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REFERENCE

Karen Arrigoni was excited to show me her spectacular nature photographs when we met for her JMCP interview last month. She was getting ready to exhibit her photos in the visitor/gift center at historic Fort Snelling State Park in St. Paul, Minnesota. Arrigoni will display framed and matted prints of plants, birds, and animals that she photographed in locations near and far—from the garden in her front yard in Eagan, Minnesota, to the Minnesota Valley National Wildlife Refuge that stretches for 34 miles from Fort Snelling State Park to the city of Jordan. She has also traveled to the neighboring states of Wisconsin and Iowa for additional photo opportunities.

The highlights of Arrigoni’s impressive collection included photographs of Canadian geese in flight, a colorful cardinal perched on a snowy tree branch, a peaceful frog, an inquisitive doe, and of course, her gorgeous flowers. Kaleidoscopic Kreation I was definitely the star of the floral group. She photographed her garden’s orange zinnias and fuchsia pentas with a Nikon D50 digital camera and then manipulated the image using Adobe Photoshop to achieve the mesmerizing kaleidoscopic effect.

A traditional kaleidoscope is a viewing instrument containing loose bits of colored material held between two flat plates, and two rectangular lengthways mirrors set at 45° that create eight duplicate images of the objects. Kaleidoscopic Kreation I, as its name suggests, also has eight identical images. They merge in the center to form a flower that isn’t an actual flower at all, but one composed of the reflected centers and petals of the zinnias. Several shades of green from the flowers’ leaves and stems provide depth and contrast to the stunning photograph. Arrigoni said, “The process is a matter of trial and error. No two pictures will ever look alike. …” She likes to show people the original photograph that was used as the basis for her kaleidoscopic works—the difference between the two images can be striking.

Arrigoni is a self-taught photographer and has become adept at using telephoto and macro lenses as well as various filters. “My goal as a photographer is to take the ordinary and make it extraordinary. For example, an unremarkable bird such as a common grackle can suddenly look beautiful by the way the sun’s rays bring out the iridescence of its feathers. I want to show people that there is hidden beauty all around us,” she said.

Arrigoni credits her mother with teaching her to appreciate nature, and she believes that animals, like humans, have personalities. She has spent many hours observing nature, and has learned to distinguish the subtle movements of birds and animals. For instance, Arrigoni can tell when a group of birds is ready to take flight, which gives her the opportunity to get in the right position to achieve the best shot. “A great photograph takes a lot of patience. It’s all in the timing,” she observed. Arrigoni’s love for nature is reflected in the name of her new photography business, called Along Side Nature, and she is in the process of setting up her Web site, www.alongsidenature.com. She is also busy applying to several art fairs to exhibit her photographs.

Although Arrigoni enjoys the change of seasons in the upper Midwest, she is looking forward to the summer, when her garden will be in full bloom again. She is ready to “pull the weeds and snap the photos,” and there is no doubt that she will enjoy every minute of it.
Quality of Drug Treatment of Childhood Persistent Asthma in Maryland Medicaid Recipients in Transition From Managed Fee for Service to Managed Capitation

Puneet K Singhal, BPharm, PhD; Ilene Zuckerman, PharmD, PhD; Bruce Stuart, PhD; Laurence Magder, PhD; and Haya Rubin, MD, PhD

ABSTRACT

BACKGROUND: From December 1991 to June 1997, approximately 80% of Maryland's Medicaid recipients were served through a fee-for-service (FFS) managed care delivery system in which assigned primary care providers served as gatekeepers for hospital and specialty services. The remaining 20% of recipients were voluntarily enrolled in 1 of 5 available health maintenance organizations (HMOs). Beginning in June 1997, Maryland required most Medicaid recipients to enroll in capitated managed care organizations (MCOs), also referred to as managed Medicaid plans. Although research has been conducted on the quality of asthma care among MCOs and in FFS Medicaid recipients, the quality of asthma care has been less well studied for MCO patients than for FFS patients.

OBJECTIVE: To determine whether quality of drug use among Medicaid children with persistent asthma was different after the transition from the managed care FFS system to a capitated managed Medicaid system.

METHODS: This 4-year retrospective cohort study (from June 1, 1996, to December 31, 2000) followed children aged 5 to 18 years with persistent asthma (defined by the existence of at least 1 medical claim with an International Classification of Diseases, Ninth Revision, Clinical Modification diagnosis code of 493.x and receipt of 2 or more pharmacy claims for beta-agonists in a 6-month period) enrolled in Maryland Medicaid as they transitioned from the managed FFS system to 1 of 4 large capitated MCOs. Children were selected from a review of Medicaid enrollment records and medical and pharmacy FFS claims filed between June 1, 1996, and December 31, 1997. Children with a diagnosis of cystic fibrosis were excluded. The asthma quality indicator was defined as the proportion of children with persistent asthma (who had 2 or more claims for any short-acting beta-agonists [SABAs], including metered-dose inhalers, nebulizers, or oral forms, which we defined as rescue medication, within a 6-month period), who also had at least 1 claim for a controller medication (inhaled corticosteroid, mast-cell stabilizer, or leukotriene-receptor modifier) in the same 6-month period. Subjects were followed from June 1, 1996 (or, if later, the first Medicaid eligibility date), through December 31, 2000 (or, if earlier, the last Medicaid eligibility date). Mean quality indicator rates were calculated for the 2 managed FFS periods (FFS1 and FFS2) and the 6 managed Medicaid 6-month periods. We used generalized estimating equations to test for significant trends over time and to compare changes in the quality indicator in the managed Medicaid plans.

RESULTS: There were 3,721 children who met the inclusion and exclusion criteria for the study. The quality indicator (proportion of patients who received a controller medication among those receiving SABAs for asthma) was 62% in managed FFS1 and 57% in managed FFS2. In the first 6 months of managed Medicaid plans, the quality indicator rose from 56% to 57%, 59%, 61%, 66%, and 59% in the ensuing five 6-month observation periods. The results from the generalized estimating equations suggested slight improvement in the quality indicator in the managed Medicaid plans, but the difference was not significant (relative risk 1.01, 95% confidence interval, 0.95-1.08). There was no significant trend in the asthma quality indicator over time in the managed Medicaid plans.

CONCLUSION: There was no distinct improvement or worsening in asthma care as measured by the quality indicator (proportion of patients who received a controller medication among those receiving SABAs for asthma) as children moved from managed FFS to managed Medicaid. Larger sample sizes with no data loss may have produced a different result.

KEYWORDS: Medicaid managed care, Managed Medicaid, Fee-for-service, Quality indicator, Asthma, Children

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What is already known about this subject

- Studies evaluating access and quality of care in managed Medicaid versus FFS Medicaid plans have reported results that are mixed but that generally favor managed care.
- Almost all of the published work makes cross-sectional comparisons between care received in managed Medicaid and FFS Medicaid, and no study has assessed care quality in a longitudinal analysis.

What this study adds

- This longitudinal cohort design without a control group found that quality of care, defined as the proportion of children with persistent asthma who received a controller medication as well as SABAs, was no different in two 6-month managed Medicaid FFS periods than in six 6-month managed Medicaid periods.
- A quality indicator calculated as the ratio of Medicaid children in a 6-month period who have at least 2 pharmacy claims for acute rescue medications (SABAs) (the denominator) and at least 1 pharmacy claim for a controller medication (the numerator) requires large sample sizes to detect clinically meaningful quality improvement when measured longitudinally because of the absence of pharmacy claims for the cohort of patients in 1 or more 6-month periods.

Since the 1990s, managed care has become the dominant form of health care delivery for Medicaid recipients in states seeking to curb health care costs and improve access and quality of care. According to recent statistics, about 63% of
Medicaid recipients (28.6 million) in 49 states were enrolled in a Medicaid managed care organization (MCO, managed Medicaid plan) as of June 2005.4 Numerous studies have evaluated access and quality after transition from fee-for-service (FFS) to a managed Medicaid plan.4,5 A 1993 General Accounting Office (GAO) report summarized the studies examining access and quality issues under several state managed Medicaid plans, focusing on a variety of quality indicators such as pregnancy outcomes and prenatal care, well-child care and sick-child visits, preventive care for children and adults, and childhood immunization rates.2 The GAO report concluded that there was a slight improvement in access and the same level of quality of care in managed Medicaid plans as in the traditional FFS plan.

Another study reviewed access and quality in 6 Medicaid demonstration projects.3 The study found that access as perceived in Medicaid consumer surveys was generally greater for the demonstration (managed Medicaid) sites than for nondemonstration (FFS) comparison sites. However, access measured using objective measures, such as travel time and waiting time for appointments and in physicians' offices, was mixed between sites. Further, the review found that quality of care, assessed by using chart abstractions, showed no differences for birth outcomes and complications between demonstration and comparison sites. The other acute and chronic conditions studied for females, such as vaginitis, urinary tract infection, pelvic inflammatory disease, and hypertension, presented a mixed picture: equivalent or slightly worse care in 1 demonstration (managed Medicaid) site and equivalent or somewhat better care in another demonstration (managed Medicaid) site compared with FFS comparators.

Another review summarized access and quality of care studies for Arizona's managed Medicaid plan and New Mexico's FFS plan.4 The review found that children and pregnant women received earlier, more frequent, and more complete health care in Arizona managed Medicaid compared with FFS in New Mexico. Maternity care and pregnancy outcomes were similar in the 2 states.

Less well studied is the possible effect of managed Medicaid on chronically ill populations. The review of nursing home records in Arizona's managed Medicaid and Medicaid FFS plans in New Mexico suggested that Arizona's elderly and disabled were more likely to have pressure sores, fever, or a catheter inserted and were less likely to be offered an influenza vaccine.4 The fall and fracture rates and psychotropic drug use were similar between the 2 states.

Assessment of care quality is particularly important for children with chronic conditions because of higher ongoing costs associated with managing their illness.5,7 There is limited research examining quality of care received by Medicaid children with chronic conditions in managed Medicaid plans compared with an FFS plan.8-10 One study reported the Health Employer Data and Information Set (HEDIS) asthma measure for comparing quality of care received by New York Medicaid children enrolled in FFS with managed Medicaid.8 Using administrative datasets, the study compared the percentage of children with asthma aged 5 to 17 in the 2 plans. These children were continuously enrolled in their health plans for 2 years and received at least 1 medication acceptable as primary therapy for long-term control. Those in managed Medicaid had a higher rate on the quality measure compared with those in FFS (53% vs. 51%, P <0.001).

Shields et al. (2002) compared the process of care received by Massachusetts Medicaid children with asthma served by 2 managed Medicaid plans—a primary care plan and a staff model health maintenance organization (HMO)—with an FFS plan.9 The primary care plan comprised provider groups such as community health centers, hospital outpatient departments, and solo/group physicians. Adjusted analyses compared solo/group physicians in primary care plans with other provider types, including 2 primary care plans (community health centers and hospital outpatient departments), an HMO, and an FFS plan. The comparison was conducted on 5 process-of-care measures derived from administrative claims, including (1) access to a specialist for children with persistent asthma and for children with moderate/severe asthma, (2) appropriate use of controller medications, (3) overuse of beta-agonists, and (4, 5) follow-up visits after asthma-related emergency department visits or hospitalization. Compared with solo/group physicians plans, the FFS plan performed similarly on 4 measures and better on 1 measure (follow-up visits after asthma-related hospitalization).

Comparison of health care use and medication use patterns for children with asthma covered under Medicaid or non-Medicaid (commercial) payers within the same HMO found higher use of emergency department visits and hospitalizations and lower use of controller medications in Medicaid children compared with non-Medicaid children.10 Ambulatory visits and use of beta-agonists was similar in the 2 populations. This study by Finkelstein et al. examined the quality of care for Medicaid children compared with non-Medicaid children enrolled in the same health plan but did not report on quality of care for Medicaid members in managed Medicaid plans compared with FFS plans.

We conducted the present study as part of the oversight of the implementation of the Maryland HealthChoice program, a mandatory managed Medicaid program that enrolls most Medicaid recipients in the state. Previous evaluations of this program used cross-sectional designs to focus on access issues such as ambulatory care, well-child visits, and emergency department visits for the general population and, to a limited extent, for children with selected chronic conditions.11,12 The state's professional review organization (PRO), the Delmarva Foundation, also examined quality of care for children with

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chronic conditions under the HealthChoice program through onsite audits. To our knowledge, no published study has used a longitudinal design to compare the HealthChoice capitated managed Medicaid plan to pre-HealthChoice managed FFS.

To fill this gap, we analyzed the experiences of children with asthma in HealthChoice. We chose asthma because of its high prevalence among Maryland Medicaid children and because complications associated with the disease can be prevented by proper treatment and monitoring, outcomes that are anticipated in managed care. Our objective was to determine whether quality of prescribing for pediatric asthma treatment improved during the transition from FFS to the HealthChoice program. We hypothesized that HealthChoice managed Medicaid plans would be better able to communicate with providers and emphasize standards of care according to the national asthma guidelines than would an FFS plan. HealthChoice plans would do this by relying on better monitoring of drug therapy to minimize the costs of hospitalization and emergency department treatments. To test our hypothesis, we retrospectively followed a cohort of children with asthma from FFS into HealthChoice and tracked the quality of their asthma treatment using a variant of the HEDIS measure of quality of asthma treatment. This variant was the proportion of study subjects receiving 2 or more claims for short-acting beta_2-agonists (SABAs: metered-dose inhalers, nebulizers, or oral forms) as rescue agents in a 6-month period (a marker for persistent asthma) who also received at least 1 controller medication (an inhaled corticosteroid, a mast-cell stabilizer, and/or a leukotriene-receptor modifier) concurrently.

