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Robots evolved during the second half of the twentieth century when integrated circuits were first made and computers began to increase in power. The first truly modern robot was invented by George Devol in 1954. It was digitally operable and programmable, and he named it the “Unimate.” In 1960, Devol sold his first Unimate to General Motors; it was installed in a plant in Trenton, New Jersey, to lift and stack hot pieces of metal from a die casting machine. Since then, robots have become an integral part of many industries, performing such tasks as assembly, welding, and packaging. In the medical field, a specialized robot known as the da Vinci allows surgeons to perform complex procedures using a minimally invasive approach. By enhancing surgical capabilities, the da Vinci is improving clinical outcomes and redefining standards of care.

Daniel Buettner chose a group of vintage toy robots from the 1950s and ’60s for the subject of his acrylic painting You Will Be Judged By a Jury of Your Peers. At 33, he is too young to have played with these toys as a child, but the various shapes, sizes, and colors of the robots, as well as the topic of science fiction, inspired him to put brush to canvas. The detailed version of You Will Be Judged By a Jury of Your Peers shows 7 of the 14 robots found in the actual painting. It was part of the “Objects of Affection” exhibition held in February 2007 at the Rosalux Gallery in Minneapolis, Minnesota. Promoted as “A tribute to all things made, bought, sold, and then lost or stolen, but not thrown away,” the exhibit featured the work of Buettner and Ingrid Restemayer, 2 of the 24 artists in the Rosalux collective. Its members have created their own self-sustaining gallery; each artist participates in a 2-person show every year and has a space on the collective’s Web site, www.rosaluxgallery.com.

In describing his artistic style, Buettner says, “Too often artists go through great pains to create paintings that look good, but they are devoid of any real meaning or significance. Having done work of that nature myself, I have become more interested in creating art that is appealing and easily understood.” But looks can be deceiving. With Buettner’s superior artistic skill and the cryptic titles he chooses for his paintings, what seems to be fairly simple at first can become rather complex and mysterious as one ponders the artwork. “I don’t usually explain the meaning or intent of my work—I like to leave the interpretation up to the observer,” he says.

Buettner was born in Green Bay, Wisconsin, and raised in a small town outside of Rochester, New York, and later in Kalamazoo, Michigan. He says that he grew up surrounded by artists, including 4 of his neighbors and the father of one of his friends. Pablo Picasso once said, “Every child is an artist. The problem is how to remain an artist once he grows up.” Buettner recalls, “At a very young age I knew that being an artist was something you could do as a job. In my teen years, my parents started recognizing and nurturing my interest in art. My high school art teacher in Michigan was the first person who really taught me how to draw, and see as an artist sees.” Buettner graduated from Western Michigan University in Kalamazoo, with a BA in art education. He is currently enrolled in a master’s degree program in education at Saint Mary’s University of Minnesota in Minneapolis.

Buettner has been a schoolteacher for the past 9 years, and now teaches art for students in kindergarten through fifth grade in the St. Francis, Minnesota, school district. He has also written and illustrated 2 children’s books, Larry the Band Saw Wants to be Special and Twenty Tails of Jesse and Boo, which have been published independently. In addition, Buettner is working on a young adult novel titled Hindsight is 20/40 about the experiences of a seventh-grade boy. “Over the past few years, I have experimented with making paintings that are meant to be exhibited with works of writing—mainly children’s stories,” he says. Twenty Tails of Jesse and Boo was originally an exhibition of art and literature for people of all ages. This delightful collection of 20 short stories chronicles the adventures of Buettner’s cats, Jesse and Boo, while their owners are at work. The feline friends converse with each other and address childhood topics like the reasons why we cry and why the sky becomes dark at night.

Buettner’s Aunt Marnie, also an artist, has provided him with valuable vocational advice for more than 10 years. He says, “My aunt has been a major supporter of my art career. She understands what it’s like to try to be an artist and still enjoy other aspects of your life like having a family, a home, quality health care, etc.”

Presently, Buettner shows his work exclusively in Minnesota. In addition to the Rosalux Gallery, other galleries that represent him include the Mezzolago Art Gallery in Minneapolis, the Bloomington Art Center, the Hopkins Art Center, and the Albert Lea Art Center.

Sheila Macho
Cover Editor

COVER CREDIT

SOURCE
Interview with the artist.
Use of Secondary Prevention Drug Therapy in Patients With Acute Coronary Syndrome After Hospital Discharge

Helen Y. Lee, PharmD, MBA; Catherine E. Cooke, PharmD, BCPS, PAHM; and Teisha A. Robertson, PharmD, MBA

ABSTRACT

BACKGROUND: Acute coronary syndrome includes life-threatening clinical conditions ranging from unstable angina to non-Q-wave myocardial infarction and Q-wave myocardial infarction that are a major cause of emergency medical care and hospitalization in the United States. The American College of Cardiology/American Heart Association (ACC/AHA) guidelines on the management of patients with unstable angina and non-ST-segment elevation myocardial infarction (2002-2004) recommend (1) angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs) for ACE inhibitor intolerance, (2) beta-blockers, and (3) statins for long-term treatment of patients after an acute coronary event.

OBJECTIVE: To examine rates of use of 3 key evidence-based drug therapies (ACE inhibitors/ARBs, beta-blockers, and statins) after hospital discharge for patients with acute coronary syndromes (ACS).

METHODS: The study cohort was identified using medical claims from commercial health plans within a managed care organization located in the Mid-Atlantic states, with approximately 3.4 million members with medical benefits of whom 1.2 million members (35.3%) had pharmacy benefits. Members were included if they were (1) aged ≥18 years, (2) continuously enrolled with the same commercial plan from January 1, 2003, through December 31, 2005, (3) had any medical claims for hospitalization for ACS defined by International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes 410.xx (acute myocardial infarction) or 411.1 (intermediate coronary syndrome) during the sample identification period from July 1, 2003 through June 30, 2004, and (4) had no medical claims for ACS hospitalizations from January 1, 2003, through June 30, 2003, in any of 10 diagnosis fields on an inpatient hospital claim. Pharmacy claims for ACE inhibitors, ARBs, beta-blockers, and statins were obtained for 18 months following each index date, defined as the earliest ACS diagnosis date during the identification period. Utilization was defined as the member having at least 1 pharmacy claim within each class from index date to 3 months post-index date. Five time periods were examined to assess exposure rates: (a) 0 to 90 days, (b) 91 to 180 days, (c) 181 to 365 days, (d) 366 to 548 days, and (e) 18 months following the index date. ACE inhibitors and ARBs were considered together (i.e., a patient had to have at least 1 pharmacy claim for an ACE inhibitor or an ARB). Logistic regression analyses were used to predict use of the 3 drug classes for patients with different clinical (diagnosis and prior use) and demographic (sex and age) characteristics.

RESULTS: The study cohort included 1,135 patients (0.27% of 424,526 continuously enrolled members) with ACS as defined by ICD-9-CM codes in medical claims from July 1, 2003, to June 30, 2004. Nearly 65% of the sample patients were men (n = 734 men and n = 401 women), with a mean (standard deviation [SD]) age of 63.8 (SD 13.1) years. Of the 1,135 members with ACS, 588 (51.8%) had at least 1 pharmacy claim for an ACE inhibitor or ARB, 725 (63.9%) for a beta-blocker, and 710 (62.6%) for a statin during the 3-month follow-up period; receipt of at least 1 prescription in all 3 classes was found in 339 (29.9%) of patients. Patients who were aged <45 years, 65-79 years, and ≥80 years were significantly less likely than patients aged 45-64 years to receive statins (P<0.05). In addition, patients who were aged ≥80 years were significantly less likely to receive ACE inhibitors/ARBs (P=0.003), beta-blockers (P<0.001), or all 3 classes (P=0.002). Women were less likely than men to receive statins (P=0.004) and all 3 drug classes (P=0.012). Patients with intermediate coronary syndrome were significantly less likely than those with acute myocardial infarction to receive any of the study drugs (P<0.001). Those patients who had used ACE inhibitors/ARBs, beta-blockers, statins, and all 3 drug classes during the 6 months prior to the index diagnosis of ACS were more likely than those without prior use (odds ratios of 12.2, 9.4, 8.3, and 4.9, respectively, P<0.001) to have these medications continued after ACS diagnosis.

CONCLUSION: At 3 months following the index ACS hospitalization, the majority of the patients were not receiving the 3 guideline medication therapies. ACS patients with intermediate coronary syndrome and those aged 80 years or older were less likely to be receiving any of the 3 therapies, and women were less likely than men to receive statin therapy.

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What is already known about this subject

• There is evidence of decreased cardiovascular morbidity and mortality from secondary prevention therapies (ACEIs or ARBs, beta-blockers, and statins) alone and in combination in patients after acute coronary syndromes (ACS).

• Previous research has documented rates of use of the following secondary prevention therapies in patients with ACS at hospital discharge: 57% to 81% for ACE inhibitors, 71% to 79% for beta-blockers, and 35% to 91% for statins.

What this study adds

• In an analysis of real-world use of secondary prevention therapies in the 90 days following a hospitalization for ACS, we found exposure rates of 52% for ACE inhibitors or angiotensin II receptor blockers (ARBs), 64% for beta-blockers, and 63% for statins; these rates are lower than those reported in some studies.

• Only 30% of the patients had at least 1 pharmacy claim in all 3 key drug classes in the 90-day period following the ACS hospitalization.

• At 3 months after discharge, patients with intermediate coronary syndrome and those aged 80 years or older were less likely to be receiving any of the 3 therapies, and women were less likely than men to receive statin therapy.

• During 18 months of follow-up, 65% of ACS patients had at least 1 pharmacy claim for an ACE inhibitor or ARB, 76% for a beta-blocker, 77% for a statin, and 46% for all 3 medication classes.

Note: A commentary on the subject of this article appears on pages 312-15 of this issue, and an editorial appears on pages 316-17.
Cardiovascular (CV) disease continues to be the number one cause of morbidity and mortality in the United States. Unstable angina, non-ST-segment elevation myocardial infarction, and ST-segment elevation myocardial infarction are life threatening CV disorders that are major causes of emergency medical care and hospitalizations in the United States. Guidelines recommend that physicians aggressively manage these diseases to reduce the risk of morbidity and mortality in these patients. The American College of Cardiology/American Heart Association (ACC/AHA) guidelines on the management of patients with unstable angina and non-ST-segment elevation myocardial infarction recommend angiotensin-converting enzyme (ACE) inhibitors, beta-blockers, statins, and antiplatelet therapy for long-term treatment of patients after an acute coronary event.

Numerous clinical trials have demonstrated the value of long-term management with ACE inhibitors, beta-blockers, statins, and aspirin (ASA) in reducing the risk of CV events and mortality in patients after acute coronary syndromes (ACS). Unfortunately, there is evidence that these therapies are neither consistently prescribed when appropriate nor adhered to by patients. It has been shown that use of medications after discharge from hospital is enhanced when the prescription is written at discharge, but it is unknown whether long-term adherence is improved. The present study was conducted to evaluate the use of guideline-recommended pharmacotherapy for patients within a managed care organization (MCO) who have had an ACS.

Study Objectives
The study objectives were to examine (1) rates of exposure to the 3 key evidence-based therapies (ACE inhibitors/ARBs, beta-blockers, and statins) after hospital discharge for patients with ACS and (2) clinical and demographic factors associated with exposure to these drugs.

Methods
Study Population
Medical and pharmacy claims data were obtained from an MCO located in the Mid-Atlantic states with approximately 3.4 million members with medical benefits, of whom 1.2 million members (35.3%) had pharmacy benefits. The study cohort was obtained from the population of members with continuous enrollment within the same commercial plan from January 1, 2003, through December 31, 2005, for medical and pharmacy benefits (N = 424,526). Continuous enrollment within the same plan meant that if members switched from one plan to another within the MCO, they were excluded. Members were included in the cohort if they had at least 1 medical claim for hospitalization from July 1, 2003, through June 30, 2004, with diagnosis of ACS using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes of 411.1 (intermediate coronary syndrome) and 410.xx (myocardial infarction [MI]).

The health plan’s database included a separate file consisting of all inpatient hospitalizations, identified using a combination of room and board revenue codes with length-of-stay (difference between the first and final dates of service) of at least 1 day. In the medical claims database, each patient had up to 10 diagnosis codes for each hospitalization. Patients were included if the ACS code was anywhere within these 10 diagnosis fields; 76.7% of ACS diagnoses were primary, and 88.8% were primary, secondary, or tertiary. Each patient was assigned an index date, which represented the first date of one of the above diagnoses from July 1, 2003, through June 30, 2004. Patients were excluded if they had any inpatient admissions for ACS diagnoses from January 1, 2003, through June 30, 2003 (n = 73), or were aged younger than 18 years (n = 1) on their index date (Figure).

The medical claims dataset contained the following fields: unique de-identified patient number, ICD-9-CM codes for ACS hospitalizations, date of hospital discharge, patient age (as of index date), and patient sex. The pharmacy claims dataset contained the following fields: unique de-identified patient number, patient sex, prescription number, date filled, drug name, drug strength, MCO paid quantity, and number of paid days supplied. All data conformed to Health Insurance Portability and Accountability Act (HIPAA) patient privacy standards, and the dataset was delivered to the researchers with de-identified patient information. The University of Maryland Institutional Review Board assigned exempt status to the research protocol.

Pharmacy Claims Analysis
Pharmacy claims for ACE inhibitors, ARBs, beta-blockers, and statins were identified by drug name (Appendix) from 6 months before through 18 months following each patient’s index date. Utilization was defined as having at least 1 pharmacy claim for any agent in a class during the first 3 months following the index date (defined as day 0). Five time periods were examined to assess use of therapy: -180 to 0 days (6 months prior), 0-90 days (3 months), 0-180 days (6 months), 0-365 days (12 months), and 0-548 days (18 months) following index date. ACE inhibitors and ARBs were considered together (i.e., a patient was considered to have received the target drug therapy if there was at least 1 pharmacy claim for an ACE inhibitor or an ARB). Patients were defined as receiving treatment per guidelines if they had at least 1 pharmacy claim for (1) an ACE inhibitor or ARB, (2) a beta-blocker, and (3) a statin, filled at any time within 3 months following the patient’s index date.

Pharmacy Benefits
There was some variation in the design of pharmacy benefits for these MCO members during the 3-year time period of this study from January 1, 2003, through December 31, 2005. However, the predominant pharmacy benefit plan during the period of this study was a 3-tier copayment plan with a mail-order pharmacy option and copayments per 30-day supply of $10 for generic...
Use of Secondary Prevention Drug Therapy in Patients With Acute Coronary Syndrome After Hospital Discharge

**FIGURE 1** Population of Approximately 1.2 Million Members

Continuous enrollment in same medical and pharmacy plan from January 1, 2003, through December 31, 2005  
N=424,526

Hospitalized ACS patients (identified by ICD-9-CM code 410.xx or 411.1 for the hospital admission) from January 1, 2003, to December 31, 2005  
n=2,142

Included those patients with ACS hospitalization (identified by ICD-9-CM codes 410.xx or 411.1 for the hospital admission) from July 1, 2003, through June 30, 2004  
n=1,208

Excluded: age <18 years  
n=1

After age exclusion  
n=1,207

Excluded: Patients with ACS hospitalizations from January 1, 2003, through June 30, 2003 (identified by ICD-9-CM codes 410.xx or 411.1 for the hospital admission)  
n=73

After exclusion of ACS hospitalizations 6 months prior to study period (final cohort)  
n=1,135

ACS=acute coronary syndromes; ICD-9-CM=International Classification of Diseases, Ninth Revision, Clinical Modification
Use of Secondary Prevention Drug Therapy in Patients With Acute Coronary Syndrome After Hospital Discharge

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Patient Characteristics and Key Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort of Members With Acute Coronary Syndromes</td>
<td>n = 1,135</td>
</tr>
<tr>
<td>Male, number (%)</td>
<td>734 (64.7)</td>
</tr>
<tr>
<td>Age in years, number (%)</td>
<td></td>
</tr>
<tr>
<td>&lt;45</td>
<td>40 (5.5)</td>
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<tr>
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<tr>
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<tr>
<td>Female, number (%)</td>
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<tr>
<td>Mean age [SD] range, years</td>
<td>63.8 [13.1]</td>
</tr>
<tr>
<td>Index diagnosis, number (%)</td>
<td></td>
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<tr>
<td>ICD-9-CM Code</td>
<td>Number of Patients (% of cohort)</td>
</tr>
<tr>
<td>411.1 Intermediate coronary syndrome</td>
<td>846 (74.5)</td>
</tr>
<tr>
<td>410.xx Acute myocardial infarction</td>
<td>289 (25.5)</td>
</tr>
<tr>
<td>Initial</td>
<td>267 (92.4)</td>
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<tr>
<td>Subsequent</td>
<td>10 (3.5)</td>
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<tr>
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<td>12 (4.2)</td>
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<td>Unknown</td>
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<tr>
<td>Number (%) receiving any of the 3 drug therapies in guidelines* within 3 months of index diagnosis</td>
<td>974 (85.8)</td>
</tr>
</tbody>
</table>

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*American College of Cardiology/American Heart Association (ACC/AHA) 2002 guideline update for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction (2002) and ACC/AHA Guidelines for the Management of Patients with ST-Elevation Myocardial Infarction (2004).1,2

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### Statistical Analysis

Statistical analysis included calculations of percentages for discrete variables and means and standard deviations (SD) for continuous variables. Logistic regression analyses were used to predict use of each of the 3 drug classes (at least 1 claim in 3 months of follow-up) for patients with different clinical (i.e., diagnosis and prior use) and demographic (i.e., sex and age) characteristics. Statistical significance was set at an accepted alpha (P < 0.05).

Statistical analysis was performed with Minitab Statistical Software (Minitab, Release 13 Minitab, Inc., State College, Pennsylvania).

### Results

#### Member Demographics

The study cohort included a total of 1,135 patients (0.27% of the member population with continuous enrollment in medical and pharmacy plans) with ACS as defined by ICD-9-CM codes from medical claims data from July 1, 2003, to June 30, 2004. Nearly 65% of the sample patients were men (n = 734 men and n = 401 women), with a mean (SD) age of 63.8 (13.1) years (Table 1). The majority of members were aged between 45 and 64 years (n = 579, 51.0%) followed by those aged 65-79 years (n = 319, 28.1%), those aged 80 years and older (n = 173, 15.2%), and those aged 44 or younger (n = 64, 5.6%). There were disproportionate differences in sex by age category. Proportionately fewer women were aged between 45 and 64 years (40.1%) than were men (56.9%), and more women (26.2%) than men (9.3%) were aged 80 years or older. Almost 75% of the cohort had intermediate coronary syndrome. Of the remaining 25% with acute MI, 92.4% were coded as having an initial MI. PPO and traditional indemnity enrollees constituted 28.4% and 26.7% of the sample, respectively. About 10% of the cohort had an unknown health plan, which included members with a discount program.

#### Drug Use for Secondary Prevention

Of the 1,135 members with acute coronary syndromes, 588 (51.8%), 725 (63.9%), and 710 (62.6%) patients had at least 1 pharmacy claim for an ACE inhibitor/ARB, beta-blocker, and statin, respectively, during the first 90 days post index (Table 2). Of the patients who received therapy at any time during 18 months of follow-up, approximately 80% had their first claim within the first 90-days post-index date. For example, the percentage of study patients with at least 1 pharmacy claim was 79.6% (588 at 90 days/739 at 18 months) for ACE inhibitor/ARBs, 84.6% for beta-blockers, and 81.7% for statins. Of all study patients, 397 (35.0%), 412 (36.3%), and 429 (37.8%) patients had claims for ACE inhibitors or ARBs, beta-blockers, and statins, respectively, both during the 6 months prior to and within the 3 months after ACS discharge. These patients accounted for 67.5% (397/588), 56.8% (412/725), and 60.4% (429/710) of patients with at least 1 pharmacy claim for ACE inhibitors/ARBs,

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**Table 1**: Patient Characteristics and Key Findings

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</table>

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**Drugs**: $20 for preferred brand drugs, and $35 for non-preferred brand drugs. A 90-day supply could be obtained from community pharmacies or mail order for copayments of $20, $40, $70; fewer than 5% of members used mail order. No Medicare+ Choice (Medicare Advantage) plans were offered by the MCO during the study period; 68.5% of Medicare-eligible members (n = 38,749) had the same pharmacy benefits as other commercial members, and 31.5% (n = 17,812) had a senior pharmacy benefit program that provided coverage up to $1,100 in annual expenditures and then discounted price (i.e., 100% copayment) after $1,100 maximum annual benefit.
beta-blockers, and statins, respectively, within 3 months after ACS discharge (Table 2). A little less than one half of the patients who had no use of beta-blockers or statins during the 6 months prior to the index date were receiving them at 3 months, 48.2% and 45.0%, respectively. The percentages of use for ACE inhibitors and all 3 drug classes in patients without prior use were less than 30%. Although more than 85% of patients had at least 1 claim for any of the 3 classes, only 339 (29.9%) of patients had at least 1 pharmacy claim in all 3 classes in the 3 months after ACS discharge; of these patients 37.8% (128/339) had received at least 1 claim in all 3 drug classes within 6 months prior to ACS discharge.

More than 50% of patients aged 45-64 years and aged 65-79 years had at least 1 claim for an ACE inhibitors/ARB, beta-blocker, or statin (Table 3). Within 3 age classes, younger than 45 years, 65-79 years, and 80 years and older, the drug class with the highest prevalence of use was beta-blockers (rates of 57.8%, 62.7%, and 48.0%, respectively). Statins were the most commonly used class in patients aged between 45 and 64 years at 73.2%. Patients with intermediate coronary syndrome and acute MI had a higher use of beta-blockers and statins compared with ACE inhibitors/ARBs. Similarly, patients in HMO, PPO, and POS plans had a higher use of beta-blockers and statins compared with ACE inhibitors/ARBs. In the traditional indemnity plan, the use of each of the 3 classes was about 48%.

Patients in both of the older age categories (aged 65-79 and aged 80 and older) were less likely than patients in the 45-64 year group to receive beta-blockers and statins (P<0.002 for aged 65-79 vs. aged 45-64 and P<0.001 for aged 80 years and older vs. aged 45-64 years, Table 4). Additionally, patients aged 80 years and older were less likely than younger patients to receive ACE inhibitors/ARBs, or all 3 drug classes (P=0.003 and P=0.002, respectively). Patients who were aged younger than 45 years were less likely to receive statins and all 3 drug classes compared with those aged 45-64 years (P=0.032 and P=0.049, respectively). Women were significantly less likely than men to receive statins (P=0.004). Patients who had used a therapy before index diagnosis of ACS were more likely to have that therapy continued after ACS diagnosis. Patients who had used ACE inhibitors or ARBs, beta-blockers, statins, and all 3 drug classes within 6 months before the index diagnosis of ACS were 12.2, 9.4, 8.3, and 4.9 times as likely to have these medications continued after ACS diagnosis, respectively (P<0.001 for all 4 equations). Patients with intermediate coronary syndrome were significantly less likely than patients with acute MI to receive any of the therapies (P<0.001 all comparisons). There were no differences in exposure to therapies based on health plan type except that patients enrolled in a traditional indemnity health plan were less likely to receive statins compared with patients in the HMO plan (P=0.018). Hosmer-Lemeshow goodness-of-fit tests.

### Table 2

**Utilization of Secondary Prevention Drug Therapies in Patients With ACS (N=1,135)**

<table>
<thead>
<tr>
<th>Time Period</th>
<th>ACE Inhibitor or ARB</th>
<th>Beta-blocker</th>
<th>Statin</th>
<th>All 3 Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post ACS discharge use, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 months</td>
<td>588 (51.8)</td>
<td>725 (63.9)</td>
<td>710 (62.6)</td>
<td>339 (29.9)</td>
</tr>
<tr>
<td>6 months</td>
<td>666 (58.7)</td>
<td>783 (69.2)</td>
<td>787 (69.3)</td>
<td>426 (37.5)</td>
</tr>
<tr>
<td>12 months</td>
<td>708 (62.4)</td>
<td>834 (73.5)</td>
<td>834 (73.5)</td>
<td>484 (42.6)</td>
</tr>
<tr>
<td>18 months</td>
<td>739 (65.1)</td>
<td>857 (75.5)</td>
<td>869 (76.6)</td>
<td>525 (46.3)</td>
</tr>
<tr>
<td>Pre ACS discharge use, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 months prior</td>
<td>495 (43.6)</td>
<td>486 (42.8)</td>
<td>510 (44.9)</td>
<td>210 (18.5)</td>
</tr>
<tr>
<td>Post ACS discharge use for patients with prior use, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 months</td>
<td>397 (80.2)</td>
<td>412 (84.8)</td>
<td>429 (84.1)</td>
<td>128 (61.0)</td>
</tr>
<tr>
<td>Post ACS discharge use for patients without prior use, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 months</td>
<td>191 (29.8)</td>
<td>313 (48.2)</td>
<td>281 (45.0)</td>
<td>211 (22.8)</td>
</tr>
</tbody>
</table>

a Number (%) with at least 1 pharmacy claim in the time periods indicated:
- 6 months prior ACS = 6 months before index date through index date
- 3 months post ACS = index date through 3 months after index date
- 6 months post ACS = index date through 6 months after index date
- 12 months post ACS = index date through 12 months after index date
- 18 months post ACS = index date through 18 months after index date

b As a percentage of patients with use of the drug class in the 6 months prior to the index ACS hospitalization.

c As a percentage of patients without use of the drug class in the 6 months prior to the index ACS hospitalization.

