.

A recently completed systematic review sponsored by the Agency for Healthcare Research and Quality (AHRQ) (Matchar et al, 2008), evaluates evidence on the comparative effectiveness of ACEIs and ARBs in the treatment of hypertension. For the majority of patients, the report finds no evidence of improved effectiveness of the newer ARBs compared to ACEIs. In spite of this, previous studies have found that prescriptions for ARBs increased rapidly in the years since their introduction (Stafford et al, 2006; Ma et al, 2006; Fisher et al, 2007).

In this study, we make use of a nationally representative person level database that contains detailed patient characteristics to extend previous research and develop the implications of the AHRQ report in two ways. First, instead of examining prescription-based measures (e.g., total prescriptions per 1000 persons), we use person-level data that allows us to directly examine trends in the total population of patients with ARB and/or ACEI use. Second, within the population of patients who used a RAAS-modifier, we
analyze the patient level characteristics associated with being prescribed an ARB versus an ACEI. Clinicians can better appreciate the significance of the new evidence report when they are aware of existing prescribing patterns for these two related classes of antihypertensive medications, ACEIs and ARBs.

**Data and Methods**

This analysis uses data from the Medical Expenditure Panel Survey (MEPS) for the years 1997-2004, a period following the introduction of the first ARBs in 1995-96. The MEPS, which is sponsored by AHRQ, is an ongoing household survey that began in 1996 and undergoes annual IRB review. As a national probability sample, the MEPS contains unique power in explaining patterns of medical care use. The MEPS collects nationally representative data on health care use, expenditures, sources of payment, insurance coverage, and health status for the U.S. civilian, non-institutionalized population. Individuals are followed for two years and additional demographic and socioeconomic data are collected for all individuals in sampled households through computer-assisted personal interviews (CAPI) during five rounds of interviews. During the years of our study, the annual MEPS response rates ranged from 67 percent in 1997 to 63 percent in 2004. Sample weights are constructed to correct for potential non-response bias (Cohen, 2003).

Data on prescription drug use in the MEPS were collected both directly from households and from a pharmacy follow-back survey. In each survey round, household respondents were asked for the names of all prescribed medications purchased or obtained by each member of the household. Recall is assisted by asking the respondents to gather all of the household’s prescription drug bottles, containers or bags. Then, with
respondent permission, a follow up survey asks pharmacies to provide computerized printouts containing information about each drug mentioned including the medication name and the national drug code (NDC). Each drug mentioned in the MEPS is assigned to therapeutic classifications by using the NDC to link the MEPS PMED data to the Multum Lexicon database, a product of Cerner Multum, Inc\(^1\). The collection and editing of MEPS drug data include detailed consistency checks and benchmarking with other national data sets (Moeller et al, 2001) and the data have been used extensively to examine prescription drug use and expenditures in the U.S. community population (see for example: Haas et al, 2005; Banthin and Miller, 2006; Stagnitti, 2004; Zhan and Miller, 2001).

Household survey respondents also provide information on the condition(s) associated with health care use (e.g., the condition(s) associated with an office visit, a drug purchase, or other healthcare use). One respondent reports for the entire household. Clinical condition data are collected as verbatim text and are then coded by professional coders using the International Classification of Diseases, Ninth Revision (ICD-9). Because they are self-reports, conditions identified by household respondents may not always conform to physician diagnoses. A recent AHRQ study, however, found that in the overwhelming majority of cases there was agreement between the household and provider reported conditions (Machlin et al, 2009). This is particularly true for the types of conditions included in this study which are highly salient to patients and which typically require specific, ongoing treatment. In this study hypertension and selected comorbidities were defined using three digit ICD-9 codes (see Appendix One). In addition to condition variables, we also examined use of five major classes of

\(^1\) Information on the Multum Lexicon is available at [http://www.multum.com/Lexicon.htm](http://www.multum.com/Lexicon.htm).
antihypertensive drugs (ACEIs, ARBs, calcium channel blockers, beta blockers and diuretics) and construct indicator variables for the number of classes used by each person. These indicator variables provide proxy measures of hypertension severity.

**Study Sample**

The study sample is comprised of an unweighted total of 14,703 person-years of data for adults ages 35 and older in the U.S. community population who were reported to have treatment for hypertension and who used a RAAS-modifier. The unweighted number of persons by year are: 1398 in 1997, 1058 in 1998, 1180 in 1999, 1406 in 2000, 2003 in 2001, 2568 in 2002, 2368 persons in 2003, and 2722 persons in 2004. Variations in sample sizes across years reflect both the overall sample size and response rate of the MEPS, in a given year, and the proportion of these samples who used a RAAS-modifier. We combined data for 2002 through 2004, a total of 7658 persons, to estimate the logistic regressions which are reported in Table One.