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**Maryland's HealthChoice Managed Medicaid Program**

Authorized under a federal section 1115 waiver, Maryland implemented its full-risk HealthChoice managed Medicaid program in July 1997 and required mandatory enrollment of most of the state's Medicaid recipients in 1 of 9 managed care plans (by 2002, the number of individual plans declined to 6 because of withdrawals and mergers). Excluded from the mandatory HealthChoice program were certain recipients, such as those dually eligible for both Medicaid and Medicare, and residents of nursing homes, chronic hospitals, and mental hospitals. In addition, individuals with qualifying “rare and expensive” medical conditions were permitted to opt out into an FFS case management plan. Eligible beneficiaries received a unified provider directory serving their region and listing HealthChoice MCOs. Beneficiaries were given 21 days to select both a health plan and provider (children in foster care were given 60 days) after which they were automatically assigned to a managed Medicaid plan based on geographic location and other factors. Five guiding values defined the purpose of HealthChoice: (1) provide a patient-focused system with a medical home for all patients; (2) provide comprehensive, prevention-oriented systems of care; (3) build on the strengths of the Maryland health care system; (4) achieve better value and predictability for state expenditures; and (5) hold MCOs accountable for high quality of care.

Under the program, the plans were contracted to provide the full range of health care services covered under the HealthChoice MCO benefit package, which was equivalent to benefits covered by the Medicaid FFS plan as of January 1, 1997 (except for certain carved-out services). The payment for enrollees’ health care services was based on a fixed monthly capitation rate, risk adjusted by the state for the enrollees’ health status.

The implementation of the HealthChoice program replaced other forms of less comprehensive managed Medicaid programs in the state, including an HMO program and a primary care case management program called Maryland’s Access to Care (MAC). The HMO program had been available since 1975 and had provided Medicaid services to recipients who enrolled voluntarily. The enrollment in the HMO program was limited; just about 20% of Medicaid recipients were enrolled in an HMO in 1997 before HealthChoice.

The MAC program had been a mandatory managed FFS Medicaid program, in operation since 1991. Under this program, most Medicaid recipients, except those enrolled in an HMO and some others meeting certain criteria, were required to either choose or be assigned to a primary medical provider (PMP). The PMPs acted as gatekeepers to the health care system, providing primary and preventive care and making referrals to specialty care as needed. The PMPs were paid on an FFS basis for all services provided and were not put at direct financial risk for the patients enrolled with them.

The MAC program, however, lacked the infrastructure to implement a comprehensive care management process (such as disease management and utilization review) for its enrollees and lacked incentives to limit the volume of services. In the end, despite improving access to primary and preventive care, the program cost more to the state than the program it replaced. With a fixed capitation rate arrangement under HealthChoice, the state placed health plans at direct financial risk and provided them with incentives to implement appropriate care management processes to control costs and improve access and quality.

Maryland’s HealthChoice managed Medicaid program enrolled more than 300,000 recipients between July 1997 and January 1998. The state required all plans to submit detailed patient-provider encounter data (also known as “pseudo” claims, since they were used to track use of services and not to give direct payment to providers) in order to set risk-adjusted capitation rates and to monitor quality. The state contracted with the Delmarva Foundation to provide quality oversight through periodic audits and client satisfaction surveys.

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**Methods**

Our 4-year study of the HealthChoice program involving...
Quality of Drug Treatment of Childhood Persistent Asthma in Maryland Medicaid Recipients in Transition From Managed Fee for Service to Managed Capitation

Children with asthma, dubbed Project INHALE (Initiative to Help Asthmatics Live Easier), is described elsewhere. Project INHALE was designed to use FFS claims, plan enrollment data, and MCO encounter forms to follow members of the study cohort through the transition into HealthChoice. Study subjects (n = 5,804) were selected on the basis of a review of Medicaid enrollment records and medical and pharmacy FFS claims filed between June 1, 1996, and December 31, 1997. Selection criteria included age (between 5 and 18 years at the time of MCO enrollment), a minimum of 3 months of continuous Medicaid enrollment during the baseline FFS period, and evidence of asthma at baseline. Evidence of asthma was based on meeting 1 or more of the following 3 criteria during the baseline period of at least 3 months: (1) at least 1 medical or hospitalization claim with an asthma diagnosis (International Classification of Diseases, Ninth Revisions Clinical Modification [ICD-9-CM] code 493.x) and at least 1 claim for an asthma-related drug, (2) at least 2 medical or hospitalization claims with an asthma diagnosis, or (3) at least 3 pharmacy claims for an asthma-related drug. Children with a diagnosis of cystic fibrosis (ICD-9-CM code 277.0x) were excluded from the study. The study was approved by institutional review boards at the University of Maryland at Baltimore and the Maryland Department of Health and Mental Hygiene.

We limited the present study to enrollees in the 4 largest HealthChoice managed Medicaid plans (n = 3,721). Using unique recipient identifiers, we merged FFS claims, plan enrollment data, and managed Medicaid encounter forms and created data files with information on Medicaid eligibility, setting (FFS or managed Medicaid with plan indicators), dates of managed Medicaid enrollment and disenrollment, and prescription drug use before and after transition to managed Medicaid. Date of first managed Medicaid enrollment was defined as the index date of the study, and enrollment plan was defined as the index plan. We followed each plan member in the study from June 1, 1996 (or, if later, first Medicaid eligibility date), through December 31, 2000 (or, if earlier, last Medicaid eligibility date). We censored observations after an enrollee lost Medicaid eligibility or switched from the index plan.

To measure the quality of asthma treatment during the FFS and managed Medicaid periods, we used a variant of the National Committee for Quality Assurance's HEDIS measure for the use of appropriate medications for people with persistent asthma. The HEDIS asthma measure identifies individuals with persistent asthma based on their medical and/or asthma drug use in one year, and then in the next year, determines the proportion of these individuals who used at least 1 medication recommended by the National Heart, Lung, and Blood Institute as primary therapy for long-term control of asthma. These medications, referred to as controller medications, include inhaled corticosteroids, mast-cell stabilizers, and leukotriene-receptor modifiers.

In Maryland, the managed Medicaid plans had inconsistent and erratic reporting (i.e., variations across plans and time) of encounter data, causing the HEDIS asthma measure to potentially produce invalid or misleading results if applied in its original form. The inconsistent and erratic encounter data reporting may have occurred for several reasons, including (1) lack of incentives for plans to submit data since there was no direct tie with reimbursement, and (2) data collection problems at both ends; that is, by plans from their network providers or subcontractors and by states from individual plans. We expected our quality indicator measure to overcome the problem with erratic reporting (i.e., variations across plans and time) of encounter data, causing the HEDIS asthma measure to potentially produce invalid or misleading results if applied in its original form. The latter is especially true for pharmacy services that are generally outsourced to a third-party administrator, which must collect data from network providers in a format compatible with the MCOs' systems, which, in turn, had to conform with the state's system. Eventually, these data problems were solved through active efforts on the part of both the state and MCOs, but in the interim, the problem with data completeness remained.

We adapted the HEDIS asthma measure to our current situation. To be consistent with the literature, we defined individuals with persistent asthma based on their receipt of 2 or more pharmacy claims for rescue medications (SABAs—metered-dose inhalers, nebulizers, or oral forms) in a 6-month period. Once we identified patients in this manner as having persistent asthma in a 6-month period, we determined the number of these patients who also had at least 1 pharmacy claim for a controller medication in the same 6-month period. Presence of a pharmacy claim for a rescue or a controller medication was operationally defined as the receipt of the medication. Thus, we defined the quality indicator measure as the proportion of study subjects who had 2 or more pharmacy claims for beta₂-agonists, and who had at least a pharmacy claim for a controller medication during the same 6-month period. Higher values on this measure indicate better quality of asthma care. The quality indicator measure for a 6-month period was computed as follows:

\[
\frac{\text{# of subjects who had at least 1 pharmacy claim for a controller medication among those who had 2 or more pharmacy claims for beta}_2\text{-agonists}}{\text{# of subjects who had 2 or more pharmacy claims for beta}_2\text{-agonists}}
\]

We expected our quality indicator measure to overcome the incomplete administrative claims reporting by the HealthChoice managed Medicaid plans, since the measure was based on a proportion of 2 types of asthma medications (controller and rescue) and there was no a priori reason to believe that prescription records for 1 type were more likely to be reported than for the other type; that is, administrative claims for a given patient would be either present or absent during any given 6-month period. We formally tested this presumption in an
earlier study and found the quality indicator measure to be robust to data loss. \(^{17}\)

We characterized the study sample on key sociodemographic factors, including age, sex, and race. As noted, the analyses focused on individuals with 2 or more rescue medication prescriptions in a 6-month period. For each person in the cohort, 6-month periods were defined based on time before and after the person’s index date of enrollment in a managed Medicaid plan. Two 6-month periods, FFS1 and FFS2, were defined as the FFS baseline, and six 6-month periods, T1 to T6, were defined as the managed Medicaid exposure (Figure 1). For each 6-month period, we identified all individuals continuously enrolled during the 6-month period who had 2 or more pharmacy claims for rescue medications (the denominator of the quality indicator). Then we determined the number of these patients who also had at least 1 pharmacy claim for controller medication (the numerator of the quality indicator). Using these data, we calculated mean quality indicator rates for each 6-month period before and after HealthChoice.

To assess the trends in the quality indicator rates over time, we plotted quality indicator rates from FFS1 through T6. To formally assess the statistical significance of observed trends, we fit log-binomial generalized estimating equations (GEE) regression models, which accounted for the correlation between repeated measures from the same individuals over time. \(^{20,21}\) The unit of analysis in these models was each 6-month period for each person. Only those periods were used in which the patient had at least 2 pharmacy claims for SABA (rescue) medication.

The outcome variable was binary: whether the patient received a controller medication. The exposure (independent) variable was whether it was an FFS or managed Medicaid period. In these models, we controlled for demographics (age, sex, and race) and season. The analysis accounted for increasing age of individuals over time. Season was dichotomized as fall and spring and defined on the basis of the most days falling between June and November (fall season) and December and May (spring season). For these regression analyses, we collapsed the baseline periods (FFS1 and FFS2) into a single reference category. Thus, the final pooled dataset consisted of individuals with only FFS, only managed Medicaid, or both FFS and managed Medicaid observations.

Individuals with only FFS (or only managed Medicaid) were those who either did not have a 6-month continuous eligibility during the managed Medicaid periods (or FFS periods) or did not have 2 or more prescriptions of rescue medications in the 6-month period if they were continuously eligible during the managed Medicaid periods (or FFS periods). The GEE analyses sample restricted to individuals with at least 1 eligible 6-month period in FFS or managed Medicaid resulted in a total of 1,604 unique people contributing 3,114 person-observations over 6 months. Figure 2 describes the study sample selection up to the sample for regression analysis. Table 1 describes the study measures employed in the regression analyses.

We used 2 models for the GEE analyses. Model 1 estimated whether managed Medicaid made a difference in the receipt of a controller medication. The model had the following structure:
where \( \log(p) \) is the log of the probability that the individual with 2 or more rescue medications received concurrent controller medication during the 6-month observation period; managed Medicaid is a binary indicator of whether the 6-month period was in managed Medicaid; Demographics is a vector of predictors (age, sex, race), and Season is an indicator of whether the 6-month period fell in the fall. In this model, \( b_1 \) coefficient represents the relative probability of receiving a controller medication in a managed Medicaid plan compared with the FFS baseline. The coefficient is interpretable as a percentage increase or decrease in the probability of receiving a controller medication during managed Medicaid compared with the baseline.

Model 2 estimated the change in the relative probability of receiving a controller medication over time during managed Medicaid periods. For estimating this model, we added terms interacting the main managed Medicaid impact with a time variable coded 1 to 6, representing the observation periods after baseline. The model structure was as follows:

\[
\log (p) = \alpha + b_1 \text{managed Medicaid} + b_2 \text{Demographics} + b_3 \text{Season}
\]

In this model, the parameter associated with the interaction term \( b_3 \) was interpretable as the degree to which the relative probability of using a controller changed over time within managed Medicaid relative to FFS. We conducted all analyses using SAS v. 8.2 (SAS Institute, Inc., Cary, NC).

**Results**

The mean age of the study sample was 10.5 (standard deviation, 3.8) years, and males constituted 56.8% of the sample. African Americans represented 59.1%, whites 36.4%, and others 3.5% of the sample. The plan enrollees were mostly similar in sociodemographic characteristics across 4 plans included in the study (data not shown).

The raw data to compute quality indicator rates and the computed rates from the 2 baseline FFS periods (FFS1 and FFS2) and 6 follow-up periods of managed Medicaid exposure (T1 to T6) are shown in Table 2. The quality indicator rates are presented in graphical form in Figure 3. The quality indicator rates for the 2 FFS baseline periods were 62% during FFS1 and 57% during FFS2 (Table 2). During the 6 managed Medicaid periods, the quality indicator values ranged from a low value of 56% during T1 to a high value of 66% during T5.