ACE=angiotensin-converting enzyme; ACS=acute coronary syndrome; ARB=angiotensin II receptor blocker.
indicated good model fit ($P = 0.519$ for ACE inhibitors/ARBs, $P = 0.953$ for beta blockers, $P = 0.621$ for statins, and $P = 0.899$ for use of all 3 therapy classes).

**Discussion**

Our study evaluated the rates of exposure to 3 evidence-based drug therapies after hospital discharge for patients with ACS in an MCO. We found that 588 (51.8%) of ACS patients had at least 1 pharmacy claim for an ACE inhibitor or ARB during the 3 months following discharge, 725 (63.9%) for beta-blockers, and 710 (62.6%) for statins. Several other studies have examined the proportion of hospitalized cardiac patients discharged on secondary prevention medications.10-12 Birkhead et al. examined processes of care for patients discharged with MI during 2004 and 2005 in England and Wales. Using records extracted from a national audit database, this research found rates of use of 80.5% for ACE inhibitors, 74.1% for beta-blockers, and 91.3% for statins in a group of 57,508 patients during hospitalization.12 Doyle et al. evaluated treatment for 1,356 cardiac ACS patients admitted to Intensive/Coronary Care units in Ireland. Use rates for ACE inhibitors, beta-blockers, and statins at hospital discharge were 57%, 79%, and 73%, respectively.11 Austin et al. abstracted charts from hospital records to evaluate the use of statins at hospital discharge for 7,285 patients with acute MI between April 1, 1999, and March 31, 2001, in Canada. Patients who had relative contraindications to statin therapy, such as liver disease, cholestasis, or treatment with fibrates, were excluded from the analysis. Overall, 2,597 (35.6%) patients received a statin medication at discharge. The authors also reported the use of ACE inhibitors (58.2%) and beta-blockers (71.0%) at discharge.10

The percentage of use in these 3 studies ranged from 57%-81% for ACE inhibitors, 71%-79% for beta-blockers, and 35%-91% for statins.10-12 Our reported use rates are lower than these ranges except for the Austin et al. study that showed an extremely low rate of statin use (36%) after hospital discharge (from April 1, 1999, through March 31, 2001).10 Our lower exposure rates may be explained partly by a difference in methodology. Specifically, the previous studies noted the use of medications at discharge, but we report use based on pharmacy claims within 3 months of discharge for ACS. Patients may have been

### TABLE 3 Number and Percent of Patients Using Secondary Prevention Drug Therapies in 3 Months of Follow-up After ACS Discharge, by Patient Subgroup

<table>
<thead>
<tr>
<th>Age in years, n (%)</th>
<th>ACE Inhibitor or ARB</th>
<th>Beta-blocker</th>
<th>Statin</th>
<th>All 3 Drug Classes</th>
<th>N of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;45</td>
<td>30 (46.9)</td>
<td>37 (57.8)</td>
<td>32 (50.0)</td>
<td>13 (20.3)</td>
<td>64</td>
</tr>
<tr>
<td>45-64</td>
<td>320 (55.3)</td>
<td>405 (69.9)</td>
<td>424 (73.2)</td>
<td>214 (37.0)</td>
<td>579</td>
</tr>
<tr>
<td>65-79</td>
<td>176 (55.2)</td>
<td>200 (62.7)</td>
<td>193 (60.5)</td>
<td>88 (27.6)</td>
<td>319</td>
</tr>
<tr>
<td>≥80</td>
<td>62 (35.8)</td>
<td>83 (48.0)</td>
<td>61 (35.3)</td>
<td>24 (13.9)</td>
<td>173</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sex, n (%)</th>
<th>ACE Inhibitor or ARB</th>
<th>Beta-blocker</th>
<th>Statin</th>
<th>All 3 Drug Classes</th>
<th>N of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>396 (54.0)</td>
<td>478 (65.1)</td>
<td>505 (68.8)</td>
<td>250 (34.1)</td>
<td>734</td>
</tr>
<tr>
<td>Female</td>
<td>192 (47.9)</td>
<td>247 (61.6)</td>
<td>205 (51.1)</td>
<td>89 (22.2)</td>
<td>401</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Prior use, n (%)</th>
<th>ACE Inhibitor or ARB</th>
<th>Beta-blocker</th>
<th>Statin</th>
<th>All 3 Drug Classes</th>
<th>N of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE inhibitor or ARB</td>
<td>397 (80.2)</td>
<td>345 (69.7)</td>
<td>333 (67.3)</td>
<td>211 (42.6)</td>
<td>495</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>277 (57.0)</td>
<td>412 (84.8)</td>
<td>342 (70.4)</td>
<td>181 (37.2)</td>
<td>486</td>
</tr>
<tr>
<td>Statin</td>
<td>293 (57.5)</td>
<td>350 (68.6)</td>
<td>429 (84.1)</td>
<td>197 (38.6)</td>
<td>510</td>
</tr>
<tr>
<td>All 3 drug classes</td>
<td>169 (80.5)</td>
<td>179 (85.2)</td>
<td>176 (83.8)</td>
<td>128 (61.0)</td>
<td>210</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Index diagnosis, n (%)</th>
<th>ACE Inhibitor or ARB</th>
<th>Beta-blocker</th>
<th>Statin</th>
<th>All 3 Drug Classes</th>
<th>N of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>411.1—intermediate coronary syndrome</td>
<td>408 (48.2)</td>
<td>503 (59.5)</td>
<td>503 (59.5)</td>
<td>204 (24.1)</td>
<td>846</td>
</tr>
<tr>
<td>410.xx—acute myocardial infarction</td>
<td>180 (62.3)</td>
<td>222 (76.8)</td>
<td>207 (71.6)</td>
<td>135 (46.7)</td>
<td>289</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Health plan, n (%)</th>
<th>ACE Inhibitor or ARB</th>
<th>Beta-blocker</th>
<th>Statin</th>
<th>All 3 Drug Classes</th>
<th>N of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>HMO</td>
<td>109 (52.7)</td>
<td>139 (67.1)</td>
<td>145 (70.0)</td>
<td>68 (32.9)</td>
<td>207</td>
</tr>
<tr>
<td>PPO</td>
<td>178 (55.3)</td>
<td>212 (65.8)</td>
<td>235 (73.0)</td>
<td>114 (35.4)</td>
<td>322</td>
</tr>
<tr>
<td>POS</td>
<td>117 (60.9)</td>
<td>132 (68.8)</td>
<td>129 (67.2)</td>
<td>75 (39.1)</td>
<td>192</td>
</tr>
<tr>
<td>Traditional indemnity</td>
<td>147 (48.5)</td>
<td>188 (48.5)</td>
<td>145 (47.9)</td>
<td>58 (19.1)</td>
<td>303</td>
</tr>
<tr>
<td>Unknown</td>
<td>37 (33.3)</td>
<td>54 (48.6)</td>
<td>56 (50.5)</td>
<td>24 (21.6)</td>
<td>111</td>
</tr>
</tbody>
</table>

ACE = angiotensin-converting enzyme; ACS = acute coronary syndrome; ARB = angiotensin II receptor blocker; HMO = health maintenance organization; POS = point-of-service; PPO = preferred provider organization.
# Use of Secondary Prevention Drug Therapy in Patients With Acute Coronary Syndrome After Hospital Discharge

## TABLE 4

Logistic Regression Analyses: Predictors of Using Secondary Prevention Drug Therapies During 3 Months of Follow-up\(^*\) (n=1,135)

<table>
<thead>
<tr>
<th>Predictor Variable</th>
<th>ACE Inhibitor or ARB</th>
<th>Beta-blocker</th>
<th>Statin</th>
<th>All 3 Drug Classes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age—odds ratio (95% CI)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;45 yrs</td>
<td>0.84</td>
<td>0.65</td>
<td>0.53</td>
<td>0.50</td>
</tr>
<tr>
<td></td>
<td>(0.46-1.52)</td>
<td>(0.36-1.19)</td>
<td>(0.29-0.95)</td>
<td>(0.25-1.00)</td>
</tr>
<tr>
<td></td>
<td>(P=0.558)</td>
<td>(P=0.168)</td>
<td>(P=0.032)</td>
<td>(P=0.049)</td>
</tr>
<tr>
<td>45-64 yrs</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>65-79 yrs</td>
<td>0.83</td>
<td>0.55</td>
<td>0.55</td>
<td>0.74</td>
</tr>
<tr>
<td></td>
<td>(0.57-1.21)</td>
<td>(0.38-0.80)</td>
<td>(0.37-0.80)</td>
<td>(0.50-1.08)</td>
</tr>
<tr>
<td></td>
<td>(P=0.336)</td>
<td>(P=0.002)</td>
<td>(P=0.002)</td>
<td>(P=0.119)</td>
</tr>
<tr>
<td>≥80 yrs</td>
<td>0.47</td>
<td>0.73</td>
<td>0.27</td>
<td>0.40</td>
</tr>
<tr>
<td></td>
<td>(0.28-0.78)</td>
<td>(0.15-0.42)</td>
<td>(0.17-0.45)</td>
<td>(0.23-0.72)</td>
</tr>
<tr>
<td></td>
<td>(P=0.003)</td>
<td>(P&lt;0.001)</td>
<td>(P&lt;0.001)</td>
<td>(P=0.002)</td>
</tr>
<tr>
<td><strong>Sex—odds ratio (95% CI)</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Female</td>
<td>0.80</td>
<td>0.97</td>
<td>0.65</td>
<td>0.66</td>
</tr>
<tr>
<td></td>
<td>(0.59-1.08)</td>
<td>(0.72-1.31)</td>
<td>(0.48-0.87)</td>
<td>(0.48-0.91)</td>
</tr>
<tr>
<td></td>
<td>(P=0.150)</td>
<td>(P=0.836)</td>
<td>(P=0.004)</td>
<td>(P=0.012)</td>
</tr>
<tr>
<td><strong>Prior use—odds ratio (95% CI)</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE inhibitor or ARB</td>
<td>12.23</td>
<td>1.08</td>
<td>0.75</td>
<td>2.05</td>
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<td></td>
<td>(8.47-17.63)</td>
<td>(0.78-1.50)</td>
<td>(0.54-1.05)</td>
<td>(1.43-2.92)</td>
</tr>
<tr>
<td></td>
<td>(P&lt;0.001)</td>
<td>(P=0.633)</td>
<td>(P=0.098)</td>
<td>(P&lt;0.001)</td>
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<tr>
<td>Beta-blocker</td>
<td>0.85</td>
<td>9.38</td>
<td>1.52</td>
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<td>(0.60-1.21)</td>
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<td>(1.07-2.15)</td>
<td>(0.74-1.58)</td>
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<td>(P=0.366)</td>
<td>(P&lt;0.001)</td>
<td>(P=0.018)</td>
<td>(P=0.695)</td>
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<tr>
<td>Statin</td>
<td>0.59</td>
<td>0.77</td>
<td>0.25</td>
<td>0.98</td>
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<tr>
<td></td>
<td>(0.42-0.83)</td>
<td>(0.55-1.06)</td>
<td>(0.51-1.31)</td>
<td>(0.68-1.41)</td>
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<td>(P=0.003)</td>
<td>(P=0.112)</td>
<td>(P=0.001)</td>
<td>(P=0.915)</td>
</tr>
<tr>
<td>All 3 drug classes</td>
<td>1.67</td>
<td>1.10</td>
<td>0.96</td>
<td>4.92</td>
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<td></td>
<td>(0.96-2.90)</td>
<td>(0.61-1.97)</td>
<td>(0.54-1.73)</td>
<td>(2.89-8.37)</td>
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<td>(P=0.067)</td>
<td>(P=0.753)</td>
<td>(P=0.899)</td>
<td>(P&lt;0.001)</td>
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<td><strong>Index diagnosis—odds ratio (95% CI)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>411.1—intermediate coronary syndrome</td>
<td>0.36</td>
<td>0.26</td>
<td>0.40</td>
<td>0.23</td>
</tr>
<tr>
<td></td>
<td>(0.26-0.50)</td>
<td>(0.10-0.37)</td>
<td>(0.29-0.57)</td>
<td>(0.16-0.32)</td>
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<tr>
<td></td>
<td>(P&lt;0.001)</td>
<td>(P&lt;0.001)</td>
<td>(P&lt;0.001)</td>
<td>(P&lt;0.001)</td>
</tr>
<tr>
<td>410.xx—acute myocardial infarction</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td><strong>Health plan—odds ratio (95% CI)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HMO</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>PPO</td>
<td>1.10</td>
<td>1.03</td>
<td>0.98</td>
<td>1.07</td>
</tr>
<tr>
<td></td>
<td>(0.72-1.67)</td>
<td>(0.68-1.58)</td>
<td>(0.63-1.52)</td>
<td>(0.70-1.62)</td>
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<tr>
<td></td>
<td>(P=0.671)</td>
<td>(P=0.881)</td>
<td>(P=0.926)</td>
<td>(P=0.755)</td>
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<td>POS</td>
<td>1.25</td>
<td>1.04</td>
<td>0.65</td>
<td>1.07</td>
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<td>(0.78-2.00)</td>
<td>(0.64-1.68)</td>
<td>(0.40-1.05)</td>
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<td>(P=0.356)</td>
<td>(P=0.878)</td>
<td>(P=0.075)</td>
<td>(P=0.763)</td>
</tr>
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<td>Traditional indemnity</td>
<td>1.00</td>
<td>1.31</td>
<td>0.54</td>
<td>0.62</td>
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<td></td>
<td>(0.61-1.65)</td>
<td>(0.80-2.16)</td>
<td>(0.33-0.90)</td>
<td>(0.37-1.04)</td>
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<td>(P=0.095)</td>
<td>(P=0.285)</td>
<td>(P=0.018)</td>
<td>(P=0.072)</td>
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<td>Unknown</td>
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<td>0.76</td>
<td>0.84</td>
<td>0.84</td>
</tr>
<tr>
<td></td>
<td>(0.39-1.23)</td>
<td>(0.43-1.35)</td>
<td>(0.45-1.56)</td>
<td>(0.45-1.56)</td>
</tr>
<tr>
<td></td>
<td>(P=0.211)</td>
<td>(P=0.348)</td>
<td>(P=0.198)</td>
<td>(P=0.587)</td>
</tr>
</tbody>
</table>

*Binary logistic regression analysis of 4 outcomes; dependent variable is >1 claim in therapy class from index date through 3 months after index date. Cells show odds ratio (95% CI), with reference category = 1.

Hosmer-Lemeshow goodness-of-fit for ACE inhibitors or ARBs (\(P=0.519\)), beta blockers (\(P=0.953\)), statin (\(P=0.621\)), all 3 drug classes (\(P=0.899\)).

ACE = angiotensin-converting enzyme; ACS = acute coronary syndrome; ARB = angiotensin II receptor blocker; CI = confidence interval; HMO = health maintenance organization; POS = point-of-service; PPO = preferred provider organization.
prescribed appropriate pharmacotherapy at discharge, but failed to fill the prescription. According to the AHA, an estimated 12% of patients are prescribed therapy but do not have their prescription filled. In addition, a large percentage of our study patients received therapy prior to their ACS hospitalization and may have had enough medication supply to cover the first 3 months post discharge.

There is evidence of the benefits of combination therapy in decreasing cardiovascular mortality. Although we did not look at combination therapy or whether these medications were taken concurrently, we report in our study that 339 (29.9%) of patients had at least 1 pharmacy claim in all 3 classes. A study of a nationwide registry of patients admitted to intensive care units for acute MI in France found that only 27% received an ACE inhibitor, antplatelet agent, beta-blockers, and statin at discharge. We did not evaluate antplatelet therapy because much of this utilization is in the form of over-the-counter aspirin, which is not covered by the MCO.

Our study noted differences in the use of secondary prevention pharmacotherapy based on demographic variables. Patients in the higher age categories (65-79 years and ≥80 years) were less likely to receive beta-blockers and statins compared with patients in the 45-64 year category. Patients in the highest age category of ≥80 years were also less likely to receive ACE inhibitors/ARBs compared with patients in the 45-64 year category. Men were more likely than women to receive statins.

In an observational cohort of patients admitted with MI in 2004-2005, Birkhead et al. found that the proportion of patients not receiving secondary prevention drugs during hospitalization increased with age. There were 14.2% to 26% fewer patients using ACE inhibitors, beta-blockers, or statins in the age category ≥85 years compared with the younger group aged 55-64 years. Austin et al. reported that patients who were not prescribed a statin after acute MI were older (mean age 70 years for those who were not prescribed a statin compared with 64 years for those prescribed a statin, P<0.001), and a higher percent was female (40% of those not prescribed a statin and 29% of those prescribed a statin were women, P<0.001). Doyle et al. analyzed gender differences in 1,356 hospitalized cardiac ACS patients and noted far fewer women in the study, 28%, compared with men, 72%; and the average age was 6 years higher for women (69 years) than for men (63 years, P<0.001). The authors reported no difference in the use of ACE inhibitors and beta-blockers in men and women. However, they found a 6% difference between men and women in the use of statins, and the odds of being prescribed a statin were 35% higher for men than for women after adjustment for age and total cholesterol (P=0.043).

Another study by Fonarow et al. found that among patients discharged from U.S. hospitals following an acute MI, patients who were prescribed lipid-lowering agents were significantly younger (average age 63.4 years) than patients not prescribed lipid-lowering agents (average age 70.1 years; P<0.001). Lipid-lowering treatment rates were 43.6% in patients aged <55 years, 33.4% in patients aged 65-74 years, 22.8% in patients aged 75-84 years, and 9.7% in patients aged older than 84 years. Women were also less likely to be treated with lipid-lowering medications (34.8% of men were discharged on lipid-lowering therapy vs. 26.8% of women).

In addition to demographic characteristics, we report differences in use rates based on index diagnosis. Patients with MI were more likely to receive secondary prevention therapy with ACE inhibitors/ARBs, beta-blockers, and statins compared with patients with ICS. A recent study, published last month, evaluated the patient characteristics associated with medical therapy at hospital discharge for ACS. The use of optimal medical therapy (defined as discharge on antiplatelet/anticoagulant, beta-blocker, lipid-modifying agent, and ACE inhibitor in those without contraindications) was reported in 35.8% (2,091/5,833) of patients during October 2002-December 2003. This study found that patients who had a previous MI had a 35.0% rate of use of optimal medical therapy compared with a 30.9% rate for those without previous MI (P<0.001). The authors reported that patients presenting with ST-elevation MI and those with more extensive coronary artery disease, as reflected by prior MI or coronary revascularization, were more likely to be given aggressive medical treatment. Another study by Roe et al. found that high-risk clinical features, such as positive cardiac markers, were associated with use of ACE inhibitors, beta-blockers, and lipid-lowering agents (P<0.05).

Limitations
Foremost among the study limitations is the absence of clinical information about these patients that might explain the reasons (e.g., medication intolerance or contraindication) that a given patient did not have a pharmacy claim for 1 or more of the 3 classes of drugs recommended for management of patients with ACS. This limitation may result in underestimates of appropriate use.

Second, we did not assess hospital utilization in the follow-up period after the index hospitalization. Some patients may have received medication during a rehospitalization; this medication would not be recorded in outpatient pharmacy claims. Other patients may have received physician samples during outpatient visits. Therefore, our rates of use of the 3 target medication classes may under-report actual use.

Third, 43.3% of our study population was aged 65 years or older, raising the possibility that pharmacy claims data were incomplete for Medicare-eligible members. The study MCO did not offer any Medicare+ Choice (Medicare Advantage) plans during the study period. Approximately 68.5% of Medicare-eligible members had the same pharmacy benefits as other commercial members, and 31.5% had a senior pharmacy benefits program that provided coverage up to $1,100 in annual expenditures and then discounted prices after $1,100 that were not funded.
Use of Secondary Prevention Drug Therapy in Patients With Acute Coronary Syndrome After Hospital Discharge

(i.e., 100% copayment). Because members had incentives to submit claims (i.e., to obtain discount prices) even after reaching the cap, we believe that the MCO’s pharmacy claims are complete for Medicare-eligible members.

Fourth, it is possible that patients did not receive the 3 classes of guideline medication therapies concomitantly since only 1 pharmacy claim for each medication was required, and there was no requirement for concomitant use or overlap of the medications. Fifth, our data may under-report physician prescribing of the 3 guideline therapies because we did not examine medical records to determine if medications were prescribed but not dispensed to patients who failed to fill prescriptions. Sixth, we do not know the patient’s complete medical history and whether this was their first ACS event.

Conclusion
The majority of patients with a diagnosis of ACS received therapy with at least 1 of the classes of secondary prevention medications. However, 70% of patients were missing at least 1 of the guideline medication therapies. The largest discrepancies in the use of guideline medications appear to be by age, sex, and index diagnosis. Those aged 65–79 years were less likely than those aged 45–64 to receive a beta-blocker or a statin, and those aged ≥80 years were less likely than younger patients to be receiving any of the therapies. Women were less likely than men to receive statin therapy. Patients with MI were more likely to receive any of the therapies compared with patients with intermediate coronary syndrome. Future research should attempt to explain the differences in use of these secondary prevention therapies by demographic factors, evaluate adherence and persistence, and determine cost-effective interventions to improve use of the 3 secondary prevention therapies.

DISCLOSURES
The authors report no external funding for this study. All authors contributed approximately equally to the writing and revision of the manuscript. Helen Lee was primarily responsible for study concept and design, with assistance from Catherine Cooke and Teisha Robertson. Lee and Robertson were responsible for data collection, and Cooke was primarily responsible for data interpretation, with assistance from Lee and Robertson.

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REFERENCES

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### Appendix

#### List of Drugs for Which Pharmacy Claims Were Obtained

**Beta Blockers**
- acebutolol
- atenolol; atenolol with chlorthalidone
- betaxolol
- bisoprolol; bisoprolol with HCTZ
- carvedilol
- labetalol
- metoprolol; metoprolol with HCTZ
- nadolol
- pindolol
- penbutalol
- propranolol; propranolol with HCTZ
- sotalol
- timolol; timolol with HCTZ

**Statins**
- atorvastatin
- atorvastatin with amlodipine
- fluvastatin
- lovastatin; lovastatin with niacin
- pravastatin
- rosuvastatin
- simvastatin; simvastatin with ezetimibe

**ACEIs and ARBs**
- benazepril; benazepril with HCTZ
- benazepril with amlodipine
- candesartan; candesartan with HCTZ
- captopril; captopril with HCTZ
- enalapril; enalapril with HCTZ
- enalapril with felodipine
- eprosartan
- fosinopril; fosinopril with HCTZ
- irbesartan; irbesartan with HCTZ
- lisinopril; lisinopril with HCTZ
- losartan; losartan with HCTZ
- moexipril; moexipril with HCTZ
- monopril; monopril with HCTZ
- olmesartan; olmesartan with HCTZ
- perindopril
- quinapril; quinapril with HCTZ
- ramipril
- trandolapril; trandolapril with verapamil
- valsartan; valsartan with HCTZ
ABSTRACT

BACKGROUND: Accelerated bone loss is a well-known outcome of chronic treatment with glucocorticoids, making glucocorticoid-induced osteoporosis a significant cause of morbidity and a burden on health care resources. Recommendations for prevention and treatment of glucocorticoid-induced osteoporosis include therapy with a bisphosphonate or calcitonin for patients taking a prednisone equivalent of 5 mg per day or more for 3 months or more.