**Measures**

We constructed two binary indicators identifying patients with any purchase (single ingredient, or combination) of an ACEI or ARB during the year. These indicators are not mutually exclusive; some patients have use of both an ACEI and an ARB during the year.

**Statistical Analysis**

We conducted all statistical analyses using STATA Version 8 (STATA Corp. College Station, Texas) and applied sample weights to develop nationally representative estimates. We first estimated the total number of persons who purchased an ACEI only, an ARB only or both types of drugs in each year from 1997-2004. Then, combining data
for the years 2002-04, we estimated a multivariate logistic model to identify socio-economic and clinical factors associated with an increased, or decreased, probability of ARB use. In the model presented in Table One, we focus our analysis on the choice between an ACEI and an ARB by limiting the sample to persons who used at least one RAAS modifying medication during the year. We include the approximately 5 percent of individuals who used both an ACEI and an ARB and code them as having ARB use. We also test the sensitivity of our results to the exclusion of individuals who used both classes of drugs.

We coded all explanatory variables as binary indicator variables and estimated incremental effects using the method of recycled predictions (Basu and Rathouz, 2005). Estimated effects are reported as absolute (% point) differences in the probability of ARB use between a given group and a reference group (e.g., between persons with private insurance and the uninsured). Standard errors were estimated using the method of balanced repeated replication (BRR) which provides non-parametric estimates of standard errors that properly account for all aspects of complex survey design and that are particularly useful in situations where it is difficult, or impossible, to derive a closed-form solution of the Taylor Series standard error (Rao and Shao, 1999). In addition, BRR standard errors are known to be second order equivalent to bootstrap standard errors (Rao and Shao, 1996). Confidence intervals are thus adjusted to reflect the complex survey

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2 We found that the nature of these associations changed over time, so we focus on recent years of data to provide more relevant information about current patterns of use. We pool three years of data to increase sample size and statistical power.

3 The decision to use an ARB to treat hypertension will usually involve at least two choices: 1) choosing between a RAAS modifying medication, another class of antihypertensive medication or no medication; 2) choosing between and ACEI and ARB.
design of the MEPS. Only results that were significant at p<.05, or better, are discussed in the text. The authors did not receive any external funding for this research.

Results

During the period of our study, we find that 28.7 million adults over age 35 reported treatment for hypertension in 1997 and that figure grew to 43.0 million in 2004. In addition, there was a significant increase in polypharmacy. The proportion using two or more classes of drugs to treat their high blood pressure increased from 41.6 percent in 1997 to 58.5 percent in 2004. Over the same period, the proportion using three or more classes more than doubled from 11.0 to 23.9 percent (data not shown).

In keeping with these trends, the use of both ACEIs and ARBs increased rapidly from 1997 to 2004 (Figure One). In 1997 use of ARBs was limited since they had just been introduced. In that year about 10.9 million hypertensive adults used an ACEI, an ARB or both, representing about 38.2 percent of adults 35 and over reporting treatment for hypertension. Of this total, 1.1 million individuals (10.1%) used an ARB (including 0.2 million who used both an ACEI and an ARB). By 2004, the total population using a RAAS-modifier had more than doubled to 25.6 million or 59.8 percent of all adults, ages 35 and older, who reported treatment for hypertension during the year. About 9.0 million (35.4%) used an ARB (including 1.3 million who reported using both types of RAAS modifiers). Both ARBs and ACEIs had an increase of about 7.9 million persons with any use over this period. This represented more than a 700% increase in ARB use and nearly an 80% increase in ACEI use.
Table One presents results from our logistic model that investigates factors associated with the ACEI-ARB choice in the years 2002-04. Estimates in Table One provide information on differences in the probability of ARB use for a given group relative to a reference group. Results show that among hypertensive adults who used RAAS modifiers, men were 5.7% points (p<.001) less likely than women to use an ARB. Insurance coverage had a strong positive association with ARB use. Individuals with private insurance (13.0% points, p<.001) and Medicaid (5.3% points, p=.04) were both more likely than the full year uninsured to be prescribed an ARB. Individuals in high income families were 5.2 % points (p=.05) more likely to use an ARB than persons living in poor families. Regional patterns were also evident with individuals living in the Midwest (-6.3% points, p<.001) and West (-9.7% points, p<.001) less likely to use an ARB than persons living in the South.