The multivariate results from the 2 GEE models are presented in Table 3. The first panel shows the relative risk (RR) of receiving controller medications during the managed Medicaid plan periods compared with the FFS baseline periods (Model 1). Overall, the relative probability of receiving a controller medication appeared to be slightly greater (1%) during managed Medicaid than during FFS, but the effect was not statistically significant (RR, 1.01; 95% confidence interval [CI], 0.95-1.08).

The second panel in Table 3 shows the results for the changes in the relative probability of receiving controller medications over time during the managed Medicaid periods (Model 2). Overall, there was no trend in the quality indicator rates over time during the managed Medicaid periods compared with the FFS baseline (RR, 1.02; 95% CI, 0.99-1.04).
FIGURE 3 Proportion of Patients With at Least 1 Pharmacy Claim for Controller* Medication Among Those With at Least 2 Pharmacy Claims for Rescue* Medications During the Fee-For-Service and Managed-Medicaid 6-Month Periods†

* Controller medications included inhaled corticosteroids, mast-cell stabilizers, and leukotriene-receptor modifiers. Rescue medications included only short-acting beta2-agonists (metered-dose inhalers, nebulizers, and oral dose forms).
† FFS1 and FFS2 were baseline managed-fee-for-service periods and T1 to T6 were managed Medicaid periods.

TABLE 3 Impact of Transition to Managed-Medicaid on the Relative Risk of Receiving at Least 1 Controller Medication* Among Those Receiving 2 or More Rescue† Medications in the Same 6-Month Period

<table>
<thead>
<tr>
<th>Model</th>
<th>Relative Risk</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1</td>
<td>Managed Medicaid</td>
<td>1.01</td>
</tr>
<tr>
<td>Model 2</td>
<td>Managed Medicaid</td>
<td>0.93</td>
</tr>
<tr>
<td></td>
<td>Managed Medicaid x time</td>
<td>1.02</td>
</tr>
</tbody>
</table>

* Controller medications included inhaled corticosteroids, mast-cell stabilizers, and leukotriene-receptor modifiers.
† Rescue medications included only short-acting beta2-agonists (metered-dose inhalers, nebulizers, and oral dose forms).
Note: The time variable ranged from 0 to 6, representing fee-for-service baseline 6-month periods (time = 0) and managed Medicaid plan follow-up 6-month periods (time = 1 to 6).
Reference group: fee for service.
Control variables included age, gender, race, and season and their coefficients for Model 1 were age: 0.99 (0.98, 1.00), gender: 1.00 (0.92, 1.08), race: 1.06 (0.98, 1.15), and fall season: 0.98 (0.93, 1.03). P <0.05.
CI = confidence interval.

Discussion

The 1990s witnessed a major shift of Medicaid enrollees from FFS into managed Medicaid plans. Although the new health care delivery system promised to improve access and quality of care while keeping costs down, it is important to evaluate if these goals were actually achieved. These evaluations of program outcomes may attract more attention for certain subpopulations, such as children with chronic illnesses like asthma. Quality indicators based on national treatment guidelines may provide a useful tool in this regard.

The present study evaluated one small aspect of quality of care for children with asthma enrolled in the Maryland HealthChoice program. Since we were forewarned about missing encounter data during managed Medicaid periods,19 we used a HEDIS-related quality indicator that we found in an earlier study to be robust to data loss.17 Briefly, in that study, in a series of Monte Carlo simulations, we artificially simulated several degrees (3% to 95%) and types of data loss (systematic, i.e., missing data for entire periods, and random, i.e., missing data across periods) in the FFS portion of our dataset. We measured the percentage of deterioration in the quality indicator we observed on the basis of the complete data, which gave an indication of the robustness of the measure to data loss (i.e., low deterioration in quality indicator indicated high robustness to data loss). Although the measure was not validated against medical charts, it was found to be robust to data loss in simulation experiments to the extent that the data loss did not exceed 35%, meaning that the measure was found to be insensitive to data loss of the magnitude up to 35%. The state's own analysis of various types of encounter data showed pharmacy data to be more than 85% complete across MCOs during the study period (relatively less-complete data elements were physician: 75% to 90% and inpatient hospital: 50% to 75%), reassuring the use of the asthma quality measure for producing valid results in the present study.19

To evaluate how Maryland's HealthChoice program affected the quality of care, we retrospectively tracked asthmatic children enrolled into the 4 largest managed Medicaid plans during their transition from FFS to HealthChoice. Specifically, we examined whether there was any significant improvement or deterioration in the quality of drug use for the treatment of persistent asthma as measured by the quality indicator during the transition. We found none. This finding of no change from FFS to managed Medicaid compares with improved access to care found in a separate study of the HealthChoice program. In that study, over the approximate time period of our analysis, Medicaid children, on average, had a 3% higher rate of ambulatory care visits during the HealthChoice periods than during FFS periods.12 However, improved access to care seen in that study was not reflected in our study in improved quality of care.

In another study of the quality of pediatric asthma care in Maryland Medicaid, the state's PRO, the Delmarva Foundation, found that a larger proportion of chart reviews conducted at
managed Medicaid plan sites, 84% in 2000 compared with 55% in 1998, met the state's specified quality standards for pediatric asthma care. This study performed by the PRO covered the same time period as the present study, but the method for quality assessment differed from our study (i.e., chart review versus analysis of administrative claims), and there was no comparison of outcomes in managed Medicaid versus FFS.

Our findings are consistent with another evaluation of Maryland HealthChoice for substance abuse treatment patterns and outcomes. In that study, Etter et al. (2003) linked Medicaid eligibility files with treatment provider records and found that treatment utilization and outcomes did not differ in those entering the treatment in MCOs than in FFS. And although utilization was higher and outcomes were better for a subgroup of beneficiaries transitioning from FFS to MCO during the study period, the positive effect was explained to be most likely due to the switching of providers and reevaluations.

Our findings are also consistent with a study by Shields et al. (2002), who reported no difference in quality for Medicaid childhood asthma treatment on the basis of a measure similar to the one used in the present study. The quality measure used by Shields et al. was the proportion of patients who received at least 1 controller medication among patients who received 3 or more months' supply of beta-agonists (aerosols, nebulizer, or syrup) within a 6-month period. Shields et al. found that compared with children in a managed Medicaid group, children enrollees in FFS were equally likely to receive the controller medication (odds ratio, 1.17; 95% CI, 0.82-1.67).

Roohan et al., in a study reported more recently (2006), compared asthma quality of care in managed Medicaid with Medicaid FFS in New York State and found better quality under managed Medicaid: the proportion of moderate to severe asthmatics who received a controller medication was 53% in managed Medicaid compared with 51% in FFS. Our study did not find improved quality in managed Medicaid, but the findings of Roohan et al., while statistically significant, represent a small absolute difference in the comparison of managed Medicaid with FFS Medicaid.

There are at least 3 possible explanations for the null findings in the present study: One, it may be that nothing happened; that provider practice patterns are consistent and not sensitive to health plan organizational structure. An analysis of whether there was some change in the makeup of health care providers for these children with asthma in the managed Medicaid transition would have been helpful in shedding some light on this issue; however, physician-level information was not available to us.

Two, our FFS care was delivered under the MAC program, and the care delivery was already at a relatively higher quality level before HealthChoice. Previous evaluations of the MAC program have reported improved access and higher quality of care under MAC than under traditional FFS. Schoeneman et al. found that, compared with traditional FFS, the MAC program increased the use of primary and preventive care services and of prescription drugs. Similarly, Gadomski et al. (1998) found that the MAC program increased the probability of preventive and any ambulatory visits and reduced the probability of avoidable and any hospitalizations when compared with traditional FFS.

It is possible that the quality of care in certain areas, such as asthma care, reached ceiling effects before HealthChoice via MACs primary case management program; however, it is not possible to test this possibility empirically.

Three, we did not have sufficient power to detect significant differences due to the sample size limitations.

Limitations

The first and foremost limitation in the present study is the threat to validity caused by missing administrative data, particularly in the managed Medicaid time periods in which the administrative data were not the basis for provider reimbursement. While calculation of our quality indicator was previously found to be robust to missing data, the sample sizes in the present study might not be large enough to show statistical significance when the change in the quality indicator appeared to be clinically meaningful. We did not validate the observed quality indicator against the medical records, which would presumably rule out any potential bias due to missing encounter data.

Second, as in any longitudinal study without a control group, the dependent measure can be influenced by any number of unobservable factors, such as change in patient or provider behavior over time. New asthma guidelines were released before the transition of the majority of our sample into managed care. However, we do not believe this affected our results, since the 1997 guidelines did not differ from previously published 1991 guidelines in the particular aspect that we evaluated in our study; namely, the treatment of persistent asthma.

Third, we compared quality of asthma care in managed Medicaid with prior enrollment in managed FFS on the basis of only 1 measure. Using other quality measures, including access to care, provider follow-up visits, or receipt of controller drugs after an emergency department visit or hospital discharge, with an asthma diagnosis might have produced different results.

Fourth, the present study was not able to examine differences in care delivered by individual health plans because of the sample size limitations.

Conclusion

Over the entire 4-year period of this study, approximately 56% to 66% of Medicaid children in any given 6-month period received a controller medication in addition to at least 2 pharmacy claims for a SABA. There was no difference in the quality of asthma care between capitated managed Medicaid plans and Medicaid managed FFS plans for these children with persistent asthma.
Quality of Drug Treatment of Childhood Persistent Asthma in Maryland Medicaid Recipients in Transition From Managed Fee for Service to Managed Capitation

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Singhal served as principal author of the study. Study concept and design were contributed primarily by Stuart, with a significant contribution from authors Laurence Magder and Ilene Zuckerman and additional input from author Haya Rubin. Data collection, data interpretation, and writing and revision of the manuscript were the work of all authors.

REFERENCES
Comprehensive Coronary Artery Disease Care in a Safety-Net Hospital: Results of Get With The Guidelines Quality Improvement Initiative

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ABSTRACT

BACKGROUND: Adherence to published coronary artery disease (CAD) guidelines is suboptimal, particularly among minorities and the poor. While hospital-based quality-improvement programs may increase the use of evidence-based therapies, little data exist regarding the impact of such programs in sociodemographically disadvantaged (vulnerable) populations. Vulnerable patients in the United States are cared for primarily within the safety-net health system, which comprises urban public hospitals and outpatient community health centers. Denver Health is an example of an integrated system that encompasses both types of facilities.

OBJECTIVE: To assess evidence-based medication use in CAD patients after initiation of an inpatient quality-improvement program at Denver Health.

METHODS: We reviewed the medical records of 499 patients with angiographically proven CAD who were hospitalized between July 1998 and December 2002. Patients were prospectively identified through a multidisciplinary intervention led by a nurse manager, and their records were input retrospectively into the American Heart Association’s Get With The Guidelines patient management tool. The association’s program, which recommends initiating 4 cardioprotective drug classes while patients are hospitalized, was started 2 years into the observation period (August 2000). Treatment rates were compared over the ensuing years.

We evaluated temporal trends in discharge use of 4 drugs: (1) beta-blockers, (2) angiotensin-converting enzyme inhibitors (ACEIs), (3) hydroxymethylglutaryl coenzyme A reductase inhibitors (statins), and (4) aspirin. We calculated the proportion of eligible patients (no documented contraindication) who were prescribed each drug category as well as the proportion who received all 4 drug categories, our principal composite outcome. If any one drug was absent, the composite criterion was considered unmet.

RESULTS: We observed progressive improvement in discharge use of the 4-drug composite: 18% in 1998-1999 (95% confidence interval [CI], 12%-25%), 50% in 2000 (95% CI, 37%-63%), 62% (95% CI, 54%-70%) in 2001, and 72% (65%-79%) in 2002 (P < 0.001 for between-year differences). Among eligible patients discharged in 2002, 90% received beta-blockers, 91% received ACEIs, 86% received statins, and 93% received aspirin.

CONCLUSIONS: Implementation of a multidisciplinary program led by a nurse manager was associated with increased CAD guideline compliance among sociodemographically disadvantaged patients. This compliance exceeded national averages. Achievement of the composite measure of use of all 4 recommended drug categories at discharge improved from 18% in 1998-1999 to 72% in 2002.

KEYWORDS: Coronary artery disease, Get With The Guidelines, Safety-net hospital

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What is already known about this subject

- Despite strong scientific evidence and national guidelines, patients with CAD are undertreated with evidence-based drugs.
- The American Heart Association’s Get With The Guidelines program is an inpatient quality-improvement initiative; its successful implementation in safety-net hospitals has not been well characterized.

What this study adds

- Our study suggests that a multidisciplinary team intervention improves CAD process of care in a vulnerable patient population.
- To our knowledge, this is the first Get With The Guidelines study to use a composite 4-drug measure of quality, and it reinforces the need to provide comprehensive pharmacologic care to CAD patients.

Coronary artery disease (CAD) is the leading cause of morbidity and mortality in the United States, with annual costs exceeding $160 billion.1 Effective pharmacologic interventions to attenuate atherosclerotic risk have been identified, including angiotensin-converting enzyme inhibitors (ACEIs), aspirin, statins, and beta-blockers. All 4 drugs are recommended in the American College of Cardiology and American Heart Association (ACC/AHA) guidelines.2

The AHA’s Get With The Guidelines (GWTG) program is a hospital-based initiative that promotes incorporation of the ACC/AHA secondary prevention guidelines into national CAD care delivery.3 A major focus is appropriate pharmacologic treatment during hospitalization, since many patients are inadequately treated despite widespread guideline dissemination. The AHA GWTG program defines appropriate treatment based on eligible CAD patients receiving ACEIs, beta-blockers, hydroxymethylglutaryl (HMG) coenzyme A reductase inhibitors (statins), and aspirin.