OBJECTIVE: To evaluate the effects of a targeted member and physician educational intervention on the use of anti-osteoporotic drug therapy in patients using chronic oral glucocorticoid therapy.

METHODS: Pharmacy claims were analyzed for a 4-month period in each of 3 years, for claims with dates of service from April 1 through July 30, 2003, May 1 through August 31, 2004, and February 4 through May 5, 2005, to identify all adult members of a health plan of approximately 1.3 million patients using chronic oral glucocorticoid therapy.

RESULTS: The prevalence of health plan members at risk of glucocorticoid-induced osteoporosis was 0.28% in 2003, 0.29% in 2004, and 0.29% in 2005, and 0.29% during the 3 years combined. Approximately 47.5% of patients (n = 5,140) during the 3-year period who received chronic glucocorticoid therapy also received drug therapy for prevention or treatment of osteoporosis. Women made up 59.6% (6,450/10,822) of patients who received chronic glucocorticoid therapy during the 3 years; 50.9% (3,285/6,450) of the female patients, and 54.8% (2,397/4,372) of the male patients on chronic glucocorticoid therapy during the 3 years; 50.9% of female patients and 54.8% of male patients were at risk. The intervention involved direct-to-patient mailing of a cover letter and a 2-page educational brochure, and a physician mailing that included the same 2-page educational brochure, a 1-page table of recommended drug therapies for prevention of osteoporosis, and an invitation for physicians to request by fax-back a list of at-risk patients. Follow-up claims analyses were conducted for 120 days after each of the 3 intervention periods to determine the number and percentage of target patients who were initiated and maintained on a medication to prevent osteoporosis.

What is already known about this subject

- The use of oral glucocorticoids, such as prednisone, during a period as short as 90 days contributes to the reduction in bone mineral density and has been associated with increased risk of vertebral, hip, forearm, and non-vertebral fractures. The rate of increased risk varies with type of fracture and the dose and duration of therapy with glucocorticoids.

What this study adds

- During 3 years of observation, from 2003 through 2005, 0.29% of health plan members received 90 days or more (chronic) therapy with an oral glucocorticoid, and 47.5% of these patients also received an anti-osteoporosis drug.
- Slightly more than half of the patients who received 90 days or more of glucocorticoid therapy were at increased risk of fracture due to the absence of anti-osteoporosis therapy; 50.9% of female patients and 54.8% of male patients were at risk.
- Using a pre-post study design without a control group, a simple intervention program using direct-to-patient and physician mailings was associated with 6% to 9% (7.1% during 3 years) of targeted at-risk patients starting anti-osteoporosis drug therapy following the intervention.
- Only 4.9% of targeted physicians (accounting for 6.8% of at-risk patients) who received the mailing requested a list of their patients at risk for glucocorticoid-induced osteoporosis. The number of physicians contacted regarding patients at risk for glucocorticoid-induced osteoporosis decreased from 2,153 in 2003 to 1,202 in 2004 and 625 in 2005. However, the number of patients at risk for glucocorticoid-induced osteoporosis remained relatively constant: 1,782 (48.9%) in 2003, 2,191 (61.0%) in 2004, and 1,709 (47.6%) in 2005.

3-Year Results of a Member and Physician Intervention to Reduce Risk Associated With Glucocorticoid-Induced Osteoporosis in a Health Plan

Mona M. Chitre, PharmD, CGP, and William Hayes, BS

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Osteoporosis is a disease characterized by low bone mass and structural deterioration of bone tissue resulting in bone fragility and an increased susceptibility to fractures, especially of the hip, spine, and wrist. Osteoporosis is a major public health issue that affects an estimated 10 million Americans.\(^1\) It has a large economic impact in the United States because of the loss of productivity and independence following fractures. The estimated national direct expenditure for osteoporotic fractures is $18 billion per year in 2002 dollars, and costs are rising due to the aging population in the United States.\(^2\)

Osteoporosis may be primary (postmenopausal or age-related) or secondary to an identifiable cause, such as a drug, a disease, or a condition.\(^2\) Osteoporosis affects women disproportionately, with a 4-to-1 female-to-male ratio,\(^1\) and most commonly affects those aged >50 years.\(^3\) Efforts at preventing osteoporosis have been directed primarily at minimizing accelerated bone loss during menopause and the early postmenopausal period in women, leaving other patient populations potentially overlooked. The common causes of secondary osteoporosis, which can occur in patients of all age groups, include hypogonadism (men), hyperparathyroidism, thyrotoxicosis, malnutrition, malabsorption, chronic immobilization, rheumatoid arthritis, alcoholism, vitamin D deficiency, and chronic glucocorticoid therapy.\(^2\) The most frequent cause of drug-induced osteoporosis is chronic glucocorticoid therapy.\(^4-7\) Glucocorticoids alter bone metabolism such that bone formation is reduced and resorption is increased, leading to rapid bone loss after initiation of therapy.\(^8\)

Decreases in bone mineral density have been demonstrated after as little as 90 days of treatment with glucocorticoids and with a daily dose of as little as 5 mg of prednisolone or its equivalent.\(^9\) In a large cohort study of 244,235 patients receiving oral glucocorticoids, the rate of vertebral fracture in glucocorticoid users (0.3%, \(n=1,033\)) was higher than that in 244,235 control patients who did not receive oral glucocorticoids (0.1%, \(n=465\)), relative risk [RR] = 2.60, 95% confidence interval [CI], 2.31-2.92).\(^10\) In addition, the risk of fractures is dose related; patients taking higher daily doses of oral glucocorticoids (i.e., at least 7.5 mg per day of prednisolone or equivalent) had significantly increased risk of non-vertebral fractures compared with low-dose (i.e., <2.5 mg per day of prednisolone or equivalent): absolute rate 2.6 fractures per 100 person-years for the high-dose group versus 1.6 fractures per 100 person-years in the low-dose group, RR = 1.44, 95% CI, 1.34-1.54), hip fractures (RR = 2.21, 95% CI, 1.85-2.64), and vertebral fractures (RR = 2.83, 95% CI, 2.35-2.40).\(^7\)

Table 1 lists risk factors for glucocorticoid-induced osteoporotic fractures. The American College of Rheumatology (ACR) Ad Hoc Committee on Glucocorticoid-Induced Osteoporosis in 2001 published recommendations for prevention and treatment of this disease.\(^11\) The recommendations of this committee, last updated in 2001, include lifestyle changes (e.g., weight-bearing exercise, smoking cessation, and reduction of alcohol consumption), supplementation with calcium and vitamin D, and therapy with bisphosphonates (Table 2). Hypogonadal patients receiving long-term glucocorticoids should receive hormone replacement therapy or testosterone. Treatment with a bisphosphonate is recommended for all men and postmenopausal women who receive long-term glucocorticoid treatment with 5 mg or more per day of prednisone or its equivalent, as well as for men and postmenopausal women receiving long-term glucocorticoids in whom the bone mineral density T-score at either the lumbar spine or hip is below normal.\(^11\) Furthermore, the committee recommends that therapy to prevent or treat bone loss should be continued as long as the patient continues to receive glucocorticoids.

Despite the availability of effective therapies for glucocorticoid-induced osteoporosis prevention and treatment, and ACR's recommendations for prevention and treatment of glucocorticoid-induced osteoporosis, studies have shown that many patients receiving glucocorticoid therapy do not receive prophylaxis. In a study of 295 men receiving glucocorticoids for more than 3 months, bone mineral density testing was performed for less than half of the patients (44.1%) and less than one fourth (23.5%) were taking bisphosphonate therapy.\(^12\) A study of 224 patients within a managed care population found that 37.9% of members receiving long-term glucocorticoid therapy had no documented intervention aimed at osteoporosis prevention, with men less likely than women to receive such an intervention (56.2% of men and 21.8% of women had no documented intervention).\(^13\) In a retrospective cohort study of 3,031 patients (60.3% women) within a large managed care population (450,000 members) identified as receiving a glucocorticoid and at risk for osteoporosis, bone mineral density testing was performed in 9.6% of the

### TABLE 1

**Risk Factors for Fracture in Patients Taking Steroids**

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<tr>
<td>Age</td>
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<tr>
<td>Previous osteoporotic fracture</td>
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<tr>
<td>Family history of osteoporosis</td>
<td></td>
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<tr>
<td>Hypogonadism</td>
<td></td>
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<tr>
<td>Smoking</td>
<td></td>
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<tr>
<td>Low body weight</td>
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<tr>
<td>Poor health and/or frailty</td>
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<tr>
<td>Inadequate calcium intake</td>
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<tr>
<td>Inadequate vitamin D intake</td>
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<tr>
<td>Inadequate exercise</td>
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<tr>
<td>Alcohol intake (&gt;2 drinks per day)</td>
<td></td>
</tr>
<tr>
<td>Dose and duration of glucocorticoids</td>
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</tr>
</tbody>
</table>

Patients (13.0% of women and 4.9% of men), and antiresorptive medications other than hormone replacement therapy were dispensed to 14.5% (18.3% of women and 8.9% of men).14

Data from a survey completed more than a decade ago by 194 U.S. physicians (including 30 family practitioners, 52 internists, 25 gastroenterologists, 18 nephrologists, 33 rheumatologists, 16 neurologists, and 20 pulmonologists), a 49% response rate, revealed that while 80% of the physicians were aware that postmenopausal women have an increased risk of fracture during glucocorticoid therapy, only 10% considered it an important risk for males and 25% for premenopausal women.15 In addition, differences were noted in physicians’ knowledge and attitudes toward glucocorticoid-induced osteoporosis by specialty. Physicians with the greatest experience in prescribing glucocorticoids (e.g., rheumatologists and pulmonologists) were the most likely to report that they would prescribe preventive treatments for osteoporosis.15 As this retrospective survey suggests, barriers to effective prophylaxis and treatment of glucocorticoid-induced osteoporosis may include lack of recognition by physicians of the frequency of glucocorticoid-induced osteoporotic fractures in men and premenopausal women or a lack of awareness of the existence and effectiveness of prophylactic therapy.13,14,16,17

We implemented an intervention program with the goal of increasing awareness of the risk of glucocorticoid-induced osteoporosis and the importance of its prevention in this health plan with approximately 1.3 million members in 2003 and 1.2 million members in 2005. The objectives of the program were to: (1) identify members receiving glucocorticoids and at risk for glucocorticoid-induced osteoporosis; (2) create awareness among members and physicians about the risk of glucocorticoid-induced osteoporosis; and (3) educate members and physicians about the options for preventing and treating this drug-induced disease, with the goal of increasing the use of preventative medications in patients who are receiving chronic glucocorticoid therapy.

### Methods

Members of Excellus BlueCross BlueShield at risk for glucocorticoid-induced osteoporosis were identified through a pharmacy claims analysis. The analysis consisted of a 120-day measurement period of pharmacy claims for all adult patients (aged ≥21 years) within the plan and identified patients who were receiving an oral prednisone equivalent of ≥5 mg per day for at least 90 of 120 days without a prescription medication for prevention or treatment of osteoporosis, which was defined as 1 or more pharmacy claims for bisphosphonate (e.g., risedronate, ibandronate, etidronate, or alendronate), raloxifene, teriparatide, or calcitonin, during the same 120-day time frame. Pharmacy claims fitting the criteria were identified using the Generic Product Identifier (GPI) numbers listed in Table 3. Claims that included 1 of the products listed were reviewed by a clinical pharmacist to determine if they matched the criteria.

Between September 2003 and May 2005 (Table 4), interventions with both members and their physicians were conducted 3 times. Each intervention consisted of identifying patients at risk, mailing the intervention packet, and evaluating pharmacy claim records for a 4-month period immediately following each of the mailings (Table 4). Each patient could receive subsequent mailings if there was no (a) physician or patient response or (b) addition of osteoporosis-prevention treatment per the evaluation of pharmacy claims data.

Patient interventions included a direct-to-member mailing of a 1-page cover letter and a 2-page educational brochure that described the risk for glucocorticoid-induced osteoporosis and encouraged a conversation with the member’s physician. The 2-page brochure defined osteoporosis, identified risk factors, and
promoted lifestyle changes to minimize the risk of osteoporosis. It also instructed members not to discontinue their steroids without first discussing discontinuation with their physician.

The physician intervention included (a) a 1-page letter describing the program, (b) the same 2-page brochure about osteoporosis and its prevention and treatment that was sent to patients, and (c) a 1-page table listing options for drug treatments for osteoporosis, including bisphosphonates, raloxifene, intranasal calcitonin, and teriparatide (parathyroid hormone); the table included the notation that “combination hormone replacement therapy is no longer recommended as monotherapy for osteoporosis” based on the results of the Women's Health Initiative.

### TABLE 3

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<td>22100010002010</td>
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<td>Entocort EC oral capsule extended release 24 hour 3 mg</td>
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<td>22100015100310</td>
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</table>
The 1-page physician letter included a fax-back box by which the physician could request a list of the patients “for whom I have prescribed steroids.”

The physician letters were sent by first-class mail without return-receipt notification. However, there were very few physician mailings returned with incorrect addresses, and these few mailings were resent after the address corrections. Physicians who requested the fax-back information about individual patients were sent the following data for each member at risk (i.e., taking more than 90 days of a steroid without an accompanying medication for osteoporosis prevention): patient name, date of birth, date of last fill of glucocorticoid prescription, and strength of glucocorticoid prescribed. (The quantity dispensed was not included in the list.)

Physician specialty was identified by the health plan claims system that matched the physician’s name with the medical specialty. The medical specialty of 47.9% of the prescribers could not be determined from claims data, and these unknown specialty physicians were included in the “other specialties” category. In the analysis, patients who initiated a bisphosphonate during the 4-to-6-week time lag between the end of the patient identification time period and the intervention start date were not documented.

### Results

Table 5 shows the number of at-risk patients at the time of each analysis during the 3-year period. Less than 1% (n=10,822) of our members were receiving chronic oral glucocorticoids, but 52.5% of these patients were not receiving drug therapy for prevention or treatment of osteoporosis. On average, women made up 59.6% of patients receiving chronic glucocorticoid therapy during the 3-year study period and 53.8% of patients defined as being at risk for glucocorticoid-induced osteoporosis (i.e., not receiving preventative medication). About half of the female patients (50.9%, 3,285/6,450) and male patients (54.8%, 2,397/4,372) were at increased risk of fracture due to receipt of 90 days or more of glucocorticoid therapy without anti-osteoporosis drug therapy.

Table 6 shows a breakdown of patients who were receiving chronic glucocorticoids with or without osteoporosis prevention...
3-Year Results of a Member and Physician Intervention to Reduce Risk Associated With Glucocorticoid-Induced Osteoporosis in a Health Plan

| TABLE 6 | Breakdown of Patients Treated With Glucocorticoids by Physician Specialty During the Identification Periods |
|---|---|---|---|---|
| **Physician Specialty**— % Patients (n) | 2003 N = 3,643 | 2004 N = 3,590 | 2005 N = 3,589 | 3-Year Total N = 10,822 |
| **Primary care** | | | | |
| with osteoporosis treatment | 39.1% (479) | 39.6% (481) | 67.5% (780) | 48.4% (1,740) |
| without osteoporosis treatment | 60.9% (745) | 60.4% (735) | 32.5% (375) | 51.6% (1,855) |
| **Allergy** | | | | |
| with osteoporosis treatment | 49.2% (31) | 57.1% (32) | 76.5% (62) | 62.9% (125) |
| without osteoporosis treatment | 50.8% (32) | 42.9% (24) | 23.5% (19) | 37.1% (75) |
| **Endocrinology** | | | | |
| with osteoporosis treatment | 27.5% (28) | 24.4% (20) | 67.9% (33) | 38.5% (101) |
| without osteoporosis treatment | 72.5% (74) | 75.6% (62) | 32.1% (25) | 61.5% (161) |
| **Gastroenterology** | | | | |
| with osteoporosis treatment | 23.6% (17) | 33.0% (34) | 61.3% (37) | 40.3% (108) |
| without osteoporosis treatment | 76.4% (55) | 67.0% (69) | 38.7% (36) | 59.7% (160) |
| **Pulmonary** | | | | |
| with osteoporosis treatment | 39.8% (33) | 43.6% (34) | 73.3% (35) | 51.7% (122) |
| without osteoporosis treatment | 60.2% (50) | 56.4% (44) | 26.7% (20) | 48.3% (114) |
| **Rheumatology** | | | | |
| with osteoporosis treatment | 44.8% (187) | 40.0% (128) | 70.1% (237) | 51.3% (552) |
| without osteoporosis treatment | 55.2% (230) | 60.0% (192) | 29.9% (101) | 48.7% (323) |
| **Other specialties or specialty unknown** | | | | |
| with osteoporosis treatment | 64.6% (1,086) | 38.6% (670) | 36.0% (636) | 46.1% (2,392) |
| without osteoporosis treatment | 35.4% (596) | 61.4% (1,065) | 64.0% (1,133) | 53.9% (2,794) |
| **Total** | | | | |
| Patients on glucocorticoids (n) | 3,643 | 3,590 | 3,589 | 10,822 |
| with osteoporosis treatment | 51.3% (1,861) | 39.0% (1,399) | 52.4% (1,880) | 47.5% (5,140) |
| without osteoporosis treatment | 48.9% (1,782) | 61.0% (2,191) | 47.6% (1,709) | 52.7% (5,682) |

by physician specialty. The “other specialties” group includes physicians for whom the specialty could not be determined (e.g., hospital outpatient physicians, hospital clinic physicians). The other specialties group accounted for the largest number of patients receiving steroids (47.9%, n = 3,186) of which 53.9% (n = 2,794) were at risk for glucocorticoid-induced osteoporosis because they were not receiving preventative medications. The primary care specialty group had the second largest number of patients receiving steroids (33.2%, n = 3,595) of which 51.6% (n = 1,855) were at risk for glucocorticoid-induced osteoporosis for not receiving preventative medications. These 2 specialties groups account for 81.1% of the patients at risk for glucocorticoid-induced osteoporosis.

The specialty with the largest increase in percentage of patients treated for glucocorticoid-induced osteoporosis across the 3 years of the intervention was endocrinologists, a group for whom 27.5% of at-risk patients were treated with an osteoporosis medication at the time of the first analysis in 2003 versus 67.9% at the time of the final analysis in 2005 (40% increase). However, endocrinologists were associated with only 2.4% of all patients in this health plan who received long-term glucocorticoid therapy during 3 years.

Increases in anti-osteoporosis drug use from 2003 to 2005 were noted for glucocorticoid-treated patients of primary care physicians (from 39.1% to 67.6%), allergists (from 49.2% to 76.5%), gastroenterologists (from 23.6% to 61.3%), pulmonologists (from 39.8% to 73.3%), and rheumatologists (from 44.8% to 70.1%). The other specialties group was unique in that a marked decrease in the use of anti-osteoporosis medication was noted, 64.6% of patients in 2003 to 36.0% of patients in 2005.

Anecdotal feedback from physicians regarding the program was consistently positive, and 196 physicians (4.9%), accounting for 387 patients (6.8%) at risk for glucocorticoid-induced osteoporosis, requested a list of their patients at risk via the fax-back opportunity.

Table 7 shows the changes in the use of preventative medication for osteoporosis following the interventions. Of the at-risk members who were subjects of the educational intervention during the 3 years, 404 (7.1%) were started on an osteoporosis medication following the mailings. Of these, 84.9% of patients (n = 343) continued on both glucocorticoid therapy and an anti-osteoporosis medication for the 4-month follow-up period. Of the patients who started on preventative therapy after the intervention, 72.8% were women, and 96.3% of the women were aged ≥40 years.

**Discussion**

Glucocorticoid-induced osteoporosis was targeted for this intervention because it represents a disease that is underdiagnosed and undertreated, and we suspected that there were a significant number of at-risk patients within our health plan. Our intervention was designed to identify the at-risk patients and provide educational materials to increase awareness among members and physicians about the risk of glucocorticoid-induced osteoporosis and the importance of its prevention. An objective of our program was to promote dialogue between members and their clinicians.
regarding options for preventing or treating glucocorticoid-induced osteoporosis. While we expected to see an increase in percentage of patients receiving medication to prevent glucocorticoid-induced osteoporosis, this is only 1 possible outcome of the member-physician discussion.

On average, 52.5% of patients receiving a glucocorticoid were not receiving medication to prevent glucocorticoid-induced osteoporosis. Women represented 53.8% (3,058/5,682) of the at-risk patient group (i.e., long-term glucocorticoid therapy without osteoporosis prevention drug therapy), which is high compared with the rates found in previous research (24.2%, 42.1%, 14 and 30.4%). The intervention was associated with a 9.6% increase (294/3,058) in the number of women who received osteoporosis-preventive drug therapy. We wonder why so many women are at risk and not being managed with medications to prevent glucocorticoid-induced osteoporosis. Nearly all the women (96.3%) who started preventative medications following the intervention were aged ≥40 years. One possibility is that a large percentage of those who are not being treated are premenopausal and treatment is inappropriate, but our data does not provide this level of detail. We included premenopausal women in our intervention because the goal was for the physicians and patients to discuss their care and determine the most appropriate course. Of the 5,682 patients who were at risk for glucocorticoid-induced osteoporosis during the 3-year intervention, 2.7% (11) of the women who started preventative therapy were clearly premenopausal women, which is less than 1% of the at-risk population. We considered this to be reasonable and consistent with our goal that physicians and patients would make individualized decisions. However, including premenopausal women in the intervention without breaking them into specific age bands limited the utility of the data.

Even though raloxifene and teriparatide are not included in the ACR recommendations, we included them in our educational materials. Teriparatide (Forteo) is an agent that contains recombinant human parathyroid hormone (PTH 1-34), and it was approved by the U.S. Food and Drug Administration (FDA) in November 2002. Although the ACR recommendations were published in July 2001, the anabolic agent PTH 1-34 (i.e., teriparatide) was considered, and the recommendations state that there were not enough data in glucocorticoid-treated patients to draw conclusions. Our health plan added teriparatide to the formulary in 2006 as a tier-3 drug that could be used as part of step therapy; teriparatide was included in the educational materials for completeness.

Raloxifene is a selective estrogen receptor modulator approved by the FDA in December 1997 for the treatment and prevention of postmenopausal osteoporosis. At the time the ACR recommendations were published, there were no data describing the efficacy of raloxifene in glucocorticoid-induced osteoporosis. However, we considered it a viable option in postmenopausal women receiving glucocorticoids who are unable or unwilling to take other available therapies (e.g., antiresorptive medications). Raloxifene was added to our formulary prior to beginning the intervention in 2003 as a tier-2 copayment (preferred) drug.

The proportion of patients at risk from osteoporosis in our intervention falls in the approximate midpoint of the data range reported in the literature. In our patient population during 3 years, 50.9% of women (3,285/6,450) and 54.8% of men (2,397/4,372) on chronic glucocorticoid therapy were at risk for glucocorticoid-induced osteoporosis because of the absence of medication to prevent osteoporosis. Others have reported percentages between 24% and 89% for women and between 56% and 95% for men. The percentage of patients within the health plan receiving glucocorticoids during the 3 years (0.29%) is similar to 0.3% reported elsewhere. Overall, 7.1% of the patients at risk for glucocorticoid-induced osteoporosis started preventative therapy, of which 72.8% were women, and 8.9% of the women at risk and targeted by our intervention (n=294) started preventative therapy for osteoporosis. Without a control group, we cannot conclude with certainty that our intervention is responsible for the very modest changes. It’s likely that other educational efforts and marketing by the pharmaceutical industry contributed as well.

Kaufman et al. in JMCP (2005) described a 4-year physician intervention program in a health plan of about the same enrollment as our health plan. The goal of their intervention was to minimize the use of medications contraindicated in older adults, and the objective was to change the prescribing habits of physicians within the health plan. Their intervention involved direct mail to physicians of elderly patients who were prescribed inappropriate medications, publishing educational pieces in the health plan newsletter, and making follow-up phone calls to a subset of high-volume prescribers of the target drugs defined as

| TABLE 7 | Changes in the Use of Preventative Medication for Osteoporosis Following Intervention |
|---|---|---|---|---|
| No. of patients in intervention group (N) | 2003 | 2004 | 2005 | 3 Years |
| 1,782 | 2,191 | 1,709 | 5,682 |
| % (n) patients starting anti-osteoporosis medication | 7.4% (131) | 5.6% (122) | 8.8% (151) | 7.1% (404) |
| % (n) female (aged 0-39 years) | 5.3% (7) | 0.8% (1) | 2.0% (3) | 2.7% (11) |
| % (n) female (aged 40-59 years) | 24.4% (32) | 23.0% (28) | 17.2% (26) | 21.3% (86) |
| % (n) female (aged ≥ 60 years) | 48.1% (63) | 49.2% (60) | 49.0% (74) | 48.8% (197) |
| % (n) male | 22.1% (29) | 27.0% (33) | 31.8% (48) | 27.2% (110) |
| % (n) patients continuing on glucocorticoid and anti-osteoporosis medication 4 months later | 70.2% (92) | 93.4% (114) | 90.7% (137) | 84.9% (343)
physician requests for fax-back lists of patients for glucocorticoid-induced osteoporosis who received prevention during the 3 years was the result of the intervention or 404 patients who started on medication for prevention of osteoporosis. Their seemingly greater success in affecting physician prescribing may be related, in part, to the higher-intensity intervention that involved telephone contact of high-volume prescribers.