Three comorbidity variables were also associated with ARB use. Individuals who reported diabetes were 4.8% points (p=.002) less likely and individuals who reported coronary artery disease were 6.3% points (p=.003) less likely to be prescribed an ARB than persons without these conditions. Persons with upper respiratory diseases were 4.3% points (p = .02) more likely than others to use an ARB. Finally, persons who used two classes of medications were 6.9% points (p<.001) more likely and persons who used three or more classes of medications were 17.3% points (p<.001) more likely to have used an ARB than those who used a single class of drugs to treat their high blood pressure.

Overall, in the years 2002-2004, about one-third (33.4%) of adults with RAAS-modifier use used at least one ARB during the year. One method of gauging the size of
the associations reported in Table One is to compare them to the mean probability of ARB use. For example, the reduced probability of use for men represents a 17.1% (5.7/33.4) reduction relative to the mean level of ARB use while the increased use for persons with private insurance represents a 38.9% (13.0/33.4%) increase in ARB use relative to the mean.

We re-estimated our model to test the sensitivity of results to the exclusion of persons who used both an ACEI and an ARB during the year. With this exclusion, the results for the high income group lost significance and the magnitude of the association between using two or more, or three or more classes of drugs and ARB use was diminished. Otherwise, excluding individuals who used both an ACEI and an ARB during the year did not result in any qualitative changes in results (data not shown).

**Discussion**

The time period of our study, 1997 to 2004, closely follows the introduction of the first ARBs: losartan (1995) and valsartan (1996). Our findings demonstrate how quickly patterns of use can change after the introduction of a new class of drugs, even when comparative evidence is lacking. During the period of our study, the total population with RAAS-modifier use increased from 10.9 to 25.6 million and the proportion of this population with ARB use more than tripled from 10.1 to 35.4%. Previous researchers found similar increases in prescription-based measures of ARB use (Stafford et al, 2006; Ma et al, 2006; Fisher et al, 2007). It is important to note that the rapid increase in

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4 Previous estimates on trends in ARB use from other nationally representative data sets are very similar to the MEPS. For example, MA et. al. (2006) use the National Ambulatory Medical Care Survey to examine office based physician visits in which antihypertensive drug(s) were prescribed. They find that the percentage of these visits in which an ARB was prescribed increased from about 5% in 1997 to about 23%
RAAS-modifier use occurred concurrently with a large increase in the total population of U.S. adults receiving pharmaceutical treatment for hypertension, and a marked increase in polypharmacy (use of two or more classes of drugs) to treat high blood pressure (Miller and Zodet, 2006).

The prescription drug purchases that we observe in the MEPS data reflect a combination of physician behavior, patient preferences and other factors which we cannot always explain. For example, in our multivariate analyses, we found strong regional variation in ARB use. This is an interesting phenomenon that suggests further research. People with insurance were more likely than the uninsured to purchase ARBs which may reflect differences in medication costs. During the period of our study several ACEIs were available as lower priced generics while all ARBs were still under patent. Insurance coverage can significantly reduce the out of pocket cost of antihypertensive drugs (Blustein, 2000; Adams et al, 2001), and thus mitigate ACEI-ARB cost differences for the insured.

Finally, findings related to comorbidities were generally in accord with the evidence. Increased use of ARBs by patients with upper respiratory diseases may be supported by findings that ARBs cause fewer coughs than ACEIs. Further, the estimated lower ARB use for diabetics potentially concurs with very limited evidence summarized in the AHRQ-sponsored review (Matchar et al, 2008).

There are several data and methodological issues that limit our ability to reach stronger conclusions: our study does not examine ARB use after 2004; the MEPS relies on self-reporting; the data are cross-sectional and we identify associations, not causal in 2004. Using the MEPS, we find that among people who received pharmaceutical treatment for hypertension, the percentage using at least one ARB during the year increased from 4.4% in 1997 to 22.8% in 2004 (data available from author on request).
relationships. In addition, we cannot distinguish between simultaneous and sequential prescribing within the year.