Despite the fact that these medications are recommended in evidence-based guidelines,2 a substantial treatment gap remains, particularly among minorities and the poor.4-6 The mission of Denver Health is to care for poor and uninsured people, but it also provides a broad spectrum of care, including trauma and emergency (911) services, to all citizens in the Denver metro area. In 2000, we instituted a multidisciplinary program at our safety-net institution to enhance care for hospitalized patients...
with CAD. We piloted this program for 1 year but were able only to demonstrate significant improvements in ACEI and statin use, not in aspirin or beta-blocker use.\(^7\)

We therefore evaluated the program over a longer period (4.5 years). Specifically, we assessed whether compliance with all 4 guideline-based medication classes had increased. The Joint Commission (previously known as the Joint Commission on Accreditation of Healthcare Organizations) continues to emphasize isolated medication core measures but has begun to shift its focus toward more comprehensive care. The 5 Million Lives Campaign suggested that hospitals aspire to “perfect care” across 7 treatment domains, 6 of which are medication related.\(^8\) Given recent data suggesting an additive mortality reduction when all 4 drugs are used for hospitalized CAD patients,\(^9\) we sought to assess compliance with this more comprehensive quality-of-care measure after patients were discharged.

### Methods

#### Patients and Setting

The Colorado Multiple Institutional Review Board approved the study. The patient population consisted of patients with angiographically documented CAD who were admitted to the cardiology service at Denver Health between July 1998 and December 2002. Denver Health is a member of the National Association of Public Hospitals and Health Systems. It is organizationally unique since it integrates both inpatient and outpatient community health services and maintains an academic affiliation with the University of Colorado.\(^6\) Denver Health is a safety-net hospital with 466 staffed beds and serves a population that includes a high proportion of minorities and many financially disadvantaged patients. Our hospital actively screens hospitalized patients for enrollment in an indigent care program, which provides discounted prescription drug benefits to all financially disadvantaged patients who do not qualify for Medicare or Medicaid. At the time of the study, Denver Health provided nearly one third of the uncompensated care for indigent patients in Colorado and was one of the first medical centers in the state to adopt the GWTG program.

#### Intervention

Beginning in August 2000, we assembled a multidisciplinary GWTG hospital team, including a physician champion, a clinical pharmacist, and a dedicated nurse manager who directly participated in daily Coronary Care Unit (CCU) teaching rounds with cardiology attending staff and resident physicians. Each month, new resident physicians were oriented by the nurse manager, who emphasized the importance of prescribing the 4 classes of evidence-based medications (aspirin, beta-blockers, statins, and ACEIs) to all CAD patients unless their use was contraindicated.\(^7\)

Mandated treatment algorithms or printed orders were not used; however, a sticker reminding staff of the importance of the 4 guideline-based drugs was placed on all patients’ charts. Although prescribing decisions were left to the discretion of the responsible physicians, during CCU rounds, the nurse manager was encouraged to highlight patients who were not receiving target medications. The clinical pharmacist also alerted resident physicians by pager about similar oversights when the pharmacist was reviewing medication orders.

The nurse manager provided educational materials and individual counseling to CAD patients. The encounter was documented in the medical record. Counseling focused on smoking cessation, activity recommendations, dietary suggestions (e.g., minimizing intake of saturated fat and cholesterol), and medication teaching. Medication teaching principally focused on the need for long-term medication adherence to reduce the risk of future MI and, if needed, for navigating our medication assistance program. The hospital team participated in semiannual GWTG workshops and monthly teleconferences to identify barriers to providing optimal care.

#### Data Abstraction and Definitions

Patient data were stored using an Internet-based patient management tool designed specifically for AHA GWTG participating hospitals. The electronic medical record was reviewed to confirm clinical, demographic, and outcome data for all CAD patients. The chart abstraction process focused on the provision of evidence-based cardiovascular drugs recommended by the GWTG program (aspirin, beta-blockers, statins, and ACEIs) and determining eligibility (lack of documented drug contraindication). Initiation of the target drugs, as well as of documented educational counseling, during hospitalization was ascertained. We required the drug to be explicitly written in the discharge orders and therapeutic lifestyle counseling to be clearly recorded in the progress record. Clinical comorbidities and sociodemographic characteristics of the patients were also assessed. Acute MI was defined according to the revised Joint European Society of Cardiology/ACC consensus document.\(^10\) Patients were included for analysis only if they had angiographically significant CAD, defined as a \(>50\%\) diameter obstruction of a major epicardial coronary artery.\(^11\)

#### Statistical Analysis

Medication treatment rates were compared temporally as the proportion of eligible patients receiving a guideline-based drug at hospital discharge. We calculated the proportion of eligible patients prescribed each drug as well as the proportion receiving all 4 drugs each year. If any one drug was absent, the composite criterion was considered unmet. Hospitalizations between 1998 and 1999 were randomly selected and served as historical controls and were compared with patients discharged after the program started in 2000.
Comprehensive Coronary Artery Disease Care in a Safety-Net Hospital: Results of Get With The Guidelines Quality Improvement Initiative

### TABLE 1 Patient Sociodemographic Characteristics*

<table>
<thead>
<tr>
<th></th>
<th>All Patients (N = 499)</th>
<th>1998-1999 (n = 131)</th>
<th>2000 (n = 54)</th>
<th>2001 (n = 148)</th>
<th>2002 (n = 166)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female gender</td>
<td>35%</td>
<td>39%</td>
<td>41%</td>
<td>36%</td>
<td>31%</td>
<td>0.41</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>38%</td>
<td>41%</td>
<td>35%</td>
<td>39%</td>
<td>37%</td>
<td>0.51</td>
</tr>
<tr>
<td>Latino</td>
<td>42%</td>
<td>44%</td>
<td>33%</td>
<td>41%</td>
<td>43%</td>
<td></td>
</tr>
<tr>
<td>African American</td>
<td>18%</td>
<td>15%</td>
<td>29%</td>
<td>18%</td>
<td>17%</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>2%</td>
<td>2%</td>
<td>2%</td>
<td>3%</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>Below high school education</td>
<td>53%</td>
<td>53%</td>
<td>56%</td>
<td>50%</td>
<td>53%</td>
<td>0.92</td>
</tr>
<tr>
<td>Insurance status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uninsured</td>
<td>54%</td>
<td>54%</td>
<td>50%</td>
<td>54%</td>
<td>55%</td>
<td>0.73</td>
</tr>
<tr>
<td>Medicare/Medicaid</td>
<td>36%</td>
<td>40%</td>
<td>39%</td>
<td>36%</td>
<td>33%</td>
<td></td>
</tr>
<tr>
<td>Private/HMO</td>
<td>10%</td>
<td>6%</td>
<td>11%</td>
<td>11%</td>
<td>12%</td>
<td></td>
</tr>
<tr>
<td>Current tobacco use</td>
<td>45%</td>
<td>52%</td>
<td>48%</td>
<td>41%</td>
<td>41%</td>
<td>0.12</td>
</tr>
<tr>
<td>Alcohol abuse</td>
<td>18%</td>
<td>18%</td>
<td>19%</td>
<td>22%</td>
<td>13%</td>
<td>0.22</td>
</tr>
<tr>
<td>Illicit drug abuse</td>
<td>12%</td>
<td>11%</td>
<td>17%</td>
<td>13%</td>
<td>8%</td>
<td>0.19</td>
</tr>
</tbody>
</table>

* Values are expressed as simple proportions or means with standard deviation [SD].

### TABLE 2 Clinical Characteristics*

<table>
<thead>
<tr>
<th></th>
<th>All Patients (N = 499)</th>
<th>1998-1999 (n = 131)</th>
<th>2000 (n = 54)</th>
<th>2001 (n = 148)</th>
<th>2002 (n = 166)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-C (mg/dL)</td>
<td>102 [37]</td>
<td>105 [38]</td>
<td>102 [40]</td>
<td>103 [37]</td>
<td>90 [35]</td>
<td>0.75</td>
</tr>
<tr>
<td>History of COPD</td>
<td>16%</td>
<td>21%</td>
<td>8%</td>
<td>20%</td>
<td>12%</td>
<td>0.02</td>
</tr>
<tr>
<td>Diabetes</td>
<td>39%</td>
<td>34%</td>
<td>28%</td>
<td>41%</td>
<td>43%</td>
<td>0.11</td>
</tr>
<tr>
<td>Hypertension</td>
<td>67%</td>
<td>67%</td>
<td>65%</td>
<td>66%</td>
<td>67%</td>
<td>0.99</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>38%</td>
<td>47%</td>
<td>37%</td>
<td>35%</td>
<td>35%</td>
<td>0.14</td>
</tr>
<tr>
<td>Peripheral arterial disease</td>
<td>6%</td>
<td>7%</td>
<td>4%</td>
<td>5%</td>
<td>7%</td>
<td>0.75</td>
</tr>
<tr>
<td>Chronic renal disease</td>
<td>9%</td>
<td>8%</td>
<td>4%</td>
<td>9%</td>
<td>10%</td>
<td>0.33</td>
</tr>
<tr>
<td>History of stroke</td>
<td>10%</td>
<td>13%</td>
<td>6%</td>
<td>10%</td>
<td>9%</td>
<td>0.45</td>
</tr>
</tbody>
</table>

* Values are expressed as simple proportions or means with standard deviation [SD].
† Body mass index = weight in Kg/height in m².
BP = blood pressure; COPD = chronic obstructive pulmonary disease; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol.

Continuously distributed variables were summarized using means and standard deviations. Means across years were then compared using analysis-of-variance models. Categorical variables were summarized as proportions, and 95% confidence intervals (CIs) were calculated for the principal outcome variables (individual and composite drug use). Proportions were compared using chi-square tests. A Cochran Armitage test was conducted to determine if the proportion of patients treated...
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With all 4 drugs as well as the individual component medications increased over time. All tests were 2-sided and conducted at the 5% level of statistical significance. Statistical analyses were performed using SAS version 8.0 (SAS Institute, Cary, NC).

Results

Sociodemographic characteristics reflected a vulnerable population and are listed in Table 1. The overall mean age was 59 ± 12 years, and 59% (296 of 499) of patients were Latino or African American. Nearly half of the patients (49%, 244 of 499) were uninsured, and 53% of the overall population did not complete high school. In addition, tobacco, alcohol, and illicit drug use were common in this population. Overall, the distribution of sociodemographic characteristics did not differ across time. Clinical comorbidities are depicted in Table 2 and were similar across all time periods, except for a history of chronic obstructive pulmonary disease, which was lower in 2000 and 2002. Hypertension and diabetes mellitus were prevalent, and acute MI was documented on admission in one third of the total cohort.

Overall, we observed progressive improvement in guideline-based drug therapy over the duration of the study period (Figure 1). Exact proportions with 95% CIs are depicted for each drug class in Table 3, and demonstrate that a significant increase in use of all 4 guideline-based drugs was observed over time (P <0.001). By the end of the observation period (2002), absolute increases from baseline were 6% for aspirin (87% to 93%), 17% for beta-blockers (73% to 90%), 35% for statins (51% to 86%), and 42% for ACEIs (49% to 91%). Overall, use of each individual drug class approached or exceeded 90% in 2002, and the composite use of all 4 medication classes was 72% compared with 18% among the historical control group before the intervention. Additionally, there were significant increases in smoking cessation, lifestyle, and dietary counseling, and referral for cardiac rehabilitation (Table 4).

Discussion

We observed significant temporal improvements in guideline-based care among patients with angiographically proven CAD at a public safety-net hospital. To our knowledge, this is the first analysis of the AHA GWTG program to consider composite therapy with a 4-drug regimen as a potential core measure for overall CAD quality of care. We noted a >50% absolute improvement in this more comprehensive quality measure from baseline, simply by instituting a non-coercive intervention based on the AHA GWTG program. Overall, prescription rates at discharge in our population exceeded contemporary adherence in less vulnerable CAD populations over an identical timeframe. Among Medicare beneficiaries suffering acute MI, absolute increases during a similar timeframe (1998-2001) were only 3%, 4%, and 7% for aspirin, ACEIs, and beta-blockers, respectively. By contrast, we observed much larger absolute increases in these medications (6%, 42%, and 17%) in the present study, even though only one third of our cohort met the criteria for acute MI.

Successful implementation of this program at our institution does not by itself make the case for using a composite measure of 4 evidence-based drugs. Nonetheless, comprehensive drug therapy in CAD appears warranted, given recent data demonstrating improvement in outcomes after initiation in the hospital of all 4 drug categories. In one retrospective analysis of acute coronary syndrome (ACS) patients, providing ACEIs, beta-blockers, cholesterol-reducing agents, and aspirin led to an adjusted relative event-rate reduction of 90%. A recent analysis of 31,750 CAD patients noted that adherence to aspirin, beta-blockers, and lipid-lowering drugs was associated with reduced mortality. The study assessed longer-term drug adherence, which is likely to be lower than use at discharge as measured in our study. However, it is noteworthy that use of a composite of these 3 drugs was only 39% at the end of the study period (2002), less than half the observed use rate in our study (72%) during the same year, despite a more comprehensive 4-drug composite measure.