The overall physician response rate was 4.9% of physicians who received our mailing and requested patient information via the fax-back program (Table 8). In 2003, we contacted 2,153 physicians and 2.8% requested additional information (n=61); in 2005, we contacted less than one third as many physicians (n=625) and 7.2% responded (n=45). The number of patients at risk for glucocorticoid-induced osteoporosis remained relatively constant during the 3 years, while the number of physicians contacted by this intervention including fax-back opportunity dropped by 71% (2,153 in 2003 to 625 in 2005).

The percentage of patients at risk for glucocorticoid-induced osteoporosis who were taking a preventative medication dropped from 51.1% in 2003 to 39.0% in 2004, and then returned close to the baseline in 2005 (52.4%). Our analysis did not identify a reason for this apparent dip in 2004. In looking at trends among the physician medical specialties, there appeared to be an increase during the 3 years in the proportion of patients at risk for glucocorticoid-induced osteoporosis who received preventative medications except for the largest category of prescribers, the "other specialties," including unknown medical specialty. This group is also significant because it was responsible for prescribing glucocorticoids for nearly half (47.9%) of the patients at risk for glucocorticoid-induced osteoporosis during the 3-year study period.

**Limitations**

The foremost limitation of the present study is the absence of a control group, so we cannot be certain how many of the 404 patients who started on medication for prevention of osteoporosis during the 3 years was the result of the intervention or coincidental events. Second, we only measured 1 possible outcome of our intervention—the addition of preventative medications (i.e., bisphosphonates, calcitonin, teriparatide, or raloxifene); we did not assess other behavioral changes, such as smoking cessation, increase in weight-bearing exercise, reduction in alcohol use, or the initiation of supplementation with calcium and vitamin D that may have been related to our education-intervention.

Third, we did not measure discontinuation of glucocorticoid therapy beyond 120 days, previous failure on bisphosphonates, or the conduct of bone mineral density tests. Fourth, we could not identify patients who might have received their medications via another source, such as physician samples, or who obtained medications outside the health plan. Fifth, our intervention did not account for those patients who started therapy after the end of the identification period but prior to the receipt of the intervention-mailing, which may have contributed to underestimation of the effect of our intervention.

Sixth, we did not measure patient adherence or persistence with osteoporosis drug therapy other than the assessment of the proportion of patients remaining on preventative medication after 4 months of follow-up. For those who were started on bisphosphonates, it is likely that some were unable to tolerate the medication. Adherence to medications for the prevention of osteoporosis is often poor. Ettinger et al. found that 34.9% of women initiated on alendronate had discontinued therapy at 6 months, and the most common reason for discontinuation, gastrointestinal problems, were reported by 51.9% of the women who had stopped taking the drug.20 Others have reported rates of discontinuation of bisphosphonates in the range of 60.5% to 75% at 12 months of follow-up.21 22 During our intervention, 83.4% of those who began preventative therapy continued it for at least 4 months, but we did not identify the reasons for discontinuation of treatment.

Seventh, it is not possible from this intervention to determine what proportion of patients on chronic glucocorticoid therapy remained at risk over time. For example, a patient who received as little as 90 days of glucocorticoid therapy could have been identified as at risk because of the absence of drug therapy for prevention of osteoporosis. In other words, we do not know...
the true denominator for the patients at elevated risk. We also do not know the true numerator for patients for whom physicians and patients initiated behavioral changes or drug therapy (e.g., via physician samples) to prevent glucocorticoid-induced osteoporosis.

Eighth, despite the recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis from the ACR (2001), there is no evidence that bisphosphonates or other anti-osteoporosis drug therapy actually reduce the risk of meaningful glucocorticoid-induced fractures. Therefore, the increase in use of drug therapy to prevent osteoporosis from 47.5% of patients on chronic glucocorticoid therapy to 51.2% after the intervention in this health plan may represent a reasonable expectation of success in attaining optimal drug therapy to prevent osteoporosis.

Conclusion

Our mail-based intervention program received a response rate greater than expected with a typical direct-mail marketing campaign but significantly less than that reported by others who have conducted similar intervention programs with physicians. Our efforts were designed to educate and increase the use of drug therapy to prevent osteoporosis in patients on chronic glucocorticoids, defined as at least 90 days of dispensed drug therapy. Our intervention was associated with the initiation of medications, as measured in pharmacy claims data, to prevent osteoporosis in a small percentage of target patients (7.1% over 3 years), but because there was no control group, the proportion of new starts on anti-osteoporosis medications attributable to the intervention cannot be ascertained. This intervention program documented that slightly more than half of the patients on chronic glucocorticoid therapy were at risk of osteoporosis because of the absence of concomitant therapy with an anti-osteoporosis medication.

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DISCLOSURES

There was no external funding for this research, and the authors attest to the absence of conflicts of interest or bias associated with this study and the preparation of the manuscript. Chitre was the principal author of the article, including revisions, and contributed the bulk of the work in concept and design and data interpretation. The authors shared equally in data collection.

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Background: Pharmacotherapy constitutes an important adjunct to behavioral therapy for the treatment of overactive bladder (OAB). Tolterodine and oxybutynin are commonly prescribed drugs for OAB treatment that exert their beneficial effect by suppressing bladder muscle contractions. However, high discontinuation rates have been observed for these drugs in clinical trials, as well as in real-world settings, in part due to adverse effects. Extended-release (ER) formulations were introduced with an improved tolerability profile over immediate-release (IR) versions of the 2 drugs. No study has compared persistence and adherence to therapy for both the ER and IR versions of tolterodine and oxybutynin.

Objective: To compare persistence, adherence, and switch rates for the IR and ER formulations of oxybutynin and tolterodine for patients enrolled in a regional managed care plan.

Methods: Study patients were adults (aged ≥18 years), with at least 1 pharmacy claim for either tolterodine extended-release (tol-ER), oxybutynin extended-release (oxy-ER), tolterodine immediate-release (tol-IR), or oxybutynin immediate-release (oxy-IR) during the period from July 1, 1999, to December 31, 2003, and were continuously eligible for benefits from 6 months before through 12 months after the initial OAB pharmacy claim (index) date. A retrospective cohort study design was used following patients from the index date to the occurrence of non-persistence with the index medication (i.e., a gap of >45 days between successive prescription fills or a switch to any other OAB medication), or the end of a 1-year follow-up period, through December 31, 2004. Switching was defined as any change from the index medication, including a change in dose form (e.g., tol-IR to tol-ER), to one of the other 3 study drugs, or to a different OAB treatment (e.g., trospium chloride, oxybutynin patch, flavoxate, hyoscine hydrobromide, or propantheline bromide) during the follow-up period. Adherence was measured as the proportion of patients with a medication possession ratio (MPR) of at least 80%. MPR was calculated as (1) the sum of days supply for all pharmacy claims except the last pharmacy claim, divided by (2) the total number of days from the first fill date to the fill date of the last pharmacy claim. The association of drug therapy with study outcomes was assessed with bivariate and adjusted (multivariate) analyses. Multivariate analyses controlled for demographic and clinical characteristics, plan type, patient out-of-pocket cost for the index medication, and year of therapy initiation.

Results: 1,117 patients had at least 1 pharmacy claim for an OAB study drug (n = 454 for tol-ER [40.6%], n = 249 for oxy-ER [22.3%], n = 306 for tol-IR [27.4%], n = 108 for oxy-IR [9.7%]), of whom 81.6% were women. The mean (standard deviation [SD]) age of the study population was 55.7 (14.5) years. Only 53.7% had at least 1 OAB diagnosis recorded during the 18-month eligibility period. 44.5% of patients did not have a refill after the initial (index) pharmacy claim (39.4% for oxy-ER, 42.7% for tol-ER, 46.1% for tol-IR, and 59.3% for oxy-IR; P = 0.004). Only 13.2% persisted with treatment for at least 1 year (tol-ER = 15.0%, oxy-ER = 15.3%, tol-IR = 11.4%, oxy-IR = 6.5%; P = 0.050). The median days to discontinuation (non-persistency) were 31.0 overall, 33.0 for tol-ER, 34.0 for oxy-ER, 32.0 for tol-IR, and 0 for oxy-IR; P = 0.010. The overall switch rate as a percentage of all study patients was 13.3%, ranging from 9.9% for tol-ER, 13.7% for tol-IR, 16.5% for oxy-ER, and 19.4% for oxy-IR; P = 0.020. Of patients who refilled their initial prescription at least once, 24.0% made a medication switch. Adherence rates as measured by percentage of patients with MPR ≥80% were 30.3% overall and higher for the ER formulations: 35.2% for tol-ER, 36.1% for oxy-ER, 23.5% for tol-IR, and 14.8% for oxy-IR; P < 0.001.

Conclusions: Adherence was significantly better for ER than IR agents. The high rate of non-persistence (44.5%) following the first (index) prescription highlights the need for medication counseling by health care professionals.
Overactive bladder (OAB) is a common and chronic condition, characterized by urinary urgency, frequency, or nocturia with or without urge urinary incontinence.\(^1\) To the extent that such symptoms interfere with social functioning and hygiene, OAB is considered a medical problem.\(^2\)

Behavioral interventions are considered to be the first-line mode of treatment for OAB and include lifestyle modifications, scheduling regimens, and pelvic floor muscle rehabilitation.\(^3\) Pharmacotherapy is an important adjunct with antimuscarinic drugs, such as oxybutynin and tolterodine, considered the agents of first choice.\(^4,5\) These agents suppress bladder muscle contractions mediated by the muscarinic (primarily M\(_3\)) receptors, thereby increasing bladder capacity and reducing the number and severity of urgency episodes.\(^5,7\) However, interaction with muscarinic receptors at sites other than that of the bladder muscle or sometimes even at the bladder level itself (e.g., adverse effect of urinary retention) may lead to undesirable adverse effects.\(^7,9\) Approaches to overcoming such concerns include the development of extended-release (ER) formulations and agents with greater M\(_3\) selectivity, such as trospium, solifenacin, and darifenacin, which were introduced in 2004.

For pharmacotherapy to be beneficial, good persistence and adherence are essential. High discontinuation rates have been observed in clinical trials of OAB drugs, due in part to adverse effects including but not limited to dry mouth, constipation, blurred vision, and headache. Drug persistence and adherence patterns assessed for various OAB drugs in real-world settings are even worse with almost 70% to 90% of patients discontinuing treatment within 1 year.\(^10-15\) The persistence drops markedly within the first 6 months and is further reduced at 1 year. In studies that have a 6-month follow-up, persistence rates of 11% to 30% have been reported,\(^10,11,16,18\) and in studies with at least 1 year of follow-up, persistence rates range from 8% to 29%.\(^12,13,16-18\)

In general, oxybutynin immediate-release (oxy-IR) has the lowest persistency rate, and tolterodine extended-release (tol-ER) has the highest persistency rate. However, no studies have compared both the extended-release (ER) and immediate-release (IR) versions of oxybutynin and tolterodine simultaneously to assess differences in outcomes by both drug type and formulation. Furthermore, available published studies often exclude important covariates due to lack of data.\(^12,17\) For example, insurance coverage for prescription drugs is an excluded covariate that is likely to affect persistency patterns in OAB because pharmacotherapy in OAB usually competes with first-line, behavioral therapy techniques. In fact, 1 study found that prescription drug coverage was the most important factor determining patient preference for drug therapy.\(^19\)

The present study addresses these issues by simultaneously comparing both ER and IR forms of tolterodine (tol-ER, tol-IR) and oxybutynin (oxy-ER, oxy-IR, respectively) using various measures of adherence to treatment and accounting for additional relevant factors not previously addressed. The present study was limited to these 4 OAB compounds, because the number of patients using these drugs during the study period was sufficient to allow for statistically meaningful analysis. While measurement of persistency provides information on adherence in terms of the timeliness and consistency of refilling,\(^20\) assessment of the medication possession ratio (MPR) provides insight into the availability of medication.\(^21,22\) This measure is important as OAB patients may exhibit sporadic refilling patterns depending on their perceived need. Therefore, in this study we compared the 4 drug products, both on measures of persistency in terms of discontinuation or switching to other OAB drugs, and also adherence rates using the MPR, while adjusting for important covariates, including patient demographics, type of insurance coverage, prescriber specialty, and comorbidities.

### Methodology

#### Data Source

The study population comprised enrollees of a regional managed care health plan covering 225,000 enrollees of whom approximately 70% have prescription drug coverage. Medicaid recipients were not included in the total population of this health plan, and, consequently, data were available only for privately insured, Medicare, and self-insured employers. Information was obtained on paid pharmacy and medical claims made between January 1, 1999, and December 31, 2004 (total study period). All claims data were linked to eligibility data containing demographic and eligibility information by an encrypted identification number to protect patient and provider confidentiality. The study protocol was deemed exempt by West Virginia University’s Institutional Review Board for the Protection of Human Subjects.

The pharmacy claims database included details, such as National Drug Code, date dispensed, quantity dispensed, days supply, copayment/coinsurance amount, and prescribing
provider specialty. Prescriber specialty was obtained by matching a provider identifier on the pharmacy claim to a crosswalk table indicating each provider’s specialty. The medical claims database included details of the visits or services provided, such as International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis and procedure codes, date of service, location of service, Current Procedural Terminology procedure codes, billing codes, and provider specialty. Additional information on subjects (e.g., age, gender, plan type) and dates of enrollment were available in a separate eligibility file.

Study Design and Sample Selection
Health plan enrollees with pharmacy coverage were first selected (n approximately 154,000), and then those with a pharmacy claim for tol-ER, oxy-ER, tol-IR, or oxy-IR between July 1, 1999, and December 31, 2003, were identified (Figure). Of the 4 study drugs, 3 (oxy-ER, oxy-IR, and tol-IR) were available in the United States throughout the entire study period, while tol-ER was launched in September 2001. The date of the earliest OAB pharmacy claim for a person during this period was defined as the index date (start date), and the associated pharmacy claim was defined as the index prescription. The 6-month period before the index date was defined as the baseline period, and the 12-month period after the index date was the follow-up period, yielding a total of 18 months during which subjects were required to be continuously eligible for both medical and pharmacy benefits. Subjects were excluded if they were aged < 18 years or if they had pharmacy claims for any study drug during the baseline period (6 months before the [index] start date) to increase the likelihood that the initiation of OAB pharmacotherapy was assessed. The pattern of fills following the index prescription was evaluated for 12 months after the index date using a retrospective cohort study design to determine non-persistence, switching, and MPR.

Study Outcomes
Persistence was measured as the proportion of patients continuing therapy for 12 months without discontinuing the index drug or switching to other OAB drugs. Patients were considered to be non-persistent on their index medication if they failed to refill their index prescription within a defined ‘grace’ period of 45 days from the expected end of supply of the previous prescription, or if a person filled a prescription for an OAB drug different from the index prescription (i.e., switched, but filled it within the ‘grace’ period). Thus, non-persistence was defined as not refilling the index prescription in a timely manner or switching from the index medication. The ‘grace’ period used in previous studies has ranged from 15 to 45 days.11,17 Our study used a 45-day period to include patients with intermittent use, which is thought to be prevalent in OAB. The number of days to non-persistence was calculated as the difference between the fill date of the last prescription and the fill date of the index prescription. The count of days to non-persistence did not include the days supply in the last pharmacy claim because a discontinuation or switch could have occurred at any time during the period covered by the final claim. Consequently, excluding the entire days supply of the last filled prescription yields the lowest estimate of days of persistence.

The switch rate was calculated as the proportion of patients who refilled at any time during the 12-month follow-up but changed from the initial (index) medication to any of the other 3 study drugs, including within-drug changes to a different dose form (oxy-IR to oxy-ER), or to a different OAB treatment (e.g., trospium chloride, oxybutynin transdermal, flavoxate, hyoscyamine sulfate, or propantheline bromide).

Adherence rate was measured as the proportion of patients with an MPR of at least 80%. The MPR for each person was calculated as (1) the sum of the total number of days of a medication supplied across pharmacy claims except for the last pharmacy claim, divided by (2) the total number of days from the first fill date to the fill date of the last pharmacy claim. For example, a patient who receives 90-days supply during a 120-day period will have
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MPR=0.75. The MPR can be calculated only for patients who have at least 2 pharmacy fills. Thus, MPR is 0 for patients who did not refill their index prescription. Additionally, MPR values were capped at 1.0 for patients who refilled early.

Study Covariates and Statistical Analyses

Demographic covariates included age and gender. Covariates accounting for differences in structure and nature of coverage included the plan type (e.g., privately insured, Medicare, and self-insured employers) and average out-of-pocket (OOP) cost for the index OAB drug. The latter was computed as the mean of copayment/coinsurance costs for all pharmacy claims of the index drug. Clinical covariates included presence of an OAB diagnosis (Table 1) in any diagnosis field on the claim, specialty (e.g., urologist, gynecologist, or other) of the provider who prescribed the index prescription, a modified D’Hoore Charlson Comorbidity Index (CCI) score in the 6-month baseline period, presence of OAB-related comorbidities (e.g., urinary tract infection/vulvovaginitis, anxiety/depression, falls/fractures/skin infections/pressure ulcers) in the 6-month baseline period, and average daily dose for the index medication. Average daily dose for the index medication was calculated per patient over the period of that patient’s observation utilizing all fills of the index medication until discontinuation or switch occurred and expressed as mg per day. The effect of dose was assessed using the categories “low” and “normal to high” dose defined as follows:

<table>
<thead>
<tr>
<th>Category</th>
<th>Dose Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Dose</td>
<td>≤2 mg per day</td>
</tr>
<tr>
<td>Normal-to-High Dose</td>
<td>&gt;2 mg per day</td>
</tr>
</tbody>
</table>

These categories broadly reflect the doses recommended in U.S. prescribing information (tol-ER/IR: 2 mg-4 mg per day; oxy-ER: 5 mg-30 mg per day; oxy-IR: 5 mg-20 mg per day).27-30

Univariate analyses, such as Analysis of Variance (ANOVA), and Kruskal-Wallis test for continuous variables, and log-rank and chi-squares tests for categorical variables were used to compare study outcomes and characteristics (demographic, plan, and clinical). Appropriateness of non-parametric testing was tested after checking normality diagnostics (Kolmogorov-Smirnov tests, Q-Q plots, histograms). For the log-rank test, the Breslow test statistic was used to find differences in time to event, which provides greater weight to early observations, thereby increasing the likelihood of finding a difference, if one exists, in contrast to other test statistics that equally weight all cases. Logistic regression models were used to determine differences in switch and adherence rates between drug therapy groups. Cox-Proportional Hazards (Cox-PH) regression was used to determine differences in time to non-persistence between drug therapy groups. All multivariate analyses were preceded by testing for outliers and the assumptions of the particular regression used. The assumption of proportional hazards was tested for the Cox-PH regression using the global test of proportional hazards, including all covariates together with the interaction terms of each covariate with the logarithm of time. For the logistic regression, the possibilities of multicollinearity and near-dependency were assessed by checking for very large parameter estimates and standard errors. Three cases were found to be outliers, but study results were similar with and without the outliers. Hence, final analyses are reported for the entire sample. When necessary, continuous variables were categorized to avoid problems with outliers, and categorical variables were collapsed to produce cells of adequate size.

Tests of significance comparing each drug group to the reference drug group (tol-ER) were obtained from the regression conducted for each outcome (e.g., persistence, switch rate, and adherence). When a significant difference across the 4 drug groups was found by either drug type or formulation, a subsequent test for significance was conducted for the specific outcome measure by pooling the oxybutynin or tolterodine drug groups or the ER and IR groups. All regressions used the sequential block-entry approach, which assesses the impact of type of drug therapy after all covariates have already entered the model. Adjusted persistence rates were obtained from the Cox-PH model. Adjusted switch and adherence rates were obtained by substituting mean values for all covariates in the logistic regression equations to produce predicted values for each group. Data were manipulated using SAS version 9.1.3 (SAS Institute, Inc., Cary, NC) and analyzed using SPSS version 13.0 (SPSS Inc., Chicago, IL) and SAS version 9.1.3.
Results

Study Sample Description

To derive the study sample, enrollees with any pharmacy coverage were first selected (70% of 225,000=approximately 154,000). Of these enrollees, 2,211 patients with at least 1 pharmacy claim for an OAB study drug between July 1, 1999, and December 31, 2003, were identified (Figure). A total of 1,255 patients remained after excluding patients without continuous eligibility for both medical and pharmacy benefits from the 6-month period before through the 12-month period after the index prescription. Further, excluding patients having any OAB study drug in the pre-index period, those aged <18 years of age, and those with missing data, a final sample size of 1,117 was obtained (Figure).

For this study sample (n=1,117), the most commonly prescribed index drug was tol-ER (n=454, 40.6%), followed by tol-IR (n=306, 27.4%), oxy-ER (n=249, 22.3%), and oxy-IR (n=108, 9.7%). The average (standard deviation [SD]) age of the study sample was 55.7 (14.5) years with a predominance of women

<table>
<thead>
<tr>
<th>TABLE 2 Characteristics of Study Sample at Baseline by OAB Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristics</td>
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<tr>
<td></td>
</tr>
<tr>
<td>Gender, female</td>
</tr>
<tr>
<td>Plan type</td>
</tr>
<tr>
<td>Privately insured</td>
</tr>
<tr>
<td>Medicare</td>
</tr>
<tr>
<td>ASO</td>
</tr>
<tr>
<td>Average out-of-pocket costs per person for index OAB Rx</td>
</tr>
<tr>
<td>Median $</td>
</tr>
<tr>
<td>Mean $</td>
</tr>
<tr>
<td>Prescribing urologist or gynecologist</td>
</tr>
<tr>
<td>OAB diagnosis</td>
</tr>
<tr>
<td>Average daily dose [a]</td>
</tr>
<tr>
<td>Normal to high</td>
</tr>
<tr>
<td>Baseline $D’Hoore CCI</td>
</tr>
<tr>
<td>Mean</td>
</tr>
<tr>
<td>Baseline prevalence of urinary tract infection/vulvovaginitis</td>
</tr>
<tr>
<td>Baseline prevalence of skin infection/pressure ulcer</td>
</tr>
<tr>
<td>Baseline prevalence of anxiety/depression</td>
</tr>
<tr>
<td>Baseline prevalence of falls/fractures</td>
</tr>
</tbody>
</table>

[a] P values are for comparisons among all OAB therapies and do not represent differences between any 2 OAB therapies. Thus, a significant P value represents a difference among OAB therapy groups in the particular characteristic α=0.05. Significant values are in bold.

[b] ANOVA test.

[c] Pearson χ² test.


[e] Assessed during entire 18-month eligibility period.

[f] Dosing classification:

<table>
<thead>
<tr>
<th>Low Dose</th>
<th>Normal-to-High Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>tol-ER = 2 mg per day</td>
<td>&gt;2 mg per day</td>
</tr>
<tr>
<td>tol-IR ≤ 2 mg per day</td>
<td>&gt;2 mg per day</td>
</tr>
<tr>
<td>oxy-ER = 5 mg per day</td>
<td>&gt;5 mg per day</td>
</tr>
<tr>
<td>oxy-IR ≤ 10 mg per day</td>
<td>&gt;10 mg per day</td>
</tr>
</tbody>
</table>

[g] Assessed during 6-month pre-index period.

ASO=administrative services only; CCI=Charlson Comorbidity Index; OAB=overactive bladder; oxy-ER=oxybutynin extended-release; oxy-IR=oxybutynin immediate-release; Rx=prescription; tol-ER=tolterodine extended-release; tol-IR=tolterodine immediate-release.
(81.6%) and comparable demographics across treatment groups (Table 2). Many patients had OAB-related comorbidities; during the 6-month baseline period, 20.0% of patients were diagnosed with urinary tract infection (UTI)/vulvovaginitis, and 16.8% with anxiety/depression. These findings were consistent with published estimates and did not differ among treatment groups. However, patients prescribed oxybutynin (ER or IR) had more comorbidities (measured as higher mean baseline D’Hoore CCI scores, \( P = 0.040 \)) and patients prescribed IR formulations had higher baseline rates of falls and fractures (\( P = 0.020 \)).