Conclusions

The use of ACEIs and ARBs for the treatment of hypertension increased substantially during the period of our study. Yet the relative increase of ARB use was much larger despite the lack of evidence indicating greater clinical effectiveness. In the most recent years (2002-2004) the choice of ARB vs ACEI was most strongly related to geography, insurance and comorbidities. ARBs were used more in the South (vs west and Midwest) and among insured (vs uninsured) groups. Despite limited evidence, some comorbidities were associated with changes in the probability of ARB use. This merits additional evaluative research in the future.
References


Figure One: Hypertensive Adults Ages 35+ using an ACEI, ARB, or both 1997 to 2004.

Source: Estimates from the 1997-2004 Medical Expenditure Panel Survey, AHRQ.
*The total number of persons using both ACEIs and ARBs was 0.2 million in 1997 and 0.5 million in 1999.
| Table One: Logistic Regression  
Factors associated with ARB use among hypertensive adults ages 35+  
who used a RAAS inhibitor: MEPS 2002-2004 |
|------------------------------|------------------------------|
| % Point Change  
(95% CI) | % Point Change  
(95% CI) |
| Age | MSA |
| 35 to 44 | reference |
| 45 to 54 | -1.0 (-7.4, 5.4) |
| 55 to 64 | -2.9 (-9.9, 4.1) |
| 65 to 74 | -1.2 (-9.0, 6.7) |
| 75 and older | -0.7 (-9.2, 7.9) |
| Census region | Not in MSA |
| South | reference |
| Northeast | -1.8 (-5.0, 1.4) |
| Midwest | -6.3 (-9.6, -3.0) * |
| West | -9.7 (-13.9, -5.5) * |
| Health status | Poor |
| Fair | 0.4 (-3.6, 4.4) |
| Good | 0.7 (-3.6, 4.9) |
| Excellent/very good | reference |
| Co-morbidities | Diabetes |
| Hyperlipidemia | 9.6 (-4.0, 23.3) |
| Renal dysfunction | 2.9 (-9.3, 3.4) |
| Heart failure | CAD |
| Upper Resp. Disease | 4.3 (0.8, 7.8) * |
| Lower Resp. Disease | 1.6 (-7.4, 10.6) |
| Classes of Drugs Used | One |
| Two | 6.9 (3.9, 9.9) * |
| Three or more | 17.3 (13.2, 21.5) * |
| Family income | Year |
| Poor | 2002 |
| Near poor | -5.1 (-8.1, -2.2) * |
| Low income | 2003 |
| Middle income | -0.6 (-2.7, 1.5) |
| High income | 2004 |
| 5.2 (0.0, 10.5) * |

Number of observations = 7,658

Overall percentage with ARB use = 33.4%

Source: Estimates from the 2002-2004 Medical Expenditure Panel Survey, AHRQ.

*Percentage point changes which are statistically significant at p < .05 or better are shown in bold and followed by an asterisk.
† The uninsured have no hospital/physician insurance during the year. Other categories are based on any coverage.
'Private' and 'Medicaid' include Medicare beneficiaries with supplemental policies as well as persons for whom private insurance/Medicaid are their only source of coverage.
‡ Categories are based on family income as a percentage of the Federal poverty line: poor 0 to 100%, near poor 100 to 125%, low income 125 to 200%, middle income 200 to 400%, high income more than 400%.
§ In addition to the variables listed, the model includes the following control variables: year effects; an indicator for persons who were not in the survey for the full year because they died, or entered an institution; and an indicator for persons of Asian, other or mixed races; an indicator for persons with missing education variables (n = 66).
## Appendix One: Definitions of Hypertension and Selected Co-Morbidities

<table>
<thead>
<tr>
<th>Condition</th>
<th>ICD9(s)</th>
<th>Section of ICD9 Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>401</td>
<td>NA</td>
</tr>
<tr>
<td>Diabetes</td>
<td>250</td>
<td>NA</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>272</td>
<td>NA</td>
</tr>
<tr>
<td>Renal dysfunction</td>
<td>580-589</td>
<td>Nephritis, Nephrotic Syndrome and Nephrosis</td>
</tr>
<tr>
<td>Heart failure</td>
<td>428</td>
<td>Ischemic Heart Disease</td>
</tr>
<tr>
<td>CAD</td>
<td>410-414</td>
<td>Chronic Obstructive Pulmonary Disease and Allied Conditions</td>
</tr>
<tr>
<td>Asthma/COPD</td>
<td>490-496</td>
<td>Other Diseases of Upper Respiratory Tract</td>
</tr>
<tr>
<td>Upper Respiratory Disease</td>
<td>470-478</td>
<td>Other Diseases of Respiratory System</td>
</tr>
<tr>
<td>Lower Respiratory Disease</td>
<td>510-519</td>
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