Our postintervention utilization rates mirror data from the Comprehensive Hospital Atherosclerosis Management Program, in which increased use of all 4 drug classes led to a 50% reduction in event rates 1 year after the intervention. A retrospective analysis of 5,477 acute MI patients on background aspirin and ACEI therapy found that only a third of MI patients received
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beta-blockers or statins before hospital discharge. Despite this treatment gap, the 1-year cardiovascular death rate was 50\% lower among patients receiving both agents even after adjustment for baseline risk variables.

Improvements in outcomes appear to be mediated in large part through increased adherence when therapies are initiated in the hospital setting. Initiating evidence-based medications in the hospital reinforces to patients the importance of these therapies while allowing physicians to monitor for adverse drug effects. This practice serves as the conceptual basis for both the AHA GWTG program and the ACC's Guidelines Applied in Practice (GAP) initiative.

Initiating beta-blockers and ACEIs while patients are in the hospital is well known to reduce short-term ischemic complications in ACS patients. Recent observational data suggest that similar benefits may be obtained by initiating statins early in the hospitalization, even though statins are traditionally thought of as providing only long-term cardio-protection. In addition, greater benefits have been noted in ACS patients achieving more stringent low-density lipoprotein cholesterol (LDL-C) target levels (62 mg/dL) compared with traditional target levels (95 mg/dL).

TABLE 3  Utilization of Target Drug Therapy at Discharge*

<table>
<thead>
<tr>
<th></th>
<th>1998-1999 (n = 131)</th>
<th>2000 (n = 54)</th>
<th>2001 (n = 148)</th>
<th>2002 (n = 166)</th>
<th>P Value for Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>87% (81-93)</td>
<td>96% (91-100)</td>
<td>96% (93-99)</td>
<td>93% (89-97)</td>
<td>0.030</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>73% (66-81)</td>
<td>83% (73-93)</td>
<td>86% (80-91)</td>
<td>90% (85-94)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Statin</td>
<td>51% (43-60)</td>
<td>72% (60-84)</td>
<td>80% (73-86)</td>
<td>86% (81-91)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ACEI</td>
<td>49% (40-57)</td>
<td>74% (62-86)</td>
<td>89% (84-94)</td>
<td>91% (87-95)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>All 4 drug classes</td>
<td>18% (12-25)</td>
<td>50% (37-63)</td>
<td>62% (54-70)</td>
<td>72% (65-79)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

* Values are expressed as proportions with 95\% confidence intervals (CIs).

ACEI = angiotensin-converting enzyme inhibitor.

TABLE 4  In-Hospital Risk-Factor Intervention Counseling*

<table>
<thead>
<tr>
<th></th>
<th>1998-1999 (n = 131)</th>
<th>2000 (n = 54)</th>
<th>2001 (n = 148)</th>
<th>2002 (n = 166)</th>
<th>P Value for Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking cessation</td>
<td>4% (1-7)</td>
<td>31% (19-44)</td>
<td>26% (19-33)</td>
<td>33% (26-40)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Activity recommendations</td>
<td>15% (9-21)</td>
<td>28% (16-40)</td>
<td>41% (33-49)</td>
<td>54% (47-62)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cardiac rehabilitation referral</td>
<td>4% (1-7)</td>
<td>6% (0-12)</td>
<td>8% (4-13)</td>
<td>26% (19-33)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Weight management</td>
<td>0% (0-3)</td>
<td>19% (8-29)</td>
<td>26% (17-30)</td>
<td>30% (23-37)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Medication teaching</td>
<td>5% (1-9)</td>
<td>7% (2-18)</td>
<td>6% (2-10)</td>
<td>34% (27-41)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

* Values are expressed as proportions with 95\% confidence intervals (CIs).
during an ACS. Most important, a strategy of drug initiation for inpatients eliminates the barriers inherent in traditional stepwise approaches to care, which foster inertia and ultimately result in missed opportunities to improve outcomes.

These hospital-based data are aligned with an outpatient secondary prevention movement toward comprehensive drug therapy—the so-called “poly-pill” approach. A recent epidemiologic analysis concluded that a comprehensive pharmacologic approach to post-MI patients would reduce CAD mortality by 93% over 5 years, translating into a number needed to treat of only 16 patients. The authors note that the addition of therapeutic lifestyle changes would further enhance the effectiveness of drug therapy. While all of these nonrandomized studies have inherent limitations, their consistent results support a more comprehensive pharmacologic approach to CAD care.

Limitations

First, the current study is retrospective without a contemporaneous control group, which raises the possibility that factors other than our intervention program may be responsible for the observed improvement in care. Important confounding factors include publication of new trials and greater awareness of treatment guidelines, both of which are inseparable from our intervention. Specifically, our intervention corresponded with publication of the Heart Outcomes Prevention Evaluation trial, which demonstrated improved outcomes with ACEI therapy in a broad spectrum of CAD patients and may have contributed to the temporal improvement in ACEI therapy we observed. Nonetheless, previous data suggest that knowledge of guidelines and new publications does not necessarily translate into appropriate CAD care.

Second, an obvious limitation in choosing a new quality measure for comprehensive care is the absence of outcomes data from prospective randomized studies validating the effectiveness of initiating all 4 drugs simultaneously during hospitalization. However, such a study would be methodologically difficult and ethically untenable, given current practice guidelines. Third, our study did not assess clinical outcomes or long-term adherence associated with our intervention, as the AHA GWTG program itself focuses only on the surrogate marker of medication use at the time of discharge from the hospital. These valid surrogates, however, seem reasonable given their proven life-saving benefits in randomized clinical trials, their emphasis in Joint Commission standards, and more recently, the mortality reductions associated with implementation of a similar quality-improvement program (GAP) in Michigan.

Conclusions

We observed marked improvements in comprehensive pharmacologic care among vulnerable CAD patients after initiating an intervention based on the AHA GWTG program. Our findings may prompt other safety-net hospitals with limited resources to consider a CAD quality-improvement program. Vulnerable patients have a high risk of medication noncompliance and a tendency to rely on inpatient services. Therefore, the impact of inpatient quality-improvement programs may be greatest in vulnerable populations, since prescribing drugs at the time of discharge is one of the strongest predictors of outpatient adherence. It has been projected that optimal use of all evidence-based drugs has the potential to save 80,000 lives in the United States. We suggest that using a more comprehensive quality measure for CAD care provides a template to improve outcomes, even among vulnerable patients.

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DISCLOSURES

No outside funding supported this research. The authors disclose no potential bias or conflict of interest relating to this article. Author Mori J. Krantz served as principal author of the study. Study concept and design were contributed primarily by Krantz, with input from authors Deborah K. Haynes and Carlin S. Long. Data collection was the work of Krantz, Haynes, and authors William A. Baker and Raymond O. Estacio; data interpretation was the work of Krantz, Baker, Estacio, and authors Philip S. Mehler and Gregg C. Fonarow. Writing of the manuscript was primarily the work of Krantz, with a significant contribution from Baker and Fonarow and input from Estacio, Mehler, and Long.
REFERENCES


Pharmacoeconomic Analysis of Clopidogrel in Secondary Prevention of Coronary Artery Disease

Judy W. Cheng, PharmD, MPH

ABSTRACT

BACKGROUND: When used as an alternative to or in addition to aspirin, clopidogrel has been demonstrated by some but not all randomized controlled trials to be effective in secondary prevention of cardiovascular (CV) events in patients with (1) coronary artery disease (CAD), (2) acute coronary syndrome (ACS), and (3) coronary stent placement. However, a drawback to clopidogrel therapy is the cost to patients and the health care system. Clinical studies have also demonstrated that when clopidogrel is used in addition to aspirin, the combination has an increased bleeding risk compared with aspirin alone. Cost-effectiveness analysis may aid in developing strategies for optimal use of clopidogrel.

OBJECTIVE: To review and evaluate published pharmacoeconomic analyses on the use of clopidogrel in secondary prevention of CV events in patients who have known CAD, have ACS, or are undergoing percutaneous coronary interventions (PCIs).

METHODS: English-language peer-reviewed articles or abstracts were identified from MEDLINE and the Current Contents database (both from 1966 to August 15, 2006) using the search terms clopidogrel and pharmacoeconomics or clopidogrel and cost analyses. Citations from available articles were also reviewed for additional references.

RESULTS: Multiple cost-effectiveness analyses of clopidogrel were available for review. These pharmacoeconomic studies were performed using different clinical databases from randomized controlled trials as well as observational databases. Cost was from the perspective of different health care systems and society; it was expressed in varying cost-effectiveness terms (life-year gained vs. per quality-adjusted life-year [QALY]). Although direct comparison among studies was difficult, clopidogrel appeared to be cost effective when used for up to 12 months in combination with aspirin (compared with aspirin alone) in patients with ACS or in those undergoing PCIs, using different societal perspectives (both in the United States [average U.S.$15,000 per QALY among U.S. studies reporting per QALY] and in European countries [United Kingdom reported £18,888 (average U.S.$28,300) per QALY]). In contrast, when used as an alternative to aspirin for secondary prevention of CAD, clopidogrel had mixed results in cost-effectiveness analyses (results varied from U.S.$25,000 to $114,000 per QALY). A major limitation of the models cited is the extrapolation of outcomes far beyond the duration used in the clinical trial database.

CONCLUSION: On the basis of current cost-effectiveness data, clopidogrel should be used in addition to aspirin therapy for up to 12 months in all patients with non-ST elevation ACS as well as in those who received coronary stents. For secondary prevention of CAD, clopidogrel should be used only in those who cannot tolerate aspirin therapy.

KEYWORDS: Clopidogrel, Cost-effectiveness, Pharmacoeconomics, Coronary artery disease, Acute coronary syndrome

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What is already known about this subject

- Clopidogrel has shown statistical efficacy in secondary prevention of CAD. Optimal duration of therapy, patient subgroup selection, and cost-effectiveness are unsettled.

What this study adds

- Clopidogrel for 9–12 months in addition to aspirin therapy is likely cost effective for secondary prevention in patients who have ACS and who have received PCI.
- Clopidogrel has not been proven cost effective in patients with CAD and actually increases cardiovascular mortality in patients who have multiple cardiac risk factors. In these groups, clopidogrel should be reserved for the approximately 5% of patients who are aspirin intolerant.

Since publication of the results of the Clopidogrel Versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) and Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trials, clopidogrel (Plavix) has established a role in the management of coronary artery disease (CAD) and acute coronary syndrome (ACS). These studies, together with many other pivotal clinical trials, have demonstrated that clopidogrel in addition to aspirin can reduce cardiovascular (CV) events in patients with a broad spectrum of CAD and ACS, as well as in patients undergoing percutaneous coronary interventions (PCIs), specifically those who received coronary stents. Tables 1 and 2 summarize the results of these studies. More recently, the results of the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) clinical trial have called into question the value of PCI in high-risk patients with confirmed CAD. This large, 50-center trial with 4.6 years of median follow-up per patient may result in a reduced use of coronary stents for secondary prevention, one of the major indications for the use of clopidogrel.

The combined use of aspirin and clopidogrel, however, has been demonstrated in many studies to increase the risk of bleeding (Tables 1 and 2). In addition, because clopidogrel requires a fairly long time to achieve peak response (3 to 7 days), more recent studies have continued to evaluate the increase in loading doses of clopidogrel, from 300 mg to 600 mg to 900 mg, in an attempt to achieve maximal effects faster. However, the increased loading doses also increase the risk of bleeding. The duration of clopidogrel plus aspirin therapy used in clinical studies varied from 1 month to 1 year, and data
Pharmacoeconomic Analysis of Clopidogrel in Secondary Prevention of Coronary Artery Disease

Some clinicians recommend that patients use clopidogrel plus aspirin therapy for life to theoretically prevent the risk of future CV events. The risk versus benefit ratio of such prolonged use is unknown.

The 15,603 patients in the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial who had either clinically evident CV disease or multiple risk factors were randomly assigned to low-dose aspirin (75 to 162 mg per day) plus either clopidogrel (75 mg per day) or placebo and were followed for a median time of 28 months. Clopidogrel plus aspirin was not more effective than aspirin alone in reducing the rate of myocardial infarction (MI), stroke, or death from CV causes in patients at high risk of CV events in the group with CAD. In the group with multiple cardiac risk factors, the rate of death from CV causes was higher with clopidogrel (3.9 percent) than with aspirin alone (2.2 percent [P=0.01]). Recently, reports from long-term follow-up of patients with drug-eluting stents indicated that after stopping clopidogrel therapy at 12 months after stent placement, patients continued to experience increased risk of late-stent rethrombosis. More clinical studies are required to establish the optimal duration of clopidogrel plus aspirin therapy in this patient population.