The study population was selected on OAB prescription drug use and not on the presence of a diagnosis. A little more than half (53.7%) of patients had an OAB diagnosis. The percentage with an OAB diagnosis was higher for ER-treated patients (55.9% for tol-ER, 61.0% for oxy-ER) than for IR-treated patients (49.0% for tol-IR, 40.7% for oxy-IR, \( P = 0.001 \)). However, baseline characteristics were similar in patients with and without an OAB diagnosis, except for a higher prevalence of comorbid UTI/vulvovaginitis in the patients diagnosed with OAB (Table 3, \( P < 0.001 \)). Only 28.2% of patients received their index prescription from an urologist or gynecologist with no significant difference in specialty use by type of agent (Table 2).

Average per-patient OOP costs for the index drug differed significantly by type of index drug received, being lowest for oxy-IR ($8.38) (reflecting its generic status), and highest for tol-ER ($19.50), and oxy-ER ($17.02). The type of plan was also significantly related to type of index drug. IR-treated patients were more often members of self-insured employers than ER-treated patients, and patients prescribed tol-IR were more likely to be privately insured and less likely to be Medicare beneficiaries than were patients prescribed other therapies. There were also distinct differences between groups in their average daily doses of the index drug. More patients were in the normal-to-high dose category for tolterodine (91.6% for tol-ER and 82.0% for tol-IR) than oxybutynin (48.2% for oxy-ER and 41.7% for oxy-IR; \( P < 0.001 \)).

### Study Outcomes

**Persistence:** The percentage of patients whose treatment persisted for 12 months with the index drug without any gaps exceeding 45 days was 13.2% (tol-ER = 15.0%, oxy-ER = 15.3%, tol-IR = 11.4%, oxy-IR = 6.5%; \( P = 0.050 \)). The bivariate analysis tested for differences among all 4 therapies (\( P = 0.050 \)), with no differences seen between the ER forms (Table 4). Almost half of all patients (44.5%) did not refill their index prescription; the highest proportion of non-refills was seen for oxy-IR (59.3%), followed by tol-IR (46.1%), tol-ER (42.7%), and then oxy-ER (39.4%) (Table 4). Because the time to non-persistence was calculated as the difference in days between the fill dates of the last pharmacy claim and the index prescription, subjects who did not refill their index prescription had 0 days to non-persistence. Oxy-IR users had the shortest median time to non-persistence (0 days), and mean time to discontinuation or switch (61 days, compared with 84 to 98 days for other drug products; Table 4). However, when the drug variables were added to a Cox-PH model containing the other covariates, the drug effect was not statistically significant (\( P = 0.363 \)). Adjusted persistence rates at the end of follow-up were 11.0% for tol-ER, 13.2% for oxy-ER, 9.0% for tol-IR, and 9.0% for oxy-IR (Table 5). No other covariates were found to affect time to non-persistence, including demographics, plan type, or level of copayment.

**Switch Rate:** Only 13.3% of the cohort overall and 24.0% of patients who refilled their index prescription switched from the index medication to other OAB drugs. In the bivariate analysis, switch rates were lowest for patients initiated on tol-ER (9.9%, Table 4). Logistic regression analysis (not shown) indicated that this result was significantly influenced by the year of index OAB therapy; patients were more likely to switch if prescribed their index drug in 2000 or 2001 than in 2003 (2000: odds ratio [OR] = 2.336, \( P = 0.027 \); 2001: OR = 4.551, \( P < 0.001 \)). However, after accounting for other variables, oxy-ER or oxy-IR users remained twice as likely to switch compared with tol-ER users, while tol-IR users did not differ significantly from tol-ER users. After pooling data by drug type, the odds of switching remained significantly different between oxybutynin and tolterodine (OR = 1.751; 95% CI, 1.147–2.673; \( P = 0.009 \), data not shown).

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**Table 3:** Comparison of Characteristics of Total Study Sample by OAB Diagnosis During 18-Month Continuous Eligibility Period

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Presence of OAB Diagnosis</th>
<th>Test Statistic (P Value)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes (( N = 600 ))</td>
<td>No (( N = 517 ))</td>
</tr>
<tr>
<td>Age in years, mean [SD]</td>
<td>56 [15.1]</td>
<td>56 [13.8]</td>
</tr>
<tr>
<td>Gender, female</td>
<td>82.3%</td>
<td>80.7%</td>
</tr>
<tr>
<td>Urinary tract infection/vulvovaginitis</td>
<td>33.5%</td>
<td>24.0%</td>
</tr>
<tr>
<td>Skin infections/pressure ulcer</td>
<td>1.8%</td>
<td>2.3%</td>
</tr>
<tr>
<td>Anxiety/depression disorders</td>
<td>32.5%</td>
<td>28.2%</td>
</tr>
<tr>
<td>Falls/fractures</td>
<td>11.2%</td>
<td>9.5%</td>
</tr>
</tbody>
</table>

Overall D’Hoore CCI: 0.0, \( 153907.5^c \) (0.810)

*Statistical significance level (\( \alpha \)) = 0.05. Significant values are shown in bold print.

\( a \) t-test statistic.

\( b \) Pearson \( \chi^2 \) statistic.

\( c \) Mann-Whitney test statistic.

CCI = Charlson Comorbidity Index; OAB = overactive bladder.
Persistance, Adherence, and Switch Rates Among Extended-Release and Immediate-Release Overactive Bladder Medications in a Regional Managed Care Plan

The presence of an OAB diagnosis increased the odds of switching (OR=1.643). Additionally, patients prescribed their index drug by an urologist or gynecologist were 43% less likely to switch than those prescribed their index drug by a physician with other specializations (data not shown). Adjusted switch rates for the 4 therapies are shown in Table 5.

### Discussion

The present study assessed the persistence and adherence patterns of patients using 2 dose forms of 2 OAB medications who were enrolled in a regional managed care plan. The results demonstrated that almost half of all patients treated with an OAB study drug (44.5%) did not refill their initial prescription, and less than 1 in 7 patients (13.2%) continued their treatment for at least 1 year. Although the type of initial therapy did not significantly affect persistence in multivariate analysis, switch rates were lower for tol-ER compared with either formulation of oxybutynin, and the ER formulations were associated with higher adherence (MPR) than the IR formulations.

Like this study, many previous studies assessing persistence and adherence to OAB pharmacotherapy in clinical practice have also used prescription claims databases. Overall persistence in our study at 1 year (13.2%) was within the range reported in the literature (8% to 29%). Additionally, our study estimate of patients who did not refill the index prescription (44.5%) is within the range reported in other studies (36.9% to 48.2%).
Our study population did not necessarily have a medical claim with a diagnosis of OAB. Only 53.7% of the sample was diagnosed with at least 1 symptom (ICD-9-CM code) characteristic of OAB. This may reflect a situation of under-reporting rather than under-diagnosis, (i.e., cases of OAB are identified and treated by health professionals but not recorded as claims in the database). The relatively low proportion of patients with a recorded OAB diagnosis is unlikely to arise from coding limitations, since the ICD-9-CM diagnosis codes used for the study were comprehensive (Table 1)23,24 and incorporated the symptomatology of the recent definition of OAB by the International Continence Society.3

However, the validity of evaluating all treated patients (with or without OAB diagnosis) is supported by the broadly comparable demographics of the 2 subsets. The higher baseline prevalence of UTI/vulvovaginitis in patients diagnosed with OAB may reflect misdiagnosis in some patients, because symptoms of UTI/vulvovaginitis can resemble those of OAB.3 In addition, there were no differences in outcomes between patients with and without a diagnosis of OAB, except that those with a diagnosis had a higher rate of switching, which might be due to increased monitoring during follow-up of diagnosed individuals.

Persistence at 6 months in our study population (20%) was within the ranges reported in other studies (11% to 30%).10,11,16,18 In our study, 44.5% of patients did not refill their index prescription, suggesting that they discontinued within the first 30 days of treatment. The median days to discontinuation (non-persistence) were 31.0 overall, 33.0 for tol-ER, 34.0 for oxy-ER, 32.0 for tol-IR, and 0 for oxy-IR. It is, therefore, likely that a large proportion of patients in the present study did not achieve maximum therapeutic benefit, which may require at least 4 weeks (for oxy-ER) or 8 weeks (for tol-ER) after starting therapy or dose adjustment.3

Because low persistence may be due to inadequate or nonexistent medication counseling by prescribers, studies demonstrating the effectiveness of medication counseling on persistence rates for OAB medications may be needed.33 Unfortunately, there is currently limited evidence of the consequences of medication non-adherence to support such counseling in the OAB therapeutic area.

In our study, persistence on OAB drugs was low for all 4 study drugs, but was lowest for oxy-IR. In line with this finding, previous studies have shown lower persistence (higher discontinuation rates) with oxy-IR compared with tol-IR.11,14-16 This may reflect differences in tolerability between drugs; pooled clinical trial data have demonstrated significantly greater incidence of adverse events with oxy-IR than with tol-IR.34 Similarly, studies comparing tol-ER and oxy-ER have demonstrated both tolerability and persistence advantages for tol-ER over oxy-ER.17,18,34,35

ER drugs had significantly greater adherence (MPR) than IR drugs, corroborating clinical trial data comparing ER and IR formulations for both oxybutynin and tolterodine.36,37 Switching was influenced by both drug type and the type of prescriber; for patients prescribed their index drug from a urologist or gynecologist, the odds of switching were 43% lower than for patients prescribed their index drug from a physician with other specialty. However, the overall rate of switching in the present study was low (13.3% as a proportion of all study patients, 24.0% of patients who refilled their index prescription). Because non-persistence is the result of the combined effect of switching and treatment discontinuation, reducing discontinuations must be the most important component in maintaining persistence with therapy.

In our study, age was the only patient characteristic that affected adherence; the odds of adherence were 50% higher for patients aged ≥65 years than for those aged <65 years. In a meta-analysis, age was not consistently associated with adherence among adults with study methodology exerting greater influence than demographics.38 However, the meta-analysis evaluated adherence across 17 broad-ranging disease areas and may not reflect the situation in OAB. Based on clinical trials of OAB drugs in the elderly, some experts suggest that older patients are more
likely than younger patients to respond to these medications.\textsuperscript{39} This may translate to better perception of control and subsequent higher adherence as reported in the present study.

Drug regimen factors, such as dosing frequency, can also affect adherence.\textsuperscript{40} In our study, adherence on ER formulations was twice that on IR formulations, possibly due to the convenience of once-daily dosing afforded by the ER formulations.

Of particular interest, the level of copayment did not impact persistence or adherence. This is in contrast to results from a study in which OAB patients not currently using medication completed a questionnaire simultaneously rating 5 attributes of treatment.\textsuperscript{19} Using conjoint analysis techniques, all 5 parameters were significant considerations (all \(p<0.001\)), with prescription drug coverage of greatest importance to patients followed by sleep disturbances, symptom concern, social interaction problems, and coping. Thus, given that paying the full medication cost was a determining factor in the decision to seek pharmacotherapy, it is interesting to note that our study did not demonstrate any impact of OOP cost on drug persistence or adherence rates. The lack of influence of OOP cost suggests that other factors, including factors not measured in our study, are more important predictors of persistence than overcoming financial barriers to treatment initiation.

Limitations
Foremost among the limitations was the low percentage of variance explained by our multivariate equations (<10%), which suggests that unmeasured and possibly confounding factors affected persistence and adherence rates in our study sample. For example, no patient-reported data were available to document use and effectiveness of behavioral interventions that may impact medication persistence and adherence. Second, while logistic regression analysis indicated that oxy-ER or oxy-IR users remained twice as likely to switch compared with tol-ER users, and tol-IR users did not differ significantly from tol-ER users, it is possible that our year of initiation variable masked the drug effect because there were no tol-ER users until September 2001.

Third, the reasons for discontinuation are not reported, and therefore clinically justified discontinuations associated with adverse events or other reasons cannot be distinguished from discontinuations due to poor adherence associated with lack of perceived clinical benefit or need for therapy due to severity of symptoms.

Fourth, we have no information about mail order use in this population. An unknown portion of the patients who failed to refill their index prescription could have taken the medication for up to 90 days.

Fifth, the MPR value may be underestimated if medications are obtained through other means, such as samples, which are not captured by the database. On the other hand, the assumption of ‘a prescription filled is a prescription taken’ may not be completely true, thereby overestimating adherence. Sixth, while the level of copayment was not associated with persistence in the present study, the results are generalizable only to patients with prescription drug coverage.

\section*{Conclusion}
This study demonstrated low persistence (13\%) with the 4 OAB drugs. ER formulations of oxybutynin and tolterodine had a statistically significant adherence advantage over IR formulations. However, adherence is still low; approximately 35\% to 36\% for the ER formulation compared with 15\% to 24\% with the IR formulations. Patient-reported data on perceptions and experiences with drug therapy for OAB are needed to determine the reasons for discontinuation of drug therapy and non-adherence, particularly whether discontinuation is due to perceived lack of effectiveness or adverse effects.

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\section*{DISCLOSURES}

This study was performed for The HealthPlan of the Upper Ohio Valley Inc. and sponsored by Novartis Pharmaceuticals. Two of the authors, Joseph Doyle and Rinat Ariely, are employees of Novartis Pharmaceuticals. The results of this study were presented at the American Society of Health-system Pharmacists Midyear Clinical Meeting in December 2006 (poster abstract #81). Anna D’Souza was a PhD candidate, and Lesley-Ann Miller was an assistant professor at West Virginia University in the Department of Pharmaceutical Systems and Policy at the time of conduct of the research and writing of the manuscript.

Work on the study concept and design was shared equally by D’Souza, Smith, Miller, and Doyle. Data collection was shared equally by D’Souza, Smith, and Miller. Data interpretation was primarily the work of D’Souza with contributions by Smith, Miller, and Doyle. All authors participated in writing and revising the manuscript with D’Souza contributing the largest share.
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REFERENCES


A

Although “real-world” evidence of the effectiveness of prescription drugs is generally recognized as an important component of formulary decision making, many observers believe that studies based on “real-world” data are underutilized by managed care organizations (MCOs). To explore perceptions of the optimal use of “real-world” data and to propose a course for the future integration of observational research into the decision-making process, a roundtable meeting was held in July 2007 in Salt Lake City, Utah. Two perspectives were represented by 5 individuals with experience in pharmacoeconomic and outcomes research and 5 individuals with experience in MCO drug formulary decisions.

The group identified the following as the most significant challenges to the use of real-world data: (1) quality of the evidence and the underlying data, (2) the complexity of research necessary to ascertain true efficacy and effectiveness, (3) a lack of consistency in quality assurance and quality assessment, and (4) the time delay from product launch to the availability of real-world data. The top 3 recommendations for improvement in the use of real-world data in decision making included: (1) emphasis on education about health research methods for analyzing real-world data, (2) development and systematic use of a process that would systematically evaluate the quality of observational research designs, and (3) the consistent utilization of tools to achieve a fair evaluation of observational research. This interactive dialogue among formulary decision-making experts from managed care and academic experts in pharmacoeconomics and outcomes research identified key barriers to increased use of observational data by formulary decision makers. In addition, the dialogue led to the definition and prioritization of actionable measures to overcome these barriers.

Background

Observational research involving the analysis of data collected in a naturalistic health care setting is an expanding field of science. Internationally, the number of studies based on real-world data has increased exponentially, and the methodology has matured to overcome some of the limitations of randomized controlled trials (RCTs) by delivering information on: (1) benefits and risks of drug treatments in large populations, (2) variation in individual patient and provider preferences, and (3) economic consequences of alternative decisions. With increasing acceptance of this type of research by policymakers, discussions have begun to focus on the extent to which the results of observational studies can be used by payers and policymakers for decisions regarding drug coverage and reimbursement. Although numerous sets of guidelines for the conduct of pharmacoeconomic studies exist, the managed care pharmacy field lacks consensus on how to use these guidelines in judging the quality of research design, result presentation, and interpretation.

Because RCTs and observational studies each have unique properties, the information gained from each of these sources is complementary. RCTs maximize internal validity at the expense of the external validity needed to generalize results to populations of interest to all types of decision makers. Observational studies and models can complement RCT results by studying research hypotheses in a real-world population under conditions that match the way medications are prescribed and used in reality better than in an RCT setting. An intermediate option, the pragmatic RCT, maintains some of the rigor of traditional RCTs, most notably random assignment to treatment and control conditions, but relaxes the methodological rules typical of RCTs (e.g., restriction of the study population to comorbidity-free patients, double-blind process, requirement that each participant continue to use the assigned treatment throughout a defined follow-up period) in the interest of conducting the trial in a setting that more closely resembles actual clinical practice (e.g., real-life patient populations, treatment assignments known to patients and investigators, permitting treatment switches at any time).

However, discussions on the relevance and use of observational research persist as confirmed by publications, such as MCO survey data in 2000, a literature review in 2002, and by a JMCP editorial published in 2003 that highlighted the continuing methodological pitfalls in observational research and ongoing distrust toward the pharmaceutical industry as sponsors of this research.

For purposes of this report, “real-world data” or “observational data” and “observational research” require further definition. The Real-World Data Task Force of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) defined real-world data as data not routinely collected in Phase III drug registration studies, including administrative claims data, patient registries, large simple trials, resource use collection alongside clinical trials, and electronic medical records (EMRs). In addition, some of these types of data could be combined, and the assumption is that data are often conjoined using modeling techniques.

The purpose of the roundtable discussion among specialists from managed care and academic pharmacoeconomists was to identify key barriers and to develop some feasible action toward
the more effective application of real-world information to formulary decisions. In this report, the proceedings of the roundtable discussions are summarized.

Conduct of the Roundtable Discussion
The roundtable discussion was structured in 2 parts: (1) presentations and discussion on the current status of standardization, research, and utilization of evidence based on real-world data, and (2) moderated discussion on the direction and advancement of the use of real-world data resulting in proposed action steps.

Part One
The ISPOR Real-World Data Task Force
A presentation on the work of the ISPOR Real-World Data Task Force provided background for subsequent discussions. The objective of the task force had been to develop a framework to assist health care decision makers in dealing with “real-world” data and information in “real-world” health care decision making, especially related to coverage and payment decisions. The Real-World Data Task Force concluded that on one hand, real-world data offer new insights into areas that are not covered by RCTs (for methodological, ethical, or other reasons), but on the other hand, real-world data studies have their own limitations. The Real-World Data Task Force identified needs for: (1) good research practices for collecting and reporting real-world data and (2) good process in using real-world data in coverage and reimbursement decisions.

The ISPOR Real-World Data Task Force found considerable variation in practice across countries and jurisdictions on how extensively real-world data are required, used, funded, and which formal requirements have to be fulfilled for inclusion and acceptance in formularies. In addition, despite the task force’s conclusion that use of real-world data should “follow well-established research practices,” they also observed a lack of stringency in the application of appropriate research methodologies and validation of results by decision makers or trusted intermediaries, which hampers the interpretation of these studies for many potential users.

Observational Studies from the Pharmacoconomics Expert View
The extent and variety of observational studies were demonstrated with 3 illustrative research studies that used real-world data to answer questions relevant to managed care decision makers.19–21 The first study was a retrospective analysis of bisphosphonates in the treatment of osteoporosis; the second was an assessment of asthma-related health care utilization with inhaled corticosteroids in combination therapy; and the third was a retrospective analysis of the predictive accuracy of a decision-analytic model of Helicobacter pylori eradication. The studies were selected to represent a broad spectrum in quality and complexity of research design, result presentation, and interpretation.

Use of RCTs or Observational Studies for Decisions in Managed Care Practice
Two real-world data studies were presented to compare their results to those of RCTs with the same drugs.19,20 Some of the criteria described by the Real-World Data Task Force were also applied to evaluate the quality of the real-world data studies. In an observational asthma study example, the real-world data results were not congruent with RCT results. The roundtable group concluded that it would not be prudent to use the findings from the observational asthma study for formulary decision making, medical policy development, or cost-effectiveness analysis. In an observational osteoporosis study example, a question was addressed that had not been evaluated in RCTs; namely, whether there is a difference in fracture risk reduction among oral bisphosphonates. The researchers used a thorough, transparent, and systematic methodology. The roundtable group considered the use of the findings for medical policy development and cost-effectiveness modeling to be reasonable.

Part Two
Core Areas of Concern and Opportunities—Moderated Discussion
Based on the presentations and their own experiences, the participants identified 6 major hurdles for routine integration of real-world data into the decision making process.

1. Time Delay: The integration of real-world evidence into the decision process may be difficult because of the time gap between the availability of the product and the availability of real-world data from routine clinical practice. The time horizon problem affects observational studies, as well as economic models. It is a perplexing challenge to make predictions about long-term clinical or cost consequences using limited data from short-term clinical trials or real-world data from products that have only been available for a limited time. Both observational and modeling studies are used to peer over the time horizon and project long-term outcomes that may lie more than a decade in the future.

2. Applicability: The available data and studies are usually funded by the pharmaceutical industry, which leads to some distrust toward the validity of the results. In addition, most of the databases, analysis plans, and statistical calculations are so complex that it is difficult for a person not trained in pharmacoconomics and outcomes research to evaluate the quality of the information. This problem will become more critical in a situation, when not only health plan specialists, but prescribers, employers, or patients want to use the information. The goal is that all parties sharing the risk (financial, clinical, and personal) will be able to interpret the implications of research findings for their specific organization or situation and to take the appropriate course of action (e.g., decide for or against a therapy, reimburse or not). Roundtable group participants suggested that application of independent quality criteria is
needed to ‘standardize’ the technical complexity, which will help researchers in the conduct and publication of studies and potential users in their evaluation. This could be achieved by applying a consolidated checklist, which would take the best components of tools that already exist and combine them into a coherent set of guidelines organized by the type and application of study at hand. For example, the ‘ISPOR Checklist for Retrospective Database Studies’ would be the recommended tool for studies conducted in administrative claims or EMR databases.

3. Hierarchy of Evidence: The Real-World Data Task Force summary led to a debate as to whether a fixed hierarchy of evidence is possible and desirable. While it would be helpful for the user of evidence to have a clear and simple guidance on rating quality (e.g., quality ranking of databases, checklists for quality evaluation, definition of expected standards, or minimum confidence intervals), this seems to artificially limit the scope of research and the degree to which it reflects the real world. For example, the value of a database has to be determined in the context of the purpose and objectives of the study and by its relevance to the decision at hand. While a pharmacy claims database is well suited to analyze the cost of pharmacotherapy, adherence, and drug-related questions, it is necessary to use data from medical or health records to measure the clinical outcome of the treatment. Medical or health records, however, often lack some of the information needed to analyze drug-related questions of pharmacotherapy, such as prescribed dosing regimens. Data sources should be rated considering their structure and content type in the context of additional criteria including, but not limited to, the study purpose, type of disease, and patient population. Participants in the roundtable discussion expressed the opinion that synthesis of existing evaluation instruments into a multi-factorial combined checklist with such criteria could help guide producers and users of observational studies in judging the database quality. The group concluded that to cover the different aspects of study quality, the existing checklists and guidelines should be integrated into a consolidated checklist. For example, measurements of indirect costs (utility), effectiveness, and adherence could be evaluated simultaneously using the same instrument. Such a tool could be used by researchers and users of the studies for quality assurance and quality assessment purposes.

4. Quality Assurance: Roundtable participants expressed the view that standards for the quality of observational studies are currently inconsistently accepted and applied by users and designers of pharmaco-economic research. Some opportunity was seen by the roundtable participants in creating independent bodies for registration, evaluation, and peer review of observational studies and their design. One recommendation is that all results should be published independent of whether they are in favor of the sponsor’s product or not. This could be controlled, for example, by the need for registration with an independent body of all planned outcomes research studies prior to conducting them with the consequence that only registered studies are accepted for publication. Standardization usually means reduced flexibility. While there is a need for improved quality control, increasing standardization of study methodology and underlying data may come at the cost of failing to make the methodological adjustments necessary to measure accurately the outcomes of medication use in real-world settings and populations.

5. Education: Roundtable participants expressed the opinion that inconsistencies in accepting and applying research standards are in part attributable to insufficient knowledge. Producers and interpreters of the studies may either not be aware of existing tools or not be able to apply them effectively. The need for better education of researchers and end users in pharmaco-economics, outcomes research, and the methodology used in these disciplines was identified as a critical means to increase acceptance of the evidence resulting from observational research.