Clopidogrel compared with other oral antiplatelet medications can be costly to patients and the health care system. The discount price of clopidogrel at an Internet pharmacy in 2006 is about $4 per 75 mg tablet, translating to a cost of $120 per month. The conduct of cost-effectiveness analyses may help evaluate the risk versus benefit of clopidogrel therapy with its apparent role

### TABLE 1 Clinical Trials of Clopidogrel for Medical Management of Coronary Artery Disease and Acute Coronary Syndrome

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Regimen and Follow-up Period</th>
<th>Primary Endpoints</th>
<th>Outcomes (%)</th>
<th>Bleeding (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAPRIE 1</td>
<td>19,143 patients with ischemia, stroke, MI, and PVD subgroups</td>
<td>Clopidogrel 75 mg daily (n=9,577) vs. aspirin 325 mg daily (n=9,566) for 1-3 years</td>
<td>New fatal and nonfatal ischemic stroke, MI, and other vascular death</td>
<td>Treatment: 9.78* Control: 10.64</td>
<td>Treatment: 0.85 (total) Control: 1.19 (total)</td>
</tr>
<tr>
<td>CURE 2</td>
<td>12,562 patients with ACS</td>
<td>Clopidogrel 300 mg loading dose followed by 75 mg daily (n=6,259) vs. placebo (n=6,303) (all received aspirin) for an average of 9 months</td>
<td>Death from CV causes, nonfatal MI, or stroke</td>
<td>Treatment: 9.3* Control: 11.4</td>
<td>Treatment: 3.7* (major) Control: 2.7 (major)</td>
</tr>
<tr>
<td>CLARITY 3</td>
<td>3,491 patients with STEMI</td>
<td>Clopidogrel 300 mg loading dose followed by 75 mg daily (n=1,752) vs. placebo (n=1,739) (all received aspirin) for 30 days</td>
<td>Composite of an occluded infarct-related artery on angiography or death or recurrent MI before angiography</td>
<td>Treatment: 15* Control: 21.7</td>
<td>Treatment: 1.9 (major) Control: 1.7 (major)</td>
</tr>
<tr>
<td>CHARISMA 4</td>
<td>15,603 patients with either clinically evident CV disease or multiple risk factors</td>
<td>Clopidogrel (75 mg per day) (n=7,802) or placebo (n=7,801) (all received aspirin) for a median of 28 months</td>
<td>Composite of MI, stroke, or death from CV causes</td>
<td>Treatment: 6.8 Rate of death: 3.9* Control: 7.3 Rate of death: 2.2</td>
<td>Treatment: 1.7 (severe) Control: 1.3 (severe)</td>
</tr>
<tr>
<td>COMMIT 5</td>
<td>45,852 patients with STEMI</td>
<td>Clopidogrel (75 mg per day) (n=22,961) or placebo (n=22,861) (all received aspirin) for an average of 16 days</td>
<td>Death, reinfarction, and stroke prior to hospital discharge (up to 4 weeks)</td>
<td>Treatment: 9.3* (combined endpoint) Control: 10.1 (combined endpoint)</td>
<td>Treatment: 0.58 (major) Control: 0.54 (major)</td>
</tr>
</tbody>
</table>

*P <0.05 compared with control.

ACS = acute coronary syndrome; CAPRIE = Clopidogrel Versus Aspirin in Patients at Risk of Ischemic Events; CHARISMA = Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance; CLARITY = Clopidogrel as Adjunctive Reperfusion Therapy; COMMIT = Clopidogrel and Metropolis in Myocardial Infarct Trial; CURE = Clopidogrel in Unstable Angina to Prevent Recurrent Events; CV = cardiovascular; MI = myocardial infarction; NA = not available; PVD = peripheral vascular disease; STEMI = ST-segment elevation MI.
### **TABLE 2** Clinical Trials of Clopidogrel in Preventing Rethrombosis After Percutaneous Coronary Interventions

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Regimen and Follow-up Period</th>
<th>Primary Endpoints</th>
<th>Outcomes (%)</th>
<th>Bleeding (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Treatment</td>
<td>Control</td>
<td>Treatment</td>
</tr>
<tr>
<td>Muller et al.⁷</td>
<td>700 patients receiving coronary stents</td>
<td>Clopidogrel 75 mg daily (n = 345) or ticlopidine 250 mg twice daily (n = 355) for 4 weeks (all received aspirin 100 mg daily)</td>
<td>Death from cardiac causes, urgent target vessel revascularization, angiographically evident stent occlusion, or nonfatal MI within 30 days</td>
<td>3.1</td>
<td>1.7</td>
</tr>
<tr>
<td>CLASSICS⁸</td>
<td>1,029 patients receiving coronary stents</td>
<td>Clopidogrel 300 mg loading, then 75 mg daily (n = 345) vs. clopidogrel 75 mg daily (n = 335) vs. ticlopidine 250 mg twice daily (n = 340) for 1 month</td>
<td>Major bleeding complications, hematologic side effects, or drug discontinuation due to noncardiac adverse effects</td>
<td>2.9* (with loading dose)</td>
<td>9.1</td>
</tr>
<tr>
<td>PCI-CURE⁹</td>
<td>2,658 patients from CURE trial</td>
<td>Same as CURE ACS patients who underwent PCI (Yes)? Clopidogrel 300 mg loading, then 75 mg daily (n = 1,313) vs. placebo (n = 1,345) (all received aspirin) for an average of 9 months</td>
<td>MI, CV death, or urgent revascularization 30 days after PCI</td>
<td>4.6*</td>
<td>6.4</td>
</tr>
<tr>
<td>WRIST PLUS¹⁰</td>
<td>120 patients with in-stent restenosis</td>
<td>Clopidogrel 300 mg loading, then 75 mg daily for 6 months vs. 1 month for historical control (all received aspirin)</td>
<td>Late-stent thrombosis rate and the composite clinical events of death, MI, and target lesion revascularization at 6 months</td>
<td>23.3*</td>
<td>32</td>
</tr>
<tr>
<td>WRIST 12¹¹</td>
<td>120 patients with in-stent restenosis</td>
<td>Clopidogrel 300 mg loading, then 75 mg daily for 6 months vs. 1 month for historical control from WRIST PLUS (all received aspirin)</td>
<td>Late-stent thrombosis rate and the composite clinical events of death, MI, and target lesion revascularization at 15 months</td>
<td>29*</td>
<td>36</td>
</tr>
<tr>
<td>CREDO¹²</td>
<td>2,116 patients undergoing elective PCI</td>
<td>Clopidogrel 300 mg loading, then 75 mg daily for 1 month (n = 1,053) vs. 12 months (n = 1,063) (all received aspirin)</td>
<td>Composite of death, MI, or stroke up to 1 year; only the composite endpoint was statistically significant; all individual conditions measured separately were not</td>
<td>8.5*</td>
<td>11.5</td>
</tr>
<tr>
<td>ARMYDA¹³</td>
<td>255 patients undergoing PCI</td>
<td>Clopidogrel 600 mg (n = 126) vs. 300 mg (n = 129) loading dose</td>
<td>30-day occurrence of death, MI, or target vessel revascularization</td>
<td>4*</td>
<td>12</td>
</tr>
<tr>
<td>PCI-CLARITY¹⁴</td>
<td>1,863 patients with STEMI</td>
<td>Clopidogrel 300 mg loading dose followed by 75 mg daily (n = 933) vs. placebo (n = 930) (all received aspirin) for 30 days</td>
<td>Composite of an occluded infarct-related artery on angiography, death, or recurrent MI before angiography</td>
<td>3.6*</td>
<td>6.2</td>
</tr>
</tbody>
</table>

*P < 0.05 compared with control.

ACS = acute coronary syndrome; ARMYDA = Antiplatelet Therapy for Reduction of Myocardial Damage During Angioplasty; CLASSICS = Clopidogrel Aspirin Stent International Cooperative Study; CREDO = Clopidogrel for the Reduction of Events During Observation; CV = cardiovascular; MI = myocardial infarction; NA = not available; PCI = percutaneous coronary intervention; PCI-CLARITY = Pretreatment With Clopidogrel–Clopidogrel as Adjunctive Reperfusion Therapy; PCI-CURE = Pre-treatment With Clopidogrel and Aspirin Followed by Long-term Therapy in Patients Undergoing Percutaneous Coronary Intervention; STEMI = ST-segment elevation MI; WRIST = Washington Radiation for In-Stent Restenosis Trial; WRIST PLUS = Washington Radiation for In-Stent Restenosis Trial Plus 6 Months of Clopidogrel.
in reducing CV events in patients with certain CV conditions, the potential increased risk of bleeding when used in combination with aspirin, and its high direct drug cost. Cost-effectiveness analyses can also potentially help us to decide which patient populations may benefit the most from combination therapy.

The availability of numerous large, randomized, controlled studies of clopidogrel efficacy allows pharmacoeconomic evaluations to be performed in different patient populations, using the data from health care resources consumed (e.g., number of hospitalizations, amount of outpatient care consumed, and medication cost).

This article reviews previously published pharmacoeconomic analyses on the use of clopidogrel in patients with known CAD. These analyses include the use of clopidogrel for secondary prevention of CV events in patients with ACS and in those undergoing PCI.

Methods

English-language peer-reviewed articles or abstracts were identified from MEDLINE and the Current Content database (both from 1966 to August 15, 2006) using the search terms clopidogrel, pharmacoeconomics, and cost analyses. No exclusion criteria were used. Citations from available articles were also reviewed for additional references. The author critically evaluated all identified references regarding study methodology, the database used for analysis, assumptions, different societal perspectives, and the time horizon for extrapolation of the results.

Results

Fourteen pharmacoeconomic analyses were identified on the use of clopidogrel in the management of CAD and ACS. Among the large-scale, multicenter randomized controlled studies, the CAPRIE, CURE, Percutaneous Coronary Intervention-CURE (PCI-CURE), and Clopidogrel for the Reduction of Events During Observation (CREDO) trial databases have been used for pharmacoeconomic analyses (Table 3).1,2,9,12

Pharmacoeconomic Analyses Using Clinical Trial Database

Shleinitz et al. performed a cost-utility analysis of clopidogrel and aspirin for secondary prevention of CV events in patients with prior MI, stroke, or peripheral arterial disease (PAD).20 On the basis of event probabilities derived from the CAPRIE database,1 a Markov model was constructed using a base case of a 63-year-old patient on lifetime treatment, assuming a societal perspective and discounting costs and utilities at an annual rate of 3%. Outcome measures included costs, life expectancy in quality-adjusted life-years (QALYs), incremental cost-effectiveness ratios (ICERs), and events averted. A base case of a 50- and 75-year-old patient was used in the sensitivity analysis. Costs for type of event and for chronic care of disabled patients were derived from the Medicare diagnostic-related group reimbursement data. Costs for medications used were the U.S. average wholesale prices. All costs were reported in 2002 values.

Regarding secondary prevention of CAD, aspirin was both less expensive and more effective than clopidogrel in post-MI patients. The authors concluded that the CAPRIE data do not support use of clopidogrel in patients post-MI. It is important to note that the CAPRIE study provided patient outcome data up to approximately 2 years (not lifetime) after use of clopidogrel. Therefore, the assumption made by the investigators regarding lifetime CV events may not be correct in this group of patients. This assumption may affect the ultimate cost-effectiveness of clopidogrel.

Latour-Perez et al. performed a cost-utility analysis of clopidogrel in preventing long-term CV events.21 Based on event probabilities derived from the CURE database, the Framingham study, and the Spanish National Statistics,2,22,23 Markov models were constructed assuming a payer’s perspective, using a base case of a 64-year-old patient on lifetime treatment. All costs were reported in 1999 euros (with 1 euro equaling slightly more than US $1 throughout 1999). The cost of the drug was calculated from the retail sales cost in Spain. A discount rate of 3% yearly was applied for calculating both costs and utilities. Sensitivity analysis was performed for each of the variables included in the model. The most decisive determinants from the one-way sensitivity analysis were assessed in the best and worst possible situations.

The average cost per QALY saved owing to clopidogrel was 2,000 euros. The cost-effectiveness ratio was very sensitive to the age of the patient, the base risk of CV events, and the precision of the estimated effectiveness of clopidogrel. The cost per QALY ranged from 5,000 euros for a high-risk 40-year-old patient to 30,000 euros for a low-risk, 80-year-old patient. According to the cost-effectiveness threshold in Spain (26,710 euros per QALY), the probability that clopidogrel was cost-effective by Monte Carlo simulation in the base analysis case was 85.3%. Similar to the CAPRIE data used in the study performed by Schleinitz et al., CURE study data followed patient outcomes for a limited time—in this case, only 9 months. The assumption of lifetime events based on the Framingham study and the Spanish National Statistics data may or may not be correct for the patients enrolled in the CURE study. Therefore, the cost-effectiveness model results may be affected.

Lindgren et al. performed a cost-utility study of clopidogrel based on the CURE database, the Swedish Hospital Discharge Registry, and the Swedish Causes of Death Registry.2,24 A Markov model was constructed assuming a societal perspective, using the base case of a patient similar to those enrolled in the CURE study and of another patient similar to those in the Swedish registries, to estimate the ICER, or cost per additional event avoided, of clopidogrel plus aspirin therapy. All costs were in year 2000 values (with a discount rate between 0% and 5% for cost calculation and sensitivity analysis). Costs were obtained from studies performed by Zethraeus et al.25 and Johannesson
### TABLE 3 Cost-effectiveness Analysis of Clopidogrel for Coronary Artery Disease

<table>
<thead>
<tr>
<th>Study</th>
<th>Country of Analysis</th>
<th>Analysis Time Period</th>
<th>Source of Clinical Data</th>
<th>Cost Perspective</th>
<th>Sensitivity Analysis</th>
<th>Cost-effectiveness of Clopidogrel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schleinitz et al. (2004)20</td>
<td>U.S.</td>
<td>Lifetime of a 63-year-old patient</td>
<td>CAPRIE (clopidogrel vs. aspirin)</td>
<td>Societal</td>
<td>Probabilistic sensitivity analysis using Monte Carlo simulations (1,000 simulations)</td>
<td>MI: aspirin less expensive and more effective</td>
</tr>
<tr>
<td>Latour-Perez et al. (2004)21</td>
<td>Spain</td>
<td>12 months</td>
<td>CURE (clopidogrel + aspirin vs. aspirin)</td>
<td>Societal</td>
<td>Probabilistic sensitivity analysis using Monte Carlo simulations (1,000 simulations)</td>
<td>12,000 euros/QALY</td>
</tr>
<tr>
<td>Lindgren et al. (2004)24</td>
<td>Sweden</td>
<td>12 months</td>
<td>CURE (clopidogrel + aspirin vs. aspirin)</td>
<td>Societal</td>
<td>Outer limits of 95% CI of the relative risk of events</td>
<td>1,009-1,365 euros per life-year gained</td>
</tr>
<tr>
<td>Weintraub et al. (2005)26</td>
<td>U.S.</td>
<td>9 months</td>
<td>CURE (clopidogrel + aspirin vs. aspirin)</td>
<td>Payer</td>
<td>Bootstrap methods (5,000 replicates)</td>
<td>$6,318 per life-year gained</td>
</tr>
<tr>
<td>Schleinitz et al. (2005)25</td>
<td>U.S.</td>
<td>Lifetime</td>
<td>CURE (clopidogrel + aspirin vs. aspirin)</td>
<td>Societal</td>
<td>Probabilistic sensitivity analysis using Monte Carlo simulations (1,000 simulations)</td>
<td>$15,400/QALY</td>
</tr>
<tr>
<td>Badia et al. (2005)30</td>
<td>Spain</td>
<td>12 months and lifetime</td>
<td>CURE (clopidogrel + aspirin vs. aspirin)</td>
<td>Societal</td>
<td>Outer limits of 95% CI of the relative risk of events</td>
<td>12 months: 17,190 euros per life-year gained Lifetime: 30,000 euros per life-year gained</td>
</tr>
<tr>
<td>Lindgren et al. (2005)31</td>
<td>Sweden</td>
<td>12 months</td>
<td>PCI-CURE (clopidogrel + aspirin vs. aspirin)</td>
<td>Payer and Societal</td>
<td>Probabilistic sensitivity analysis using Monte Carlo simulations (1,000 simulations)</td>
<td>Payer: 10,993 euros per life-year gained Societal: 8,127 euros per life-year gained</td>
</tr>
</tbody>
</table>

Sensitivity analysis was performed using varying event rates from 50% of those observed to 10% more than those observed in the CURE study. The analysis demonstrated an ICER of 1,365 euros per QALY from a payer perspective and cost saving from a societal perspective. The analysis based on the registries demonstrated an ICER of 1,009 euros per QALY from both a payer and a societal perspective. The investigators concluded that clopidogrel was cost-effective. Similar to other models created, the Markov model used the Swedish Hospital Discharge Registry and the Swedish Causes of Death Registry for information regarding the incidence of CV events beyond 9 months, which was the duration of follow-up in CURE. Extrapolating results beyond 9 months may or may not represent the events experienced by the patients enrolled in the CURE study. Therefore, the cost-effectiveness results may be affected.
Cost-effectiveness Analysis of Clopidogrel for Coronary Artery Disease (continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Country of Analysis</th>
<th>Analysis Time Period</th>
<th>Source of Clinical Data</th>
<th>Cost Perspective</th>
<th>Sensitivity Analysis</th>
<th>Cost-effectiveness of Clopidogrel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mahoney et al. (2006)</td>
<td>U.S.</td>
<td>12 months</td>
<td>PCI-CURE (clopidogrel + aspirin vs. aspirin)</td>
<td>Societal</td>
<td>Considering the impact of clopidogrel on risk of fatal MI only, fatal and nonfatal MI only, as well as all death</td>
<td>Overall: $2,856-$4,885 per life-year gained Early PCI subgroup: $935 per life-year gained</td>
</tr>
<tr>
<td>Ringborg et al. (2005)</td>
<td>Sweden</td>
<td>12 months</td>
<td>CREDO (aspirin + clopidogrel 1 month vs. aspirin + clopidogrel 12 months)</td>
<td>Societal</td>
<td>Probabilistic sensitivity analysis using Monte Carlo simulations (1,000 simulations)</td>
<td>3,022 euros per life-year gained</td>
</tr>
<tr>
<td>Beinart et al. (2005)</td>
<td>U.S.</td>
<td>12 months</td>
<td>CREDO (aspirin + clopidogrel 1 month vs. aspirin + clopidogrel 12 months)</td>
<td>Societal</td>
<td>Bootstrap method (5,000 iterations)</td>
<td>Based on Framingham life-expectancy estimation: $3,685-$4,353/life-year gained Based on Saskatchewan life-expectancy estimation: $2,929-$3,460/life-year gained</td>
</tr>
<tr>
<td>Cowper et al. (2005)</td>
<td>U.S.</td>
<td>12 months</td>
<td>Patients undergoing PCI at Duke University Medical Center from January 1999 to December 2001</td>
<td>Societal</td>
<td>Single and multiway sensitivity analysis</td>
<td>$15,696 per life-year gained</td>
</tr>
<tr>
<td>Gaspoz et al. (2002)</td>
<td>U.S.</td>
<td>25 years</td>
<td>Coronary Heart Disease Model (clopidogrel vs. aspirin)</td>
<td>Payer</td>
<td>Outer limits of 95% CI of the relative risk of events based on the Antiplatelet Trial List</td>
<td>$11,400/QALY</td>
</tr>
</tbody>
</table>

CAPRIE = Clopidogrel Versus Aspirin in Patients at Risk of Ischemic Events; CI = confidence interval; CREDO = Clopidogrel for the Reduction of Events During Observation; CURE = Clopidogrel in Unstable Angina to Prevent Recurrent Events; MI = myocardial infarction; PCI = percutaneous coronary interventions; PCI-CURE = Pretreatment With Clopidogrel and Aspirin Followed by Long-term Therapy in Patients Undergoing Percutaneous Coronary Intervention; QALY = quality-adjusted life-year.

Lamy et al. also performed a cost-effectiveness study from a third-party payer perspective based on the CURE database. They calculated the average cost per patient for each country that participated in the CURE study (United Kingdom, United States, Sweden, France, and Canada) and was reported in local currency in 2001 values. A bootstrap analysis was used to calculate standard errors and 95% confidence intervals (CIs) for the difference in average costs in different countries between clopidogrel plus aspirin therapy and aspirin alone. The average cost per patient was higher in the clopidogrel plus aspirin group than in the aspirin alone group in all countries (difference in costs for a 9-month period: £208 in the United Kingdom, $451 in the United States, Skr2,571 in Sweden, 325 euros in France, Can$161 in Canada). This equated to an ICER of £10,366 in the United Kingdom, $22,484 in the United States, Skr127,951 in Sweden, 16,186 euros in France, Can$7,973 in Canada per primary event avoided. The investigators concluded that the ICER for clopidogrel was similar to that of other therapies (such as low-molecular-weight heparin and glycoprotein IIb/IIIa receptor antagonists) used for ACS management. In clinical practice, however, clopidogrel, low-molecular-weight heparin, and glycoprotein IIb/IIIa receptor antagonists are often
used together during ACS. The ICER reported in this study already took into account low-molecular-weight heparin and glycoprotein IIb/IIIa receptor antagonists as background therapy. Therefore, the conclusion that the ICER of clopidogrel is similar to other ACS therapy may not be accurate.

The same group of investigators performed another cost-effectiveness analysis based on the CURE database, but focused on a U.S. perspective. Costs were derived from average wholesale drug cost in the United States and from Medicare reimbursement. The ICER reported in this analysis was $6,318 per life-year gained with clopidogrel, with 94% of bootstrap-derived ICER estimates of <$50,000 (the U.S. threshold of cost-effectiveness) per life-year gained. It is, however, important to realize that there were only 500 patients from the United States out of approximately 12,000 patients enrolled in CURE. Most patients in CURE received medical management for ACS. For those who received PCI, the average time to PCI was 6 days. That does not reflect the usual management of ACS in the United States, where patients are referred to PCI much sooner after an ACS event.

Schleinitz and Heidenreich also performed a cost-effectiveness analysis using a Markov model assuming a societal perspective, using a base case of a 64-year-old patient on lifetime treatment. Information on incidence of CV events was obtained from the CURE database. All costs were reported as 2002 U.S. dollars. The costs of drugs were U.S. average wholesale price. Health care costs were derived from published literature. A one-way sensitivity analysis was performed for each of the variables included in the model. The ICER of clopidogrel plus aspirin therapy compared with aspirin alone was $15,400 per QALY. The authors concluded that clopidogrel plus aspirin therapy for 1 year in patients with high-risk ACS is cost effective within traditional limits (i.e., <$50,000 per QALY).

Similar to other cost-effectiveness analyses, the CURE study provides information on patient events up to 9 months only. The assumption made by the authors regarding lifetime CV events therefore may or may not represent the experiences of the patients enrolled in the CURE study. Similar to the study performed by Lamy et al., the Schleinitz and Heidenreich study had only 500 patients from the United States out of approximately 12,000 patients enrolled in CURE. Therefore, the results do not reflect the usual management of ACS in the United States.

Badia et al. performed a cost-effectiveness analysis based on the CURE study database. A Markov model covering 6 states of health reflecting the clinical progress of patients with non-ST elevation ACS was adapted to the Spanish setting. A discount rate of 3% yearly was allowed for all costs and health benefits. The unit cost of the direct health resources was obtained from a Spanish setting costs database. Univariate sensitivity analysis was performed. In the short-term analysis (1 year), the incremental cost per event avoided with the addition of clopidogrel was 17,190 euros (with 1 euro in 2005 ranging from U.S.$1.18 to $1.31). In the long-term analysis (>1 year), the incremental cost per life-year gained was 8,132 euros. These costs were below the cost-effectiveness threshold (30,000 euro per life-year gained) in Spain. Therefore, clopidogrel was considered cost effective. Once again, the long-term analysis using CV events experienced by a Spanish population may or may not represent those experienced by the CURE population.

Lindgren et al. performed a cost-effectiveness study based on the PCI-CURE database, the Swedish Hospital Discharge Registry, and the Swedish Causes of Death Registry. A Markov model was constructed assuming a third-party payer and a societal perspective, using the base case of a patient similar to patients in the Swedish registries, to estimate the ICER of clopidogrel plus aspirin therapy compared with aspirin alone. All costs were in year 2004 values (with 1 euro ranging from U.S.$1.19 to $1.34). Costs were obtained from published sources (discount rate of 3% yearly). The analysis demonstrated an ICER of 8,127 euros per QALY from a payer perspective and 10,933 euros per QALY from a societal perspective. The investigators concluded that clopidogrel used in a setting similar to that of the PCI-CURE study was cost effective. The long-term analysis performed using CV events documented by the Swedish Hospital Discharge Registry and the Swedish Causes of Death Registry beyond the 9-month follow-up period of PCI-CURE may or may not represent the actual CV events experienced by the PCI-CURE population if they had been followed beyond 9 months.

Mahoney et al. performed a cost-effectiveness study from a third-party payer perspective based on the PCI-CURE database. Unit cost of resources used were derived from the U.S. Medicare diagnosis-related group reimbursement. Costs of medication were U.S. average wholesale prices. Discounting of costs was not performed, since the duration of follow-up of PCI-CURE was only 1 year. Since patients in the clopidogrel and the placebo groups received similar background therapy, the costs of the background therapy were not taken into account during the cost-effectiveness analysis. The incremental cost per life-year gained with clopidogrel ranged from $2,856 to $4,885 overall (from dominant to $935 for the early PCI group). The investigators concluded that clopidogrel was highly cost effective when used in this patient population. Similar to other studies evaluating the cost-effectiveness of clopidogrel use in the United States based on the PCI-CURE study, in PCI-CURE, the average time to PCI was 6 days. That does not reflect the usual management of ACS in the United States, where patients are referred to PCI much sooner after an ACS event.

Ringborg et al. performed a cost-effectiveness study based on the CREDO database, the Swedish Hospital Discharge Registry, and the Swedish Causes of Death Registry. A Markov model was developed on the assumption that a hypothetical cohort of patients in a post-PCI state had certain risks of suffering one of the event endpoints in the CREDO trial. Costs were obtained from studies performed by Zethraeus et al. and Johannesson et al. All costs were adjusted to 2004 values (with 1 euro
ranging from U.S.$1.19 to $1.34). First-order sensitivity analysis was performed. The model predicted an ICER of 3,022 euros. The authors concluded that the cost-effectiveness ratio of long-term treatment with clopidogrel in patients undergoing PCI was well below the threshold values currently considered cost effective in Sweden. Like most other cost-effectiveness analyses, the assumption of CV events experienced after 1 year using the 2 Swedish registries may not represent those experienced in the CREDO study, which followed patients for only 12 months.

Beimart et al. performed a similar cost-effectiveness analysis from the CREDO database, the Framingham Heart Study, and the Saskatchewan Health database. Costs for each type of event and for chronic care of disabled patients were obtained from the Medicare diagnostic-related group reimbursement data. Costs for medications were the U.S. average wholesale price. The bootstrap method was used to estimate the 95% CIs of the distribution of ICER. Sensitivity analysis included reducing life-years gained by 50% and 80%, adding estimated costs associated with bleeding, and calculating additional costs beyond the trial period and quality-adjusted survival. The ICER based on the Framingham data ranged from C$3,685 to $4,353 per life-year gained; more than 97% of bootstrap-derived ICER estimates were below $50,000 per life-year gained. The ICER based on Saskatchewan data was $2,929 to $3,460 per life-year gained; more than 98% of estimates were below $50,000 per life-year gained (the accepted threshold of cost-effectiveness in Canada).