6. Organizational: The 2 major organizations relevant to the discussion of the utilization of real-world data in decision making in the United States are ISPOR and the Academy of Managed Care Pharmacy (AMCP). These organizations are complementary in consideration of the value of observational studies, with ISPOR often representing the theoretical viewpoint and AMCP often representing the viewpoint of MCOs in the application of these study results. Although there are opportunities for a dialogue between these 2 organizations, currently official interaction is limited. Roundtable participants expressed the belief that an increasing bidirectional communication and exchange between ISPOR and AMCP would stimulate understanding of the needs of the users of real-world data by the researchers and implementation of widely accepted measures in future study designs.

■ Outlook for the Future

After outlining the status quo, the group developed a vision of what a “better world” of decision making would look like. For the areas of data collection, research, and education, the vision included: (1) a general need to augment the knowledge base among all stakeholders, (2) the improvement of the structure and quality of the evidence base, (3) the routine utilization of the existing real-world evidence for quality improvement in health care, and (4) transparency of models and their underlying assumptions (Table).

Allowing for individual autonomy and individual involvement (consumerism) is important to the acceptance of therapy-related decisions. Because both patients and health care providers want freedom of choice in selecting therapies, the success of the real-world data movement in the United States also depends on making data available to these constituencies, convincing them
of the validity of such analyses, and providing meaningful information to them in patient-oriented formats that readily support clinical decision making.

**Advancing Toward Better Decision Making Based on Real-World Data**

The last section of the discussions focused on the identification of opportunities to support the acceptance and integration of observational evidence for managed care decision making. These discussions focused on the following 3 areas:

- Tools: Consolidation of existing standards and supporting instruments would facilitate for users the systematic evaluation of the appropriateness of the databases and methods used in real-world data studies, in context to the objectives of the study (hierarchy/checklist/scoring system). The most important part of this work would be the process of improving acceptance and adoption of these standards as quality criteria for researchers and decision makers and categorizing the tools by type of database or outcomes study and the application of results (i.e., to optimize value across what type of health plan, insurer, or employer).
- Quality Assurance: Creation of independent quality assurance procedures and formalization of the dossier review process; and
- Education: Training and increase of the knowledge base among the researchers and the decision makers as the target audience of the studies.

As outlined in the Figure, 6 opportunities were rated as having the highest expected effect on the acceptance of observational studies:

1. **Collaboration of ISPOR and AMCP** in the publication of a guide (book) synthesizing and explaining the standards for real-world data research methods and interpretation (15 points);
2. **Consolidation of quality assurance criteria** for the assessment and application of real-world data for formulary decisions (9 points);
3. **Compilation of guidelines for standardization of research methods and decision support tools** concerning which types of databases are useful in answering specific research questions regarding effectiveness (8 points);
4. **Utilization of independent bodies for writing and evaluating formulary dossiers** (8 points);
5. **Increase training and education** among potential users of the real-world data studies (7 points); and
6. **Independent bodies for validation of national models**, and support in adaptation of the model assumptions and data to local health plans (6 points).

These activities were then translated into action steps around which further planning and execution can take place.

The recommended strategies to move these concepts forward included further development of the existing tools to assist in the conduct and evaluation of observational studies by consolidating them into a single resource. An example of such guidance would be the AMCP Format for Formulary Submissions, a set of evidentiary requirements for formulary submission dossiers that is becoming the “gold standard” for collecting and presenting necessary clinical and economic information underlying the formulary review process. The Format gives the manufacturer a clear structure for how to provide all information for its products. The intention behind the creation of a standard format was to increase the weight and value given to a systematic review and presentation of evidence for formulary decisions and to assure that the “value proposition” was based on good scientific evidence. However, some doubt remains in the literature as to what degree the economic evidence is useful or usable for the decision making process. Consolidation of existing tools by building on their strength and filling the potential gaps and by supporting their adoption through a process for dissemination, communication, and training, as suggested by this roundtable can further advance the quality of the evidence.

A second area of importance as defined by the roundtable participants was to improve quality assurance of observational

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**TABLE 1  Summary of Suggested Improvements for Integration of Observation Studies in Decision Making**

<table>
<thead>
<tr>
<th>Data Collection</th>
<th>Research</th>
<th>Education/Knowledge</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Investment in data quality and quality control</td>
<td>• Transparent models as a standard—continuous</td>
<td>• Real-world analysis integrated in the curriculum of</td>
</tr>
<tr>
<td>• Database design improved for RWD analysis</td>
<td>improvement procedures</td>
<td>schools of medicine and pharmacy</td>
</tr>
<tr>
<td>• Guidelines based on RW evidence</td>
<td>• Long-term follow-up studies for chronic</td>
<td>• RWD analysis and decision analysis represented on</td>
</tr>
<tr>
<td><strong>Routine procedures:</strong></td>
<td>diseases</td>
<td>board exams</td>
</tr>
<tr>
<td>• Prospective or concurrent look at patient safety</td>
<td>• RW data used to identify best long-term</td>
<td>• Outcomes info becomes publicly available</td>
</tr>
<tr>
<td>and management</td>
<td>outcomes (public health/social)</td>
<td>• Consumers understand the information better and</td>
</tr>
<tr>
<td>• Practice pattern analysis for drug evaluation</td>
<td></td>
<td>request it</td>
</tr>
<tr>
<td>• Analysis of appropriateness of drug decisions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Improved data lead to more reliability of predictions (models)</td>
<td>Transparency and collaboration lead to higher robustness</td>
<td>Improved knowledge leads to higher acceptance</td>
</tr>
</tbody>
</table>

RW = real world; RWD = real-world data.
Incorporating Observational Data into the Formulary Decision-Making Process—Summary of a Roundtable Discussion

**Figure**

Roundtable Participant Rating of Suggested Activities and Activity Categories to Increase Acceptance and Utilization of Observational Studies in Managed Care Decision Making

<table>
<thead>
<tr>
<th>Activity</th>
<th>Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hierarchy/checklist/score</td>
<td>35</td>
</tr>
<tr>
<td>Guidelines for research methods (database types, which/when)</td>
<td>20</td>
</tr>
<tr>
<td>Checklist for matching data source to research questions</td>
<td>15</td>
</tr>
<tr>
<td>Methodology map: match methods to data source</td>
<td>10</td>
</tr>
<tr>
<td>RW database types list</td>
<td>5</td>
</tr>
<tr>
<td>ISPOR/AMCP ‘Book/Guide on RWD”—The Gold Standard</td>
<td>0</td>
</tr>
<tr>
<td>Quality assurance</td>
<td></td>
</tr>
<tr>
<td>Standard checklist to evaluate quality of planned RWD studies</td>
<td></td>
</tr>
<tr>
<td>Validation and calibration of models by independent bodies</td>
<td></td>
</tr>
<tr>
<td>Registration of studies by independent bodies before start</td>
<td></td>
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<tr>
<td>Proof of concept</td>
<td></td>
</tr>
<tr>
<td>Dossier Review Process</td>
<td></td>
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<tr>
<td>Public clearance for value or HE section in dossiers</td>
<td></td>
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<tr>
<td>Have third party write/evaluate dossiers</td>
<td></td>
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<tr>
<td>Training/knowledge</td>
<td></td>
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<tr>
<td>Combined fellowships: OR/PE academics and managed care</td>
<td></td>
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<tr>
<td>Fellowships under AMCP/ISPOR coordination</td>
<td></td>
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<tr>
<td>Incorporate in curriculum</td>
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<tr>
<td>Adherence</td>
<td></td>
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<tr>
<td>Use RWD for pilot study on patient health outcomes due to persistence</td>
<td></td>
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<tr>
<td>Value based benefit design</td>
<td></td>
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<tr>
<td>Target of RWD data</td>
<td></td>
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<tr>
<td>Consumer/patient and provider</td>
<td></td>
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<tr>
<td>Consumer advocacy groups to foster accountability</td>
<td></td>
</tr>
<tr>
<td>Target employers to increase consumer involvement in HC decisions</td>
<td></td>
</tr>
<tr>
<td>Target ‘lay press’ as key communicators of health care outcomes</td>
<td></td>
</tr>
<tr>
<td>Infrastructure</td>
<td></td>
</tr>
<tr>
<td>Local co-chapters of AMCP and ISPOR to foster dialogue and actions</td>
<td></td>
</tr>
<tr>
<td>Report local experiences at national and international meetings</td>
<td></td>
</tr>
<tr>
<td>Next steps to RW task force report</td>
<td></td>
</tr>
<tr>
<td>ISPOR RW task force follow-up; address comments to report</td>
<td></td>
</tr>
</tbody>
</table>

This figure was derived from 5 MCO representatives and 5 pharmacoeconomists who rated the categories by distributing 10 points to specific activities (gray bars) or activity categories (black bars). The activities with zero values were suggested but did not receive any votes in the rating process.

Adherence = validation of the concept that persistence improves patient health outcomes; Infrastructure = creating an infrastructure for improving the dialogue between producers and users of real world data; ISPOR = International Society for Pharmacoeconomics and Outcomes Research; RW = real world; RWD = real-world data; Target of RWD data = including all stakeholder perspectives including patients.
study results. An analysis of the decisions of the P&fT committee of a 3-million member health plan on 43 drug products between February 2004 and December 2005,20 led to the conclusion by Spooner et al. that the delivery of a dossier did not appear to influence the likelihood of a product attaining preferred formulary status. There is a relationship between the extent to which a new product represents a meaningful clinical innovation and dossier availability and quality.27 Colmenero et al. recently found that among dossiers submitted to a health plan, a positive correlation existed between whether a drug was an innovative new product and the quality of information included in its dossier.25 However, despite the existence of product dossiers, this information is not being used because of ongoing skepticism due to the development of the dossier by the manufacturer. The assurance that the material contained within the dossier has met a quality standard, separate from the industry, is paramount to optimum use of the AMCP Format. Today few dossiers actually state which, if any, standards were used for inclusion of the material contained within the economic and value sections. The work suggested by the roundtable participants would lead to an agreed upon standard, by type of study, and may be a required component of future dossier submissions.

A final area for consideration is education of researchers and decision makers in the fields of pharmacoconomics, observational research, and statistics. Retrospective analysis of data can be used inappropriately as has been outlined fundamentally in a recent JMCP editorial.28 The distrust resulting from inadequate practices and the lack of knowledge of the science leads to skepticism on the part of the health plan in the ability to project real-world effectiveness based on RCT efficacy. Another fact supporting the persistence of barriers was seen in the lack of communication between the various stakeholders or the representative associations. Consensus on standards for conducting and evaluating real-world studies is important for both parties, and, therefore, involvement of all stakeholders, consideration of each perspective, and appropriate education and communication will be an important part of improving the adoption of such standards.

Next Steps
This or a similar group of MCO representatives and outcomes researchers will convene to continue the collaborative work started in this roundtable discussion. This will involve the following actions:

• an analysis of existing tools for quality assurance and quality assessment for observational research;
• the development of a consolidated comprehensive quality assessment tool resulting from analysis of existing tools;
• the outline of a process to support increased application of such a comprehensive quality assessment tool; and
• the development of training for producers and users of observational studies in line with the objective of increased application of quality assurance and assessment tools.

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Here Is the Case for the Urge in Administrative Claims Database Research About Overactive Bladder Therapies

Sheryl L. Szeinbach, PhD, MS, RPh, and Mark Jackson, RPh, BScPhm, BComm

With an estimated 16.5% of Americans experiencing symptoms from overactive bladder (OAB) and urinary incontinence (UI), this condition deserves continued research focus. In this issue of JMCP, D’Souza et al. present a retrospective claims database analysis of adherence, persistence, and switching behaviors, comparing cohorts of patients using different medications to treat OAB. D’Souza et al. use standard approaches to calculate adherence, persistence, and switching rates. Study patients had at least 1 pharmacy claim for either extended-release (ER) or immediate-release (IR) products for tolterodine or oxybutynin during the period from July 1, 1999, to December 31, 2003. Four patient cohorts (ER vs. IR for each of the 2 drugs) were followed from the index date to either discontinuation (defined as a gap in OAB therapy of at least 45 days), a switch to any other OAB medication, or the end of a 1-year follow-up period. The medication possession ratio was calculated as the sum of the total number of days supplied across all pharmacy claims except the last claim, divided by the total number of days from the first fill date to the last fill date. Persistence was measured as the proportion of patients continuing therapy for 12 months without discontinuation or a switch to another OAB drug. The switch rate was calculated as the proportion of patients who changed from the initial index medication to any other OAB treatment, including another study drug, a different dosage form of the same drug (e.g., oxybutynin ER to oxybutynin IR), or other medications, including trospium chloride, oxybutynin patch, flavoxate, hyoscymamine sulfate, or propantheline bromide.

D’Souza et al.’s findings pose a challenge to clinicians to find better strategies to diagnose and manage the symptoms of OAB. As revealed in this study, only 55.5% of patients refilled their first prescription for OAB medication and only 13.2% persisted with the index medication for 1 year. Also telling is the finding that medication switching appears to be common practice among these patients; the switch rate was 13.3% for the overall sample and 24.0% of patients with at least 1 refill. No significant persistence advantages were observed for any of the 4 OAB drug products in the study in multivariate analysis, although the odds of adherence with IR drugs were half that for ER drugs (odds ratio [OR] = 0.504; 95% CI, 0.306-0.704; \( P < 0.001 \)).

In any study, an assessment of whether the data are appropriate for the task at hand is necessary. The finding that only 53.7% of the patients had at least 1 OAB diagnosis recorded during the 18-month eligibility period provides evidence that OAB diagnostic information obtained from large databases is not without shortcoming. These low rates for OAB diagnosis pose serious threats to study validity in that D’Souza et al. may have assessed patients with OAB, as well as patients with interstitial cystitis or other UI problems triggered by urinary tract infections. In addition, subjective measures of well being and patient satisfaction, although not reported in claims databases, may also account for patients’ predilection to discontinue medications or use them intermittently according to lifestyle. For example, when medications for OAB are used only during travel, special events, or other activities to minimize the impact of side effects on quality of life, what appears to be discontinuation or non-adherence based on days supply intervals might actually represent a planned pattern of use.

The 13.2% persistence rate for the use of these drugs for OAB found by D’Souza et al. at 1 year is extremely low compared with persistence rates for other drug therapy classes. In a study conducted using a similar methodology from 1998 to 2000 in Quebec, 1-year persistence rates for angiotensin-converting enzyme inhibitors in cardiovascular disease ranged from 64% to 72%. Similarly, a cross-national study of persistence for antihypertensive medication use in the elderly revealed that approximately 25% of the patients were without medication for at least 180 days during the first year after the initiation of treatment. After 6 years, these percentages increased to 41.1%, 36.3%, and 38.2% for patients in Pennsylvania, British Columbia, and the Netherlands, respectively. Thus, persistence rates may suggest but do not necessarily explain the rationale for discontinuing or changing drug therapy. Other factors, such as behavioral modification, dietary change, and exercise, though not reported in databases, could improve patient symptoms, in part explaining the high rate of non-persistence.

The statistical techniques employed in the study by D’Souza et al. might have been inadequate to assess intermittent drug use that appears to occur with this particular drug class. In addition to controlling for covariates, such as prescription coverage and comorbidities, intermittent, or cyclic medication use, requires special consideration in data analysis, where censoring (failing to complete treatment) and changes in diagnosis, treatment, and eligibility status complicate analyses. Analogous to employment and unemployment fluctuations that were originally modeled as duration data, similar cycles with OAB medication use may be captured more accurately with an interval-censoring modeling approach to account for variations in medication-taking behavior. In addition, sensitivity analyses, expanding the study grace period of 45 days to include a range from 30 to 90 days may have detected more subtle nuances in medication use.

These questions about persistence and adherence become all the more important as newer agents for the management of OAB.
are introduced in the market. Managed care professionals are compelled to review both new and old OAB treatments in the formulary decision-making process.

In 2002, the Canadian Agency for Drugs and Technologies in Health, in conjunction with most publicly funded Canadian provincial drug plans, began developing a process known as the Common Drug Review (CDR). The CDR examines clinical and cost effectiveness of new drugs introduced in Canada to provide formulary recommendations to most provincial drug plans. The CDR is fundamentally similar to the National Institute for Health and Clinical Excellence (NICE) in the United Kingdom. Both evaluate pharmaceuticals with respect to clinical and cost effectiveness. However, the CDR’s mandate is limited to the review of all new chemical entities and combination products, whereas NICE undertakes reviews upon request.

To date, the CDR review for solifenacin found “insufficient evidence that solifenacin provides clinically important differences in outcomes compared with less expensive alternatives.” Reviews for both darifenacin and trospium chloride observed that while theoretical advantages may exist for these agents (i.e., reduced penetration of the blood-brain barrier leading to fewer central nervous system effects), these apparent advantages had not yet been supported through clinical trials in the elderly.

These somewhat vague Canadian conclusions had been previously reported by the Oregon Health Resources Commission in a January 2006 report. In this report, the authors agreed not only that evidence of consistent differences in drug efficacy (as measured variously by micturation frequency, number of urgency or incontinence episodes, etc.) was lacking, but that available evidence did not show consistent differences in the incidence of adverse events of drug withdrawals.

The CDR has also expressed concern regarding the growing number of agents to treat OAB, the increased use of these agents, and their risk/benefit profile, urging a class review of the safety, effectiveness, and cost effectiveness of these agents. Unfortunately, such a review would fall outside the existing mandate of the CDR as it would involve existing chemical entities, such as oxybutynin and tolterodine. To date, it is unclear how, when, or by whom such a review will be conducted.

The Ontario Ministry of Health and Long-Term Care’s Committee to Evaluate Drugs echoed the concerns of the CDR when reviewing trospium chloride and darifenacin, noting that “given the prevalence of the inappropriate use of drugs to treat OAB and the significant risk of clinically important side effects, especially in the geriatric population (i.e. delirium), the Committee indicated that expanding the use of this class of drugs could negatively affect [sic] the overall health of the Ontario population.”

As the number of drugs used to treat OAB has grown, so has the confusion over where newer drugs fit into the treatment of OAB. Unfortunately, the literature is lacking in “real-world” adherence and persistency data on the newer agents. While praising the potential benefits of trospium chloride, Halaska et al. (2003) also noted that the discontinuation rates in their study group were nearly identical between those receiving trospium chloride (25.0%) and those receiving oxybutynin (26.7%). While this study rightfully notes that the relative risk of experiencing an adverse effect favors trospium chloride, the similarity of the overall discontinuation rates raises questions with respect to the clinical significance of the favorable adverse effect profile of the drug. Hegde (2006) also noted that poor persistence will limit the long-term effectiveness of all available drugs to treat OAB.

There is clearly a need for a better understanding of adherence, persistence, and switching behavior in those taking drugs to treat OAB. Without such understanding, lifestyle preferences and psychological factors will continue to interfere with the long-term benefit of OAB treatments. Research databases contain a wealth of real-world information about general trends in medication-taking behavior including adherence, persistence, and switching in large populations. However, administrative claim databases fail to account for psychological factors underlying the decision to seek treatment and generally cannot consider other factors, such as incidence and severity of side effects, insurance coverage changes, alternative therapies, and lifestyle needs that may influence adherence and persistence. A concerted effort is needed to link these large databases with other sources of clinical information including patient history, clinical evaluation, and patient surveys.

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**REFERENCES**


Here Is the Case for the Urge in Administrative Claims Database Research About Overactive Bladder Therapies


Suboptimal Utilization of Secondary Drug Prevention in Acute Coronary Syndrome: Measurement Issues and Managed Care Opportunities

Brian J. Quilliam, PhD, RPh

The management of patients with acute coronary syndrome (ACS), including unstable angina, non-ST segment elevation myocardial infarction (non-STEMI), and ST segment elevation myocardial infarction (STEMI), continues to be a challenge for the health care industry. Despite numerous health care advances, ACS remains a major source of both morbidity and mortality. In 2005, there were approximately 772,000 patients with ACS discharged from hospitals in the United States.1 Further, myocardial infarction (MI) was the primary cause of death for nearly 157,000 Americans in 2004 and a contributing cause of death for approximately 40,000 additional persons.2 In addition to primary prevention efforts, joint guidelines by the American College of Cardiology (ACC) and the American Heart Association (AHA) suggest secondary drug prevention measures to be used in patients with ACS.2,3 In conjunction with diet and lifestyle modifications, these guidelines suggest the use of statin, beta-blocker, and renin-angiotensin aldosterone system inhibitor drug therapies in ACS patients.2,3 Unfortunately, the benefits of these drug therapies can be realized only if they are routinely used in clinical practice. Adoption and maintenance of such therapies requires commitment by patients, providers, and the health care system.

The article by Lee et al. in this issue of JMCP estimates compliance with ACC/AHA-recommended treatments, including statins, beta-blockers, and angiotensin-converting enzyme (ACE) inhibitors/angiotensin II receptor blockers (ARBs), following ACS hospitalizations.4 Lee et al. used pharmacy and medical insurance claims data for patients admitted to the hospital for ACS (from July 2003 through June 2004) and concluded that post-discharge secondary prevention was suboptimal, especially when evaluating the percentage of patients prescribed all 3 medication classes concomitantly.4 Further, the authors concluded that treatment rates varied by age (i.e., patients aged ≥80 years were less likely to receive any of the therapies), gender (i.e., women were less likely than men to receive statins), and specific diagnoses (i.e., patients with intermediate coronary syndrome were less likely than patients with MI to receive any of the study medications). As managed care pharmacists, providers, and administrators seek to improve the quality of care for their patient populations, these findings suggest that secondary drug therapy following a hospitalization for ACS is one potential area for improvement. Although largely descriptive, the study provides insight into the treatment patterns of a real-world population of persons with a recent coronary event, and the authors are to be commended for publishing these data.

Despite the relevance and timeliness of these findings, it is important to highlight and discuss several important limitations of these analyses (measurement issues) that should be considered alongside the results of this study. In addition, Lee et al.’s work also serves as a springboard for a larger discussion of several prominent opportunities for managed care.

Measurement Issues

Lee et al. used medical claims data from an insured population to identify patients with International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes (411.1 for intermediate coronary syndrome and 410.xx for acute MI) indicative of a hospitalization for ACS. For these purposes, the authors evaluated the primary diagnosis and up to 9 supporting diagnoses associated with the hospitalization claim. As in any claims-based study, a key question is the degree to which formal diagnoses accurately identified the target population. A 2004 validation study published by Rosamond et al. evaluated the validity of hospital discharge codes as an identification method for cardiac events by comparing hospital codes with the Atherosclerosis Risk in Communities (ARIC) identification criteria.5 This study found that 75% of persons identified via ICD-9-CM code 410 had a “definite” or “probable” MI according to the more rigorous ARIC classification scheme. When evaluating ICD-9-CM code 411.xx, only 14% of patients met the ARIC definition for “definite” or “probable” MI. Even after accounting for Rosamond et al.’s use of a broader code than Lee et al.’s code (411.xx encompassing both MI and other cardiac conditions in Rosamond et al. vs. 411.1 for intermediate coronary syndrome in Lee et al.), Rosamond et al.’s findings raise questions about what percentage of Lee et al.’s study patients actually had ACS and were candidates for treatment according to the ACC/AHA guidelines.2,3 Thus, the ACS population identified in the Lee study may overestimate the true target population and underestimate the true prevalence of drug treatment among patients with confirmed ACS.

Lee et al. identified a number of other factors that may have caused their estimated treatment rates to be biased downward, including contraindications to therapy, physician sampling of medications, the possibility that medication was received during a rehospitalization, and missing claims data because of the large number of elderly beneficiaries included in their sample.
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(i.e., prescription drug coverage caps among some Medicare beneficiaries during the study period). These issues are well known to those using medical claims data for research purposes and highlight the importance of careful interpretation of these and other results derived solely from health care claims databases. In the absence of conducting a more thorough chart review or interviewing patients (or physicians) directly, a more transparent presentation of these limitations, including sensitivity analyses to produce estimates of potential bias, would be helpful.

As an example, an estimated 32% of the 492 Medicare-eligible members in Lee et al.’s study sample (about 14% of the sample overall) were enrolled in a senior pharmacy benefits program that provided coverage up to $1,100 annually, with discounts on purchases over the $1,100 benefit maximum. Although the authors expressed a belief that the prescription price discounts were a sufficient incentive to encourage submission of pharmacy claims through the senior program, thereby ensuring complete claims capture, sensitivity analyses would have provided more definitive estimates of the effect of including this group in the study sample. Prevalence estimates, including the elderly beneficiaries known to have capped coverage, could have been compared with prevalence estimates obtained after excluding these study subjects. Such an analysis would have provided valuable insight into the robustness of these estimates and the degree to which this bias may be operating. In addition, a simpler approach would be to compare overall drug utilization (of all medications, not just those under study) across the elderly study subjects with full versus capped coverage or to compare utilization with some external benchmark, such as pharmaceutical usage in the Current Medicare Beneficiary Survey (CMBS). If the estimates in these populations were similar, the reader might infer that the capped prescription drug coverage among a portion of the elderly beneficiaries is potentially not influencing the estimated treatment effects.

Lee et al. raise the possibility that patients may have been prescribed appropriate therapy but failed to fill the prescriptions. Previous research on the propensity for patients to fill prescriptions post MI is consistent with this view. A recent study performed in Canada by Jackevicius et al. (2008) found that post-MI patients were more likely to fill prescriptions for cardiac medications than for noncardiac medications (82% vs. 35%, respectively) within 4 months of hospital discharge. In addition, in that study, most (73%) of all medications prescribed were filled within 7 days of hospital discharge. An additional study conducted in the U.S. by Butler et al. found that 80% of patients discharged from the hospital post MI with a beta-blocker prescription filled that prescription (as evidenced by pharmacy claims) in the 30 days following hospital discharge.

Despite the inherent limitations of estimating the prevalence of secondary preventive treatments among patients with ACS, using claims databases, the Lee et al. study supports other studies demonstrating suboptimal treatment rates with secondary pharmacological agents in the management of ACS. For example, Ye et al.’s claims database study found that only 47.8% of patients not taking a statin in the 6 months prior to hospitalization for coronary heart disease (CHD) filled a statin prescription within 6 months of hospital discharge. Ye et al.’s finding is similar to the statin treatment rate of 45.0% calculated by Lee et al. for patients without statin treatment in the 6 months prior to ACS hospitalization. Although the Lee et al. study is not without bias, it is unlikely that biases accounted fully for the large gap in treatment. Despite the success of numerous quality improvement initiatives conducted by managed care organizations over the last 3 decades, collectively the results from these studies demonstrate that there is room for improvement in the management of ACS. Thus, system-level factors may be necessary to promote more effective use of these agents.

Managed Care Opportunities

In spring 2007, the National Committee for Quality Assurance (NCQA) proposed retirement of the Beta-blocker Treatment after a Heart Attack (BBH) measure collected as part of the Healthcare Effectiveness Data and Information Set (HEDIS) measures. NCQA cited several important reasons for considering the retirement of this measure: health plans consistently performed well on the measure (≥90%); there was little variation between plans; and the measure was administratively complex, placing a high burden on health plans for its completion. After careful consideration, the measure was retired starting in the 2008 measurement year. An additional measure, the Persistence of Beta-blocker Treatment after a Heart Attack, will remain and assess the percentage of patients with an MI during the measurement year who were taking a beta-blocker for 180 days following the event. In an editorial in this issue of JMCP, Curtiss examines the apparent discrepancy between Lee et al.’s findings and the high rate of compliance observed by the NCQA, noting that the HEDIS measurement algorithm for BBH excludes patients with numerous comorbidities, including insulin-dependent diabetes mellitus, asthma, heart block greater than first degree, sinus bradycardia, congestive heart failure, left ventricular dysfunction, and chronic obstructive pulmonary disease. We can assume that quality prescribing post MI is a moving target that is not simply captured through a 1-faceted measurement. Because HEDIS measures are potentially effective in promoting quality use of medications, a future, more comprehensive measure assessing the use of beta-blockers, ACE inhibitors/ARBs, and statins may be warranted.

Another important opportunity arises from the current lack of guidelines applicable to the elderly population. Lee et al. found that patients aged ≥65 years were less likely to receive statins or beta-blockers compared with their relatively younger counterparts (aged 45 to 64 years). In addition, they reported that patients aged ≥80 years were less likely to receive ACE inhibitors or ARBs than patients aged 45 to 64 years. Within the
area of secondary prevention in patients with unstable angina, non-STEMI, and STEMI, the ACC/AHA guidelines provide clear recommendations on the use of secondary prevention agents, such as beta-blockers and statins, yet evidence supporting these and other guidelines relies heavily on the results of randomized clinical trials (RCTs). Although RCTs are esteemed as the gold standard for internal validity, their generalizability to elderly patients is often limited. RCTs often either exclude older study participants altogether or limit samples to highly selected populations (e.g., lacking comorbidities common among the elderly).16 As ACS commonly occurs with advanced age, suboptimal treatment rates in the secondary prevention of ACS may, in part, be due to lack of evidence of the risks and benefits of these treatments within the target population. Therefore, it is important that researchers, clinicians, and decision makers support the expansion of clinical studies to the elderly and consider the nuances of this population when making treatment recommendations.

Lastly, a recent movement within the health care industry is the introduction of pay-for-performance (P4P) measures that reward physicians through reimbursement increases and incentives based on predefined quality measures. In 2006, a survey conducted by Rosenthal et al. asked more than 250 health maintenance organizations (HMOs) if their contracts contained P4P.17 Rosenthal et al. found that 126 of 252 HMOs utilized some P4P measures, with 90% of these plans having at least 1 program geared toward physicians. A recent study by Cutler et al. evaluated diabetes control in a P4P program instituted in California aimed at promoting quality care in diabetic patients.18 In that study, the researchers found that the rate of low-density lipid cholesterol testing was higher in patients enrolled in a diabetes care program than in the control group (91.5% vs. 67.8%, respectively). As undertreatment of chronic conditions including ACS persists, we must consider the appropriateness of P4P measures as a means to promote quality prescribing. Will this method of reimbursement stand the test of time and improve the appropriateness of medications for important chronic diseases? Only time can tell.

In conclusion, despite methodological limitations of the Lee et al. study, undertreatment of ACS is probable. After decades of research identifying suboptimal treatment, it is important that we begin to take steps to correct these deficiencies and realize the benefits of optimal treatment within the population of ACS survivors. Three potential managed care opportunities for improving the secondary treatment of ACS include the introduction of new multifaceted HEDIS measures, the further expansion of guidelines, and RCTs to be inclusive of the elderly population and the evaluation of the merits of incentivizing physicians through P4P measures.

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HEDIS, Beta-Blockers, and What More Can Be Done to Improve Secondary Prevention in ACS

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The National Committee for Quality Assurance (NCQA) announced in May 2007 that it would discontinue the quality measure of beta-blocker use within 7 days of hospital discharge for myocardial infarction (MI). The stated reasons for this decision were widespread achievement of near-maximum use of beta-blockers in post-MI patients and little variance among health plans (and, therefore, little value as a quality measure to differentiate health plans). The NCQA 2006 report on the State of Health Care Quality showed that the use of beta-blockers after a heart attack was an average 94.3% of eligible patients in 2003, 96.2% in 2004, and 96.6% in 2005. Data reported nearly 10 years earlier in the 2004 Healthcare Effectiveness Data and Information Set (HEDIS) Version 3.0 from NCQA's Quality Compass 1997 for quality-of-care data in 1996 showed average health plan performance at 62% of patients discharged after an MI, compared with 25% of patients in fee-for-service medicine. The death of the quality measure of beta-blocker use after hospital discharge for MI marks an important success for managed health care.

As managed care celebrates this milestone, there are reports of interventions to increase the use of drug therapies for secondary prevention in patients discharged after acute MI. Daugherty et al. reported in March 2008 that post-MI patients who received early follow-up with a primary care physician (PCP) or cardiologist within 1 month of discharge were more likely to be prescribed beta-blockers at 6 months of follow-up, 80.1% compared with 71.3% of post-MI patients who did not receive early outpatient follow-up ($P=0.001$). In a coincident article, Smith et al. found that 2 early follow-up mailings 2 months apart to 836 patients who had been dispensed beta-blockers after acute MI significantly improved adherence to beta-blockers. Over the 9 months of follow-up after the first mailing in 4 health maintenance organizations in Boston, Minneapolis, Atlanta, and Portland, the patients who received the mail intervention were 17% more likely (relative risk, 1.17; 95% [confidence interval], 1.02-1.29) to have received beta-blockers to cover 80% of the days in the follow-up period.

In this issue of JMCP, Lee et al. found that only 63.9% of patients with hospital claims for acute coronary syndrome (ACS, including unstable angina as well as acute MI), received beta-blockers within 3 months of hospital discharge. This report by Lee et al. from a large managed care plan and the reports 1 month earlier about interventions to improve beta-blocker utilization in post-MI patients appears to be at odds with the decision by NCQA to discontinue this quality measure. What is going on here?

The principal answer to the question involves an interesting sojourn into the world of quality measurement. In the HEDIS quality measure of beta-blocker use after acute MI, the denominator is narrowed to include only patients discharged after MI with “no evidence of contraindication.” Contraindication to beta-blockers is defined broadly in the HEDIS measure to exclude acute MI patients with International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis codes for insulin-dependent diabetes mellitus, asthma, heart block greater than first degree, sinus bradycardia, congestive heart failure, left ventricular dysfunction, or chronic obstructive pulmonary disease. The research by Lee et al. made none of these exclusions, making their denominator much larger and, therefore, their result (63.9%) much smaller than the HEDIS average (94%-96%) during this time period. Lee et al. listed additional limitations that may have contributed to an underestimate of appropriate beta-blocker use in ACS patients, including inability to measure medication use not recorded in pharmacy claims (e.g., drugs dispensed as physician samples or during rehospitalization).

The current research performed by Daugherty et al. and Smith et al. highlight the difference between ostensible quality measures and real-world medical care. Daugherty et al. investigated the use of 4 categories of secondary prevention at 6 months after acute MI, underscoring the continued real-world interest in the use of evidence-based preventive therapies 6 months or more removed from the acute event that defined ACS. Smith et al. addressed a similar but more narrow objective, the use of beta-blockers at 9 months of follow-up after hospital discharge for acute MI. In Smith et al. and Lee et al., the health plans involved in the research quite likely participate in HEDIS reporting.

So, perhaps the death of 1 quality measure is really a prelude to the birth of an equally important quality measure, the proportion of health plan members that remain on therapy for secondary prophylaxis of ACS at 6 or 12 months after the acute event that defined ACS. Unfortunately, the research reported by Lee et al. does nothing to advance our knowledge of the use of beta-blockers at specific points in time after the index hospitalization for ACS. In addition to the many limitations acknowledged by Lee et al., including the absence of assessment of rehospitalizations in the 18-month follow-up period, this research measured only the receipt of 1 or more dispensions of each of the 3 target drug categories at any time over the 18-month follow-up period. So instead of showing, for example, that the proportion of patients using beta-blockers improved over time, from 63.9% at 3 months, 69.2% at 6 months, 73.5% at...
12 months, and 75.5% at 18 months, this research showed only that the cumulative incidence of use of beta-blockers increased over time, a mathematical certainty. Lee et al. do inform us, however, about the relative proportion of beta-blocker use in ACS patients with acute MI (71.6%) versus intermediate coronary syndrome (59.5%), and in their study, the intermediate coronary syndrome patients outnumbered the acute MI patients about 3 to 1.

As for other secondary prevention therapies, Lee et al. found seemingly low use (51.8%) of angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, at least 1 dispensing during the 3 months post discharge for ACS patients. For statins, 62.6% of patients received 1 more dispensing of this secondary preventive therapy during the 3 months post-ACS discharge. And, there was a low proportion of ACS patients (29.9%) that received at least 1 dispensing of all 3 secondary prevention therapies during the first 3 months of follow-up after the index hospital discharge with an ACS diagnosis.

Compared with the 69.3% of post-ACS discharge patients who received at least 1 dispensing of a statin during the first 6 months of follow-up in the study by Lee et al., Ye et al. found that less than 50% of patients with a diagnosis for coronary heart disease (CHD) received outpatient statin therapy within 6 months of discharge.8 The seemingly large difference in clinical quality reported in these 2 studies might be explained by the lower proportion of managed care patients in the study by Ye et al. However, the more likely source of the lower use of statins is the much larger net used to define the target population in Ye et al. to include patients with at least 10 additional ICD-9-CM codes, such as angina (413.x), coronary atherosclerosis (414.0), and cardiovascular disease unspecified (429.2). Second, the apparent large shortfall in quality of care discovered by Ye et al. was assessed over a 4-year study period that ended in 2003, and the proportion of CHD patients treated with statins increased each year to 56% of patients with a CHD hospitalization in 2003. A third consideration is that Ye et al. examined only statin therapy and did not determine the proportion of CHD patients who received lipid-modifying therapy other than statins, such as niacin, fibrates, or bile acid sequestrants. Like Lee et al., Ye et al. did not determine clinical need for lipid-lowering therapy with statins; some proportion of the CHD patients without statin therapy did not have a clinical need for this therapy.

With the demise of the HEDIS measure of beta-blocker use after hospitalization for acute MI, the stage seems to be set for new measures of health care quality in secondary prevention of cardiovascular events. Daugherty et al. point us to some benchmarks for possible quality measures in acute-MI patients after discharge, following intervention with a PCP or cardiologist; 80.1% receiving beta-blockers at 6 months, 82.9% for aspirin, and 75.9% for statins.9 Unfortunately, the research reported by Lee et al. in this issue of JMCP does not address this evolving quality measure but does remind us of the importance of specifying the type of ACS patient when assessing the relative quality of care among managed care organizations. The report card presented by Lee et al. gives an inflated “grade” for the proportion of ACS patients who received beta-blockers (69.2%) and statins (69.3%) at any time over 6 months of follow-up but does so without consideration of individual patient characteristics and no exclusions for contraindications or intolerance with these therapies, factors that would cause the reported grade to be higher if included in the calculation of the quality measure.

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Perspectives on the “Generic Cliff”—Pushing and Falling

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Wall Street health sector analyst Tim Anderson, MD, now at BernsteinResearch, called it the “generic cliff” in early 2007. From the perspective of brand-name pharmaceutical manufacturers and investors, the generic cliff is indeed formidable and often foreboding. What was a relatively gentle slope in erosion of the brand share of days of drug therapy when generic ranitidine entered the market in 1997, became steeper in August 2001 with generic fluoxetine (Prozac), and steeper yet with generic citalopram (Celexa) in November 2004 and generic simvastatin (Zocor) in July 2006 (Figure). For managed care organizations (MCOs), the generic cliff is a gold mine with a huge opportunity to increase the generic dispensing ratio (GDR) for individual drugs and for therapeutic classes through therapeutic selection.

MCOs have used physician and member financial incentives to increase GDRs, and thereby reduce the drug cost per therapeutic outcome. Low generic copayments and multiple-tier copayment designs are common tools to encourage health plan beneficiaries to use generic drugs. Fairman recently (2008) summarized nicely the literature on the controversial subject of member cost-share for pharmacy benefits, including the relationship of drug manufacturer sponsorship of the research and the study findings. While much of the research sponsored by pharmaceutical manufacturers concludes that higher member cost-share is associated with reduced medication adherence, Shrank et al. (2006) showed the flip side, that patients initiating therapy with lower-cost generic drugs had higher rates of medication adherence. Research in commercial populations has generally demonstrated consumer price insensitivity in response to copayment change. And, Klepser et al. (2007) dispelled the myth that making health plan members more aware of the true cost of drugs via a coinsurance design is associated with reduction in drug utilization.

For physicians, MCOs have exercised many methods to encourage prescribing of generic drugs, including an innovative method of generic sampling to physicians as recently reported in JMCP (2007). The success of some recent MCO interventions with physicians to increase generic prescribing is evident in the push-back from brand-name pharmaceutical manufacturers, including lobbying medical societies to prevent the spread of physician-incentive programs for generic prescribing. For example, Blue Care Network (BCN), a division of BlueCross BlueShield of Michigan, conducted its Blue Reward$ program in 2007 that targeted prescribers of fluvastatin (Lescol) or atorvastatin (Lipitor), paying its participating physicians $100 for each patient converted to a generic statin from either Lescol or Lipitor. The Blue Reward$ program reportedly spent $2 million in incentive payments to physicians, saving $5 million in annual drug cost for BCN and $1 million in lower (generic) copayments for members. Other health plans such as Excellus BCBS in upstate New York use physician-incentive programs to achieve increases in GDRs, and the GDR is evolving as a fundamental measure in physician pay for performance (P4P).

MCOs and employers have also found success in step-therapy programs and pharmacy benefit designs that impose maximum allowable costs by therapeutic indication. For heartburn for example, a therapeutic maximum allowable cost (TMAC) per day of drug therapy was found to produce savings per day of more than 80% and net savings per member per month (PMPM) of more than 90% for the drug plan sponsor. Admittedly, TMAC is limited to therapeutic classes such as drugs for heartburn, where there is little if any controversy about the interchangeability of therapeutic alternatives to obtain the same clinical outcome (relief of heartburn with comparable safety).

Yokoyama et al. found that a step-therapy intervention, which required first-line use of a (generic) angiotensin-converting enzyme (ACE) inhibitor prior to use of an angiotensin II receptor blocker (ARB), was associated with 13% in drug cost savings in the antihypertensive drug class, or approximately $368,000 in savings in 1 year or $0.03 PMPM across the 1 million health plan members. Since Yokoyama et al. evaluated outcomes for only 6 months of the intervention, the annual drug cost savings could have been twice as much, $0.06 PMPM or more than $700,000. Gleason estimated drug cost savings of $0.11 PMPM from a similar step-therapy intervention for ACE inhibitors as first-line therapy before ARBs. Dunn et al. found 9.0% drug cost savings for the entire class of antidepressants associated with a step-therapy intervention that required first-line use of a generic antidepressant, excluding tricyclics, in a 440,000-member health maintenance organization. The step-therapy intervention for antidepressants produced impressive drug cost savings of $0.36 PMPM or almost $1.9 million in 2005 dollars with only a 1.5% decrease in utilization of antidepressants, less than the decrease in utilization of antidepressants (-5.0%) in the comparison group.

The generic cliff is made higher and the gold mine deeper by widespread uptake of generic drugs. Data from IMS Health show that generic drugs accounted for 63% of all prescriptions dispensed in the first 6 months of 2007, up 10 percentage points (relative 19%) in just 30 months, from 53% in 2004. This increase in the nationwide GDR translates into a relative 33% increase in the proportion of total U.S. drug spending accounted for by generic drugs, from 12% in 2003 and 2004 to 16% in the first 6 months of 2007. A separate report in March 2008 from IMS data put the nationwide GDR even higher at 67% for the full year 2007, with a 20% ratio for generic drugs of total prescription drug spending.
The gold mine could be even richer for MCOs. Pharmacy benefit manager Express Scripts, in a non-peer reviewed analysis, estimated $17.1 billion in savings to health plan members and sponsors in 2006 for increased GDR in just 2 drug classes: $10.3 billion for anti-cholesterol drugs if the GDR increased to 85% from 18.8% in 2006 and $6.8 billion from an increase in GDR for the gastrointestinal drugs to 95% from 35.4%.

A total of $24.7 billion in savings could be achieved from increased GDR for these 2 drug classes plus 4 other drug classes, $3.4 billion from a GDR increase to 85% from 57% for antidepressants, $2.1 billion from a GDR increase to 75% from 58.3% for antihypertensives, $1.2 billion for a GDR increase to 97% from 77.0% for nonsteroidal anti-inflammatory drugs, and $0.9 billion for an increase in GDR to 95% from 49.4% for calcium channel blockers. For 2005, the estimate of health plan savings from simply increasing the GDR in these 6 drug classes was $21.7 billion.

The generic cliff looms disproportionately for pharmaceutical manufacturers. According to the analysis performed in late 2007 by Anderson, Das, Kowalski, and Chou at BernsteinResearch, the average lost revenue at the generic cliff for the 10 largest pharmaceutical manufacturers for the period from 2007 through 2012 is 24.7%, meaning that these 10 companies have to replace an average of one quarter of their total annual revenue with increased sales of either existing patent-protected products or new products. However, the generic cliff looms largest for Pfizer, which between 2007 and 2012 will lose patent protection on atorvastatin (Lipitor), amlodipine (Norvasc), and cetirizine (Zyrtec), accounting for 36.9% of Pfizer’s total revenue in 2007. The generic cliff through 2012 looms large also for Bristol-Myers Squibb, which has to replace the 31.3% of annual revenue accounted for by aripiprazole (Abilify), irbesartan (Avapro), and clopidogrel (Plavix). Two other companies with above average exposure are sanofi-aventis, with 27.8% of revenue in zolpidem (Ambien), enoxaparin (Lovenox), and docetaxel (Taxotere), and Wyeth with 26.1% of total revenue in venlafaxine (Effexor), pantoprazole (Protonix), and piperacillin/tazobactam (Zosyn).

To make the situation more perilous for brand-name pharmaceutical manufacturers, the generic cliff jumpers are being pushed. Some generic drug companies became more aggressive in 2007 in launching first-time generics “at risk” after the automatic 30-month stay that is granted at the beginning of litigation but prior to resolution of the litigation. There were 8 generic at-risk launches in 2007 compared with 2 in 2006. At-risk generic launches are indeed risky since triple damages are available to the brand-name pharmaceutical manufacturer, but the absolute financial risk may be less since triple damages have never been awarded to a brand-name pharmaceutical company that sued a generic manufacturer.

Teva Pharmaceuticals has been active in pushing brand-name drugs off the generic cliff. In December 2007, Teva launched generic pantoprazole (Protonix) at risk in the United States. This bold move by Teva upended the anticipated strategy by Wyeth to launch an authorized generic to capture a large part of the generic sales of pantoprazole. Instead, the amount of generic pantoprazole that was shipped by Teva in December 2007 was sufficient to cause the projected earnings per share for Wyeth for 2008 to be downgraded by 13% in late January 2008. One month later in the week ended January 25, 2008, generic pantoprazole from Teva had captured 60.3% of the total prescriptions for pantoprazole.

Teva had used this strategy previously with the at-risk launch of generic Lotrel in 2007, with enough generic Lotrel shipped to last “well into 2008.” Teva had also teamed up with Barr Pharmaceuticals to launch generic Allegra (fexofenadine) at risk, thereby spreading the financial consequences from an unfavorable court ruling, should any occur. Brand-name products threatened with at-risk generic launches in 2008 and 2009 include Allegra D, with an at-risk launch by Barr, and a possible at-risk launch of generic Topamax (topiramate) by Mylan.

Wall Street analysts and patent attorneys have predicted an increase in at-risk generic launches, in part due to 2 recent court cases. One case involving KSR International Co. in the U.S. Supreme Court made it easier to show that obvious ideas or ideas lacking innovation cannot be patented. The second case involved Seagate Technology, in which a federal appellate court decision changed the standard for proving willful disregard for patent rights, thereby making it harder to obtain an award for triple damages.

On the horizon are some very large generic cliffs. Among the standouts, Wyeth faces loss of patent protection on Effexor XR
in July 2010. Effexor XR is a top 10 drug by sales in the United States. Effexor XR retail sales in community pharmacies were $2.25 billion in 2006, and the drug was Wyeth’s number 1 drug by manufacturer sales last year, accounting for worldwide revenue of $968 million in the fourth quarter of 2007, 67% from U.S. sales, and $3.79 billion for the year.

In terms of market financial impact, the most significant generic cliff that may be imminent is esomeprazole (Nexium), with sales of $5.22 billion in 2007, accounting for 17% of total sales of heartburn drugs. Aside from the attraction of capturing some of the more than $14 million per day in sales, 2 facts suggest a generic cliff earlier than 2018, when Nexium is expected to officially lose patent protection. Ranbaxy holds “first filer” Abbreviated New Drug Application (ANDA) status for Nexium, and the 30-month stay ends in April 2008. More important perhaps, the 30-month stay for Teva’s ANDA for Nexium expires in July 2008. So, while Ranbaxy has no experience itself with at-risk generic launches, it is conceivable that Teva and Ranbaxy could team up to launch generic esomeprazole as early as April 2008.

The nationwide increase in use of generic drugs has contributed to a slowdown in the rate of increase in total prescription drug spending. The 3.8% increase in total prescription drug sales in the United States in 2007 to $286.5 billion, up from $274.9 billion in 2006, was the smallest increase since 1961 and down significantly from the more than 8% increase in 2006. IMS Health reported in March 2008 that brand-name drugs, representing $17 billion in U.S. sales, lost patent protection in 2007, contributing to an increase in the national GDR to 67.3% and generic drugs representing 20.4% of total prescription drug expenditures. Another $13 billion in brand drugs are expected to lose patent protection in 2008 contributing to estimates of continued smaller growth in total U.S. prescription drug sales, in the range of 3% to 6% per year for 2008 through 2012.

For MCOs, the next 5 years offer the opportunity for no growth in pharmacy benefit costs, even with no increases in member copayments and the anticipated increases in drug utilization as more drugs have lower (generic) cost-share for members. MCOs welcome a larger generic cliff and most have broad generic drug promotion programs that touch employers, members, and physicians. Excellus BCBS, for example, combines physician incentive payments with broad step-therapy interventions with first-line generics in 9 therapeutic categories, contributing to reported savings of $224 million in 2007, 4.5% of about $5 billion in drug spending as the GDR increased by 3.8 percentage points to 63.9% from 60.1%. The next 5 years pose continued difficult times for most brand-name drug manufacturers but sanguine times for persons responsible for management of pharmacy benefits, certainly a situation much different than just a few years ago.

References
Perspectives on the “Generic Cliff”—Pushing and Falling


**LETTERS**

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**Quantifying the Opportunity for Pharmacists to Improve Management of Hypertension in a Primary Care Medical Clinic**

**To the Editor:**

According to the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) guidelines, 30% of the U.S. population has hypertension. Sixty-nine percent of Americans are aware that they have hypertension, and 58.4% are using some form of antihypertensive treatment. Sixty-six percent of all patients are that they have hypertension, and 58.4% are using some form of antihypertensive treatment. Sixty-six percent of all patients are uncontrolled.1 Evidence shows pharmacy services in outpatient settings have a beneficial impact on patients’ clinical parameters and economic outcomes.2-4 Despite the many beneficial outcomes that are documented, not all institutions establish collaborative agreements between physicians and pharmacists that allow pharmacists autonomy in managing disease states.

A retrospective chart review was performed to assess the current practice management of hypertension by physicians in a primary care medical clinic that provides services for fee-for-service patients within a multi-specialty physician group practice. The objectives were to determine: (1) the proportion of patients with hypertension who were treated and controlled; (2) the dose and titration of antihypertensives in uncontrolled patients; and (3) the opportunity for better management of hypertension at this outpatient clinic to provide possible support for the implementation of a pharmacist-managed hypertension clinic. A randomized sample was created from a list of patients with systolic blood pressure readings ≥150 mm Hg or diastolic blood pressure ≥100 mm Hg from January 2006 to July 2006.

A total of 300 medical charts (males, n = 150; females, n = 150) were reviewed for this 6-month period. The majority of patients were Caucasian. Approximately 65.3% of males (n = 98), and 66.7% of females (n = 100) were diagnosed with hypertension. The average blood pressure for males at the time of diagnosis was 163/91 and 165/95 for females (data not presented).

A total of 102 patients (34.0%) did not have a diagnosis of hypertension (Table 1). Of these, 88.2% were receiving no treatment, and 24.5% had uncontrolled hypertension (defined as ≥2 medications that are documented, not all institutions establish collaborative agreements between physicians and pharmacists that allow pharmacists autonomy in managing disease states.

The proportion of diagnosed patients that was started on a medication at initial diagnosis was 47.8% (males) and 89.2% (females). The most commonly prescribed classes of antihypertensive medication upon initial diagnosis were angiotensin-converting enzyme inhibitors (ACEIs) and beta-blockers. There were 100 patients (33.3%) on no medications, 84 (28.0%) on monotherapy, 70 (23.3%) on 2 medications, 32 (10.7%) on 3 medications, 10 (3.3%) on 4 medications, 5 (1.0%) on 5 medications, and 1 patient on 6 medications for the treatment of their hypertension. For the 187 patients with uncontrolled hypertension, medication titration occurred on average at a blood pressure of 153/84, and titration intervals ranged from 5 months to 27 months (Table 2).

Compelling indications (i.e., diabetes mellitus, congestive heart failure, renal disease, myocardial infarction, stroke, high coronary disease risk) were also analyzed; 36% of patients (n = 108) had 1 or more compelling indications. Of the 28.7% (n = 86) who had 1 compelling indication, 8.1% (n = 7) were untreated (3 undiagnosed, 4 diagnosed), 23.3% (n = 20) were on 1 antihypertensive, 27.9% (n = 24) were on 2 antihypertensives, 23.3% (n = 20) were on 3 antihypertensives, and 17.4% (n = 15) were on 4 to 6 antihypertensive medications. The most commonly prescribed classes of antihypertensive medication in patients with compelling indications were ACEIs, beta-blockers, and loop diuretics.

This chart review found that 34.0% of patients with hypertension are undiagnosed, and 23.5% of these undiagnosed patients are both uncontrolled and untreated. The average diagnosis of a patient at this clinic is at Stage 2 hypertension, with females being diagnosed at slightly higher blood pressures, on average. Of those diagnosed, 33.8% received monotherapy, and 66.2% were on 2 or more antihypertensives; 68.7% of the monotherapy patients had controlled hypertension, and 51.1% of the patients on 2 or more antihypertensives had uncontrolled hypertension. Titration to the middle of the dose range is common with 45% of those patients being on ≥2 concurrent medications that are also not at maximum dosages. Overall, titration intervals remain wholly suboptimal.

In summary, this chart review found 34.0% of patients with elevated blood pressure (>150 mm Hg systolic or >100 mm Hg diastolic) were undiagnosed, and about one-fourth of these

### TABLE 1

**Characteristics of Patients With Hypertension (n = 300)**

<table>
<thead>
<tr>
<th></th>
<th>Uncontrolled (n)</th>
<th>Controlled (n)</th>
<th>Total (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>With diagnosis of hypertension (n = 198)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monotherapy</td>
<td>9.6% (19)</td>
<td>22.7% (46)</td>
<td>33.8% (67)</td>
</tr>
<tr>
<td>2 or more medications</td>
<td>31.3% (62)</td>
<td>33.8% (67)</td>
<td>66.2% (131)</td>
</tr>
<tr>
<td>Total</td>
<td>40.9% (81)</td>
<td>57.1% (113)</td>
<td></td>
</tr>
<tr>
<td>Without diagnosis of hypertension (n = 102)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No treatment</td>
<td>23.5% (24)</td>
<td>64.7% (66)</td>
<td>88.2% (90)</td>
</tr>
<tr>
<td>Monotherapy</td>
<td>0% (0)</td>
<td>5.9% (6)</td>
<td>5.9% (6)</td>
</tr>
<tr>
<td>≥2 medications</td>
<td>1% (1)</td>
<td>4.9% (5)</td>
<td>5.9% (6)</td>
</tr>
<tr>
<td>Total</td>
<td>24.5% (25)</td>
<td>46.1% (77)</td>
<td></td>
</tr>
</tbody>
</table>

*Chart review over the treatment period from January 2006 through July 2006. Undiagnosed, uncontrolled hypertension was defined as ≥2 consistent blood pressure readings above 120/80 on 2 different days within 3 months. Diagnosed, uncontrolled hypertension was defined as ≥2 consistent blood pressure readings above 120/80 on 2 different days within 3 months.*

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1. Evidence shows pharmacy services in outpatient settings have a beneficial impact on patients’ clinical parameters and economic outcomes.2-4 Despite the many beneficial outcomes that are documented, not all institutions establish collaborative agreements between physicians and pharmacists that allow pharmacists autonomy in managing disease states.

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**References:**

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**Tables and Figures:**

- **Table 1:** Characteristics of Patients With Hypertension (n = 300)

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patients had uncontrolled hypertension. For the patients with a diagnosis of hypertension, 40.9% were uncontrolled. There appears to be a significant opportunity to improve blood pressure control in this managed care medical clinic; pharmacists may be able to help physicians improve patient care by collaborating with them to initiate, titrate, and manage antihypertensive medications.

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The authors disclose that no outside funding supported this research/study. Rosalyn S. Padiyara contributed to the majority of the study concept and design, with assistance from Jennifer J. D’Souza. Padiyara performed the majority of the data collection and data interpretation, with assistance from D’Souza. Also, Padiyara wrote the majority of the manuscript, as well as the revision, with assistance from D’Souza.

REFERENCES

Letters to the Editor

JMCP welcomes letters that serve to clarify subjects published in previous issues of the Journal or regarding subject matter of interest to managed care pharmacists. Letters in JMCP are not peer reviewed but are subjected to editorial review. Letters should be prepared in a word processing program, preferably Microsoft Word, and submitted electronically at jmcp.msubmit.net. See www.amcp.org for details.
Confronting Hysteria: A Reply to Fairman and Curtiss

To the Editor:

In the March 2008 issue of JMCP, Fairman and Curtiss strongly criticized our controlled evaluation of a value-based insurance design (VBID) initiative published in the January 2008 issue of Health Affairs. More broadly, they take issue with the concept of VBID itself. Given the tone, we felt compelled to reply, yet disagree with only a few points of their critique. Before delving into the specifics, however, it is important to note that there is nothing included in their commentary that renders incorrect our findings that a reduction in out-of-pocket costs for patients significantly improved chronic medication adherence. More importantly, despite their critical assessment, we continue to believe that most health care stakeholders—including managed care pharmacists—will support our premise that it is not advisable to place strong financial disincentives on the use of high valued pharmacy and medical services.

Fairman and Curtiss raised 3 main criticisms. First, they claimed the results of studies such as ours are misinterpreted by the media and the concept of VBID is oversold. Second, they contend that the publication reports insufficient data to assess the validity of the findings (yet they do not fundamentally dispute the merits of the research design or the substance of the results). Last, they imply that the VBID concept is a bad idea. This third point may be an overstatement, but given the tone of the critique (“horrible surprises being designed to test your bravery and intellect”), we believe this is a reasonable interpretation of their position.

On the first point, we completely agree and sympathize with the viewpoint that VBID is often oversold, especially when it comes to the financial implications. Of particular concern are statements in the press—incorrectly attributed to us in the commentary—that VBID will reduce health care costs. A review on this topic would quickly reveal that we do not claim that this type of VBID program would save money. For example, we wrote in a recent commentary, “In a VBID implementation that only provides copay relief [as was the Health Affairs evaluation], the employer expenditure will often exceed the aggregate costs.”

This and other articles clearly articulate that the financial impact of VBID programs depends on the specific program design and the extent the intervention can target services to high risk patients with low baseline utilization.

Perhaps the confusion is in the subtle point that savings associated with increased use of high value services may exist, but may not outweigh the costs of the actual VBID program. As the authors note, and as we explicitly state in the Health Affairs article, we do not assess the financial effects of the intervention—a separate manuscript addressing expenditures is in progress. The closest we come to claiming anything about the financial effects is noting that preliminary analysis suggests the savings in non-drug services could offset the financial costs of increased use. We feel the commentary dramatically overstated our position in this study or elsewhere. At every opportunity, we stress that VBID can improve health outcomes per dollar spent at any level of health care expenditure, and refute claims of savings. It is our explicit intent to change the dialogue from one aimed at reducing expenditures, to a discussion directed at how we should finance health. We have testified on this precise point to federal commissions and include this conservative tone in our standard presentations. Thus, we welcome the authors’ scrutiny of this common assertion of cost reduction, and would like to emphasize that we concur.

With regards to the study design and presentation, the most important issue, as Fairman and Curtiss note, is the validity of the control group. They make a minor flaw by suggesting that the critical question is whether the control group would have responded similarly to the intervention group. Instead, what matters is whether, in the absence of the intervention, the trend in the intervention group would have matched what was observed in the control group. We too would be more comfortable with this assumption if the groups were equivalent. Yet as we note in the manuscript, the groups differ. More important than additional details about the differences between groups, it is clear from the text and the figure that adherence varied at baseline.

While this feature appears troubling, several facts mitigate concern. First, in our study design, differences in baseline adherence are not a problem if trends are similar, which was the case. Second, adherence in the control group was generally stable. Our results were driven by adherence changes in the intervention group, as opposed to changes in the controls.

Fairman and Curtiss also contend that we do not describe the intervention in adequate detail, although most of that criticism was about missing details of the control—not intervention—group. In addition to the description provided, we added that that implementation was imperfect (which we adjusted for in the computation of elasticities). Providing the requested details, (e.g., average copay for the treatment group [fell from about $20 to about $13] or benefit design in the control firm [which was complicated because of differences between mail order and retail charges and the blended use of copayments and coinsurance]) would not change the results. To reiterate, the most important element of our study design was that benefit design and chronic disease management—critical elements of utilization often not addressed in the existing literature—were stable in the control firm.

In some instances there were likely misunderstandings. For example, our pre-post adherence curves for both the treatment and control groups reflected our design which requalified subjects to maintain consistency in the pre and post samples (a goal we think we reasonably accomplished, as evidenced by the similar adherence in the control firm pre and post intervention). A single cohort design, as suggested by Fairman and Curtiss would be subject to bias (that would also need slaying), because adherence declines over time making the pre-post comparisons invalid.
Before the clearly recognized and addressed in the (which would be unlikely), our conclusion would hold. By price and utilization. Unless there were strong price effects one finds symmetry in spending, since spending is determined controlled studies on copay lowering and adherence effects. We believe it is reasonable to expect symmetry in utilization if one finds symmetry in spending, since spending is determined by price and utilization. Unless there were strong price effects (which would be unlikely), our conclusion would hold.

The most serious critiques, related to generalizability, were clearly recognized and addressed in the Health Affairs article. As journal editors ourselves, we realize that the design used, like any design, cannot be definitive. Fairman and Curtiss are correct to bring to light these limitations, but they seem to be under the illusion that every study must eliminate all sources of bias. This is certainly not the case of papers published in JMCP, The American Journal of Managed Care, or any other journal. Our view is that each study is a contribution of an evolving body of evidence. This publication was unique in that it explicitly controlled for variation in disease management initiatives, a feature we consider of first order importance because it causally relates to medication adherence. Moreover, unlike several seminal studies in the adherence literature, it incorporated a fixed effects design. Many of its flaws, such as imprecision about the details of the control group formula, could easily be applied to studies based on large claims datasets. The criticism seems to be focused on issues which, though potentially important, do not immediately suggest any particular biases in the findings or change in the main interpretation of the results.

Most importantly, Fairman and Curtiss seem to take fundamental issue with the concept of VBID. In this regard, we would be interested in their response to the following statements:

1) **The utilization of maintenance medications for chronic disease is not responsive to copay changes.** This is a difficult statement to agree with, because abundant and growing evidence (including research recently published in JMCP), suggests that these high valued pharmacy services are responsive to out-of-pocket costs. It may be the case that though they support the VBID principles, they take issue with the feasibility or precise features of a VBID program, which is certainly reasonable. However, as our study and numerous ongoing initiatives demonstrate, “clinically sensitive” VBID programs can be implemented. It may also be the case that they believe that VBID is only a part of thoughtful benefit redesign and that it is unwise to expect copay relief to solve the health care cost problem or broader dysfunctions in the health care system. We could not agree more; we consider it preposterous for these authors to insinuate that we believe that VBID would “save the world.” We have written extensively that VBID should not be viewed as a panacea for our system’s ills, but that “restoring health to the health care cost debate” is merely a small step in the right direction.

2) **The utilization of maintenance medications for chronic disease is not important.** Again we consider this a difficult position to agree with, because most clinical evidence supports use of maintenance medications in the clinical conditions we studied. Most evidence-based guidelines and quality improvement programs strongly advocate their increased use. Given the clinical data available, it is hard to dispute that use of these medications improves health and therefore, likely reduce adverse events. Whether the medical and non-medical financial offsets associated with enhanced use of chronic medications will counterbalance the extra spending, is an empirical question that deserves much more rigorous evaluation. No advocate for VBID or value in general, would argue that medical services—either high or low value—should be purchased in an inefficient manner, or that pharmacy benefit plans be designed without appropriate positive and negative incentives.

If Fairman and Curtiss disagree with both of the above statements then we proudly count them as supporters of VBID. It may be the case that though they support the VBID principles, they take issue with the feasibility or precise features of a VBID program, which is certainly reasonable. However, as our study and numerous ongoing initiatives demonstrate, “clinically sensitive” VBID programs can be implemented. It may also be the case that they believe that VBID is only a part of thoughtful benefit redesign and that it is unwise to expect copay relief to solve the health care cost problem or broader dysfunctions in the health care system. We could not agree more; we consider it preposterous for these authors to insinuate that we believe that VBID would “save the world.” We have written extensively that VBID should not be viewed as a panacea for our system’s ills, but that “restoring health to the health care cost debate” is merely a small step in the right direction.

Even if VBID is not the “dragon slayer” the authors refer to, we wish to reiterate that we unconditionally oppose the establishment of high out-of-pocket financial barriers for essential medications that clinicians “beg” their patients to take. We feel that managed care pharmacists—key stakeholders in the reform debate—would support this view; the proliferation of VBID products offered by pharmacy benefit managers bear this out. If Fairman and Curtiss defend the creation of patient-level barriers that will impede access to these high value services and ultimately worsen patient health, we are happy to take the alternative position. Our message is clear: cost-sharing is an important and essential part of an efficient health care system, yet it must be clinically derived in order to mitigate the adverse health care consequences associated with cost-related decreases in utilization. Available evidence allows us to depart the archaic “one-size-fits-all” approach to raising copayments for all services equally, and instead put our money where the health is. VBID plans, though by no means perfect, can support cost containment efforts and simultaneously enhance health. While the adoption of VBID may not dress the emperor in royal vestments, we believe it will improve upon the tattered garments in which our health system is currently clothed.

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Michael Chernew and Mark Fendrick provide consulting services to Hewitt Associates LLC and ActiveHealth Management related to value-based insurance design, and accept consulting fees and speaking honoraria related to value-based insurance design. Allison Rosen is employed by the University of Michigan’s Center for Value-Based Insurance Design. Wegh, Rosenberg, and Juster are employed by ActiveHealth Management, which provides consulting services to employers, health plans, and pharmacy benefit managers. Shah is no longer affiliated with ActiveHealth Management. The study referred to in the JMCP editorial and this letter was supported by GlaxoSmithKline and Pfizer, and the Center for Value-Based Insurance Design lists 6 pharmaceutical manufacturers as supporters.

All authors were responsible for the study concept and design of this research report. All authors shared equally the data analysis, data interpretation, writing, and revision.

REFERENCES
7. Landon BL, Rosenthal MB, Normand SLT. Formulary designs in an effort to improve compliance, the key question is not whether it is desirable to encourage patients to be adherent with chronic medication therapy; any reasonable observer would agree that patients should be encouraged to take medication as prescribed. The key questions are (1) whether the proposed benefit design change(s) improve compliance to a degree that affects patient outcomes, and (2) whether the additional expenditure associated with the change is efficient, that is, whether it allocates resources in a way that maximizes their value or wastes resources that could better be spent elsewhere. Put simply, the key question is what outcome(s) a health plan “buys” when it lowers copayments, thereby increasing its net cost for prescription drugs.

The Editors Respond Regarding the Shortcomings in Reported Research on Value-Based Insurance Design
We thank Chernew and colleagues for their response to our editorial on value-based insurance design (VBID) and for their stated commitment to health care system improvement. Of course, in making improvements to prescription drug benefit designs in an effort to improve compliance, the key question is not whether it is desirable to encourage patients to be adherent with chronic medication therapy; any reasonable observer would agree that patients should be encouraged to take medication as prescribed. The key questions are (1) whether the proposed benefit design change(s) improve compliance to a degree that affects patient outcomes, and (2) whether the additional expenditure associated with the change is efficient, that is, whether it allocates resources in a way that maximizes their value or wastes resources that could better be spent elsewhere. Put simply, the key question is what outcome(s) a health plan “buys” when it lowers copayments, thereby increasing its net cost for prescription drugs.

Unfortunately, no one really knows the answer to that question, and Chernew et al’s work provides little, if any, of the needed insight. Like their original research article, their letter is regrettably more notable for what it omits than for what it says. Among the important issues raised by Fairman and Curtiss, but unaddressed by the authors’ letter, are:
1) whether the medication possession ratio effect estimated by Chernew et al., an added 7 to 14 days of therapy annually, could reasonably be expected to have any impact on patient outcomes;
2) whether the study’s results reflect selection bias associated with open enrollment, in which members with a choice of plan (e.g., spouse’s insurance) who anticipate a high level of compliance with chronic medication use in the coming year naturally gravitate toward the plan in which drugs are available at a lower copayment;
3) what the actual total cost of the intervention was; and
4) whether key characteristics of the 2 employer plans and beneficiaries (e.g., formulary content, pharmacy benefit design features, industry sector, beneficiary-to-employee ratio, baseline expenditures, and levels of chronic disease) would have supported Chernew et al’s view that their study results are valid and relevant to health plans making decisions about benefit designs, had these critical details been included in the Chernew et al. research report.
While we do not oppose VBID in concept, we await the findings of research to determine its effectiveness, since to date controlled research evidence does not support it. As Fairman pointed out in her editorial review of cost-sharing in the January/February 2008 issue of JMCP, the assertion that commercially insured beneficiaries are price-sensitive in adherence to chronic medications is based largely on studies with weak cross-sectional research designs. Controlled studies of typical copayment increase amounts in commercial populations have documented modest effects on utilization overall and little or no impact on adherence to chronic medication.\(^3\) We are aware of only 1 study of out-of-pocket (OOP) cost reduction and adherence prior to the Chernew et al. analysis. Using a quasi-experimental (pre-post with comparison group) design, that study found that providing free glucose test strips to patients with diabetes “shifted costs from patient to health plan, without improving adherence” in blood glucose monitoring.\(^4\)

While we await studies of the effect of reducing copayments for brand drugs, payers can reduce patient OOP cost by promoting the use of generic medications. Generic drugs are available in most chronic therapeutic classes and in all the classes studied by Chernew et al. (except inhaled corticosteroids, for which there was no significant association between the benefit design and adherence), for a mean OOP cost of $11 per prescription in nationwide employer-sponsored plans in 2006\(^5\) and $5 per prescription in Chernew et al.’s intervention plan.\(^2\)

We do not understand Chernew et al.’s assertion that our editorial inaccurately attributed to them statements made by others. Our editorial directly quoted Chernew et al.’s original research article and the press release put forth by the University of Michigan, which houses the Center for Value-Based Insurance Design.\(^1,2,6\) These quotations included Chernew et al.’s statements that “…we expect health improvements, although we do not quantify them in this study,” and that because of the intervention, “there might be gains in worker productivity or reduced absenteeism or disability.”\(^2\) As we noted in our editorial, Chernew et al.’s report provided neither citations to published research nor study findings to support these statements.\(^1\) In that vein, we find it troubling that the University of Michigan’s press release described the Chernew et al. analysis as a “rigorous, controlled trial,”\(^6\) a term that erroneously implied randomization in an analysis that was in fact not randomized.

We are also disappointed by Chernew et al.’s persistent refusal to present critical data about their study groups, especially since, as we pointed out in our editorial, the small amount of information presented in the study report suggested that the study groups were very different at baseline (e.g., mean age difference of 7 years, baseline cost-sharing per generic claim of $5.00 and $16.22 for intervention and comparison groups, respectively).\(^1,2\) Whether the comparison group (“Company B”\(^6\)) is adequate to represent what the experience of a true control group would have been (i.e., had beneficiaries of “Company A”\(^6\) been randomized to intervention and control groups) remains unknown. Transparent disclosure of fundamental factors, such as the actual pharmacy benefit designs, formulary content, and baseline health-related information (e.g., utilization, chronic disease) for the 2 study groups would have enabled readers to decide for themselves whether the effects claimed for this VBID intervention are based on a valid analysis that provides relevant information for their health plans. As threats to the internal validity of trend analyses of non-randomized groups (e.g., possible selection bias associated with the intervention; the possibility of “selection maturation” effects that could be associated with different levels of chronic disease) are well known,\(^7\) we dispute Chernew et al.’s contention that their analyses are valid despite baseline differences, and we remain concerned about lack of disclosure. Chernew et al.’s dismissal of legitimate questions about the missing information with the statement that transparency “would not change the results” is both unhelpful and inconsistent with basic standards for the reporting of research results.\(^8,9\)

The feedback that we have received from health plans in response to our editorial suggests widespread frustration regarding the abundance of hype without substance regarding VBID. Mindful of what Chernew et al. describe as a “proliferation of VBID products,” we continue to urge both the conduct of better-controlled studies of cost-sharing decreases and appropriate caution in the adoption of untested benefit designs described as innovations.

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**REFERENCES**