The author therefore concluded that clopidogrel therapy when used for 1 year after PCI was cost effective in preventing lifetime CV events. Similar to most other cost-effectiveness analyses, the CREDO study followed patients for 12 months. The assumption of CV events experienced after 1 year using the Framingham and Saskatchewan Health databases may not represent those experienced in the CREDO study after 1 year.

Pharmacoeconomic Analyses Using Decision Modeling of Other Databases

Cowper et al. performed a cost-effectiveness analysis of clopidogrel plus aspirin therapy in patients undergoing PCI over a 3-year period at Duke University Medical Center. The effect of prolonged clopidogrel therapy on event rates was based on the CREDO trial. Unit costs and the effect of MI on life expectancy were based on average Medicare reimbursement and the Framingham Heart Study, respectively. Single and multiway sensitivity analyses were performed for each variable in the model.

This study demonstrated that clopidogrel therapy cost $15,696 per year of life saved ($10,333 per year of life saved in the high-risk subset and $26,568 in the low-risk subset). Therefore, the use of clopidogrel for 1 year after PCI is economically attractive in the Duke University patient population. This major university medical center not only serves the population around its own community but is referred patients from other regions in North Carolina. Therefore, the number of PCI procedures performed at Duke is likely to be higher than at most other medical centers in the United States, and the incidence of outcomes and adverse events may be different. Therefore, the applicability of these data to other populations beyond Duke University may be questionable.

Gaspouz et al. used the Coronary Heart Disease Policy Model, a computer simulation of the U.S. population, to evaluate the cost-effectiveness of using aspirin, clopidogrel, or both for secondary prevention of CAD. Events data for the initial model were obtained from a review of the literature, the National Vital Statistics reports, the National Hospital Discharge Survey, the National Health Interview Survey, the second and third Health and Nutrition Examination Surveys, the Framingham Heart Study, and a variety of clinical trials and observational studies. The simulations modeled U.S. patients, 35 to 84 years old, in whom coronary disease developed during or before 2003 to 2007 and who survived their first month with it. Probability of events was based on pooled data from randomized trials for secondary prevention of coronary events in patients with prior coronary disease. Sensitivity analysis was performed by varying health care costs up to 100% and varying incidence of outcome events by using the 95% CI. The cost-effectiveness of aspirin in eligible patients for 25 years was calculated to be $11,000 per QALY, with a 31% absolute event rate reduction. The use of clopidogrel for the 5.7% of patients who were ineligible for aspirin therapy had an ICER of $31,000 per QALY, and reduced the absolute event rate by 33.7%. If clopidogrel and aspirin were used together in all patients, the ICER was $130,000 per QALY and remained financially unattractive across a broad range of financial assumptions; the combined reduction in absolute event rate was 37.2%. The investigators concluded that aspirin for secondary prevention of CAD is attractive from a cost-effectiveness perspective; clopidogrel alone was only cost effective when its price was reduced by at least 70% to U.S.$1.

Karnon et al. developed a health economic model from a third-party payer perspective to evaluate the cost-effectiveness of clopidogrel in secondary prevention of occlusive vascular disease. Patients were assumed to receive treatment with either clopidogrel for 2 years followed by aspirin for their remaining lifespan or with aspirin alone for the whole lifespan. Data from United Kingdom observation studies were used to obtain vascular event rates. Costs were expressed in 2002 values (with 1 British pound in 2002 ranging from $1.42 to $1.58). Sensitivity analysis was performed by varying key parameters randomly at the same time. The ICER of aspirin was estimated to be £18,888 per life-year gained and £21,489 per QALY gained. Sensitivity analysis suggested the model was robust to a wide range of input. Therefore, 2 years of treatment with clopidogrel can be considered a cost-effective intervention in patients at risk of secondary occlusive vascular events. Currently, the official recommendation of duration of clopidogrel therapy in
combination with aspirin is 1 year. Although 1 year may not be the optimal duration and future studies may suggest otherwise, the decision to use 2 years of clopidogrel therapy in this analysis is arbitrary and may make the results not applicable to current clinical practice.

Discussion

At least 13 randomized clinical trials published since 1996 have shown measurable statistical efficacy of (1) clopidogrel in secondary prevention of CAD compared with aspirin, (2) the efficacy of clopidogrel in combination with aspirin in ACS (including unstable angina, non-ST-segment elevation MI and ST-segment elevation MI), and (3) the prevention of rethrombosis after coronary stent placement compared with aspirin alone. The general pattern of results shows greater benefit for higher-acuity patients (ACS and PCI); patients who have multiple risk factors are actually harmed, as shown in the CHARISMA trial.

Compared with aspirin, which costs pennies per day, clopidogrel had a current cost in January 2007 of $4.11 per 75 mg tablet (for Plavix) or of $3.67 per generic 75 mg tablet. The high cost of clopidogrel combined with the clinical trials comparing clopidogrel with aspirin alone, and clopidogrel plus aspirin with aspirin alone beg for analysis of the cost-effectiveness of clopidogrel. Fourteen pharmacoeconomic analyses of clopidogrel were published through August 2006. Overall, from different societal perspectives (in the United States and in selected European countries), clopidogrel appears to be consistently cost effective when used in combination with aspirin (compared with aspirin alone) in patients with ACS or in those undergoing PCI. However, when used as an alternative to aspirin for secondary prevention of CAD, clopidogrel has mixed economic effectiveness. Schleinitz et al. demonstrated that clopidogrel is not cost effective post-MI for secondary prevention of CAD. Gaspoz et al. also demonstrated that clopidogrel was not cost effective, whereas Karmon et al. demonstrated otherwise. The routine replacement of aspirin for clopidogrel for secondary prevention of CV events in patients with CAD is not warranted from an economic point of view. This conclusion is further justified by the results of the recent CHARISMA study in which clopidogrel, when used together with aspirin, was shown to increase adverse event outcomes in patients with CAD.

Limitations

A significant limitation of the pharmacoeconomic models available for review is the decision to extrapolate data from short-term clinical trials and apply them to simulated patients for a “lifetime” of use. Assuming that the slope of the outcomes data can be merely extended in a continuous line is risky and open to error.

Another limitation of clinical modeling is the unsettled question of optimal duration of clopidogrel therapy after ACS or PCI. Most of the clinical effectiveness trials were performed based on 9 to 12 months of clopidogrel therapy. Whether this duration is optimal is not yet known. Whether extending therapy beyond 12 months in patients after ACS or PCI will extend any additional benefits clinically and economically cannot be determined in the available literature. Recent reports from long-term follow-up of patients with drug-eluting stents indicate that after stopping clopidogrel therapy at 12 months after stent placement, patients continued to experience increased risk of late-stent rethrombosis. Whether these results indicate that drug-eluting stents should be avoided or clopidogrel use should be extended is not settled. Perhaps other conclusions will be drawn from this study.

Long-term use of clopidogrel plus aspirin not only potentially increases the risk of bleeding in patients but also poses other potential problems for clinical management of patients. For example, if during the lifetime of patients they require other forms of antplatelet or anticoagulant therapy (e.g., warfarin), how should the clopidogrel plus aspirin therapy be modified? Furthermore, if the patients require surgery or invasive procedures, how is the clopidogrel plus aspirin therapy going to be managed? Current recommendations are that clopidogrel should be withheld for a minimum of 5 days before elective surgery. The risk of stent rethrombosis if clopidogrel is withheld compared with the risk of major hemorrhage during surgery if clopidogrel is not withheld is unknown. On the other hand, for non–drug-eluting stents, the minimal duration of clopidogrel therapy that has been demonstrated effective as compared with placebo is 1 month, with 12-month clopidogrel therapy more effective clinically and economically. However, the cost-effectiveness of duration of therapy between 1 and 12 months has not been evaluated. More clinical trials are underway to continue to explore the optimal duration of clopidogrel.

The majority of the cost-effectiveness analyses of clopidogrel used data from large-scale, multicenter, randomized controlled trials, whereas other analyses are from large local or national health databases. Although analyses performed based on data from large-scale clinical trials allow accurate capture of outcome events, the health care resources used in these studies may not truly reflect those in real-life clinical practice. Patients enrolled in clinical studies are monitored by specified protocols and usually received more intensive follow-up care. In real-life practice, the levels of follow-up and patient adherence to therapy may be different, thus affecting outcome events and resource use. On the other hand, cost-effectiveness analysis that used cohort population or a national/local health database may more accurately reflect real-life health care resource consumption. However, these databases were not intentionally developed for these kinds of analyses. The capture of information may be incomplete, patients may be lost to follow-up, and recall bias can never be completely ruled out, all of which affect the cost-effectiveness results.
Perspective on the Future

The role of clopidogrel in the management of CAD continues to evolve. Cost-effectiveness analyses of clopidogrel have been performed looking at clopidogrel as an alternative to aspirin for secondary prevention of CV events in patients with CAD, as well as in addition to aspirin, to reduce CV events in patients with ACS (unstable angina and non-ST-segment elevation MI) and in those undergoing PCI. Newer clinical studies have also demonstrated the efficacy of clopidogrel use in patients with ST-segment elevation MI. Cost-effectiveness of clopidogrel in this patient population should be evaluated to help justify the use of this agent. More clinical studies are also needed to establish the optimal duration of clopidogrel therapy. Finally, true generic clopidogrel is not yet available. When multiple generic manufacturers are able to market, the cost of the drug will decrease and thereby affect the cost-effectiveness analyses.

Conclusions

Management of CAD entails the use of a variety of pharmacological agents with associated direct drug costs. This article comprehensively reviews the pharmacoeconomic analyses published to date, based on major clinical trials performed on clopidogrel in patients with CAD or ACS or in patients undergoing PCI. Clopidogrel is demonstrated to be cost effective from both a payer and a societal perspective in the United States, Canada, and selected European countries (United Kingdom, Spain, Sweden) when it is used in combination with aspirin (compared with aspirin alone) for 9-12 months in patients (1) who have unstable angina and non-ST-segment elevation MI and (2) who received coronary stent placement. The cost-effectiveness of clopidogrel when it is used as an alternative to aspirin for secondary prevention of CAD has not been shown, and clopidogrel should be reserved for patients who cannot tolerate aspirin. More clinical trials are underway to explore further the optimal duration of clopidogrel therapy. The results of these ongoing clinical trials will be opportunities to update the pharmacoeconomic analyses.

REFERENCES

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Pharmacoeconomic Analysis of Clopidogrel in Secondary Prevention of Coronary Artery Disease


Observational Study of the Prevalence of Febrile Neutropenia in Patients Who Received Filgrastim or Pegfilgrastim Associated With 3-4 Week Chemotherapy Regimens in Community Oncology Practices

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ABSTRACT

BACKGROUND: Colony-stimulating factors (CSFs) significantly decrease the risk of febrile neutropenia (FN), a common complication of myelosuppressive chemotherapy. Pegfilgrastim (6 mg), introduced in 2002, has a sustained duration of action, with a single dose comparable in efficacy to daily injections of filgrastim (5 μg per kg per day) for 10 to 11 days; both agents should be initiated 24 hours after completing chemotherapy.

OBJECTIVES: To (1) describe the use of pegfilgrastim and filgrastim in oncology practices throughout the United States and (2) compare their effectiveness in actual practice as measured by the outcome of febrile neutropenia in patients who received chemotherapy regimens administered every 3 to 4 weeks for breast, lung, ovarian, colon cancer, or lymphoma and who received a CSF prior to developing FN.

METHODS: Data were retrospectively obtained from the medical records of a cohort of adult patients aged 18 years or older treated in 99 community oncology practices in the United States in 2001 and 2003. Eligible patients were treated with chemotherapy every 3 to 4 weeks for breast, lung, ovarian, colon cancer, or lymphoma and were users of filgrastim in 2001 (prior to the U.S. Food and Drug Administration approval of pegfilgrastim in January 2002) or users of either filgrastim or pegfilgrastim or both CSF agents in 2003.

RESULTS: Pegfilgrastim was initiated, on average, 2.4 days (SD ±3.2) after chemotherapy in the first cycle of use and 1.9 (±3.0) days in subsequent cycles of use. In contrast, filgrastim was started on average 7.7 (±5.5) days and 4.9 (±4.6) days after chemotherapy in the first and subsequent cycles of use in 2001, increasing to 9.6 (±6.2) and 6.4 (±5.4) days in 2003. In the first cycle of CSF use, filgrastim was administered for an average of 5.2 (±3.5) days to 583 patients in 2001 and 3.7 (±2.8) days to 868 patients in 2003 (P < 0.001). Among patients who received more than 1 cycle of filgrastim (n = 457 in 2001 and n = 489 in 2003; 78.4% and 56.3% of filgrastim users, respectively), the mean days of filgrastim administered in subsequent cycles was 6.0 (±3.5) in 2001 and 4.6 (±3.2) in 2003. Pegfilgrastim was administered as a single dose per chemotherapy course to 1,412 patients in 2003. Patients who received pegfilgrastim were more likely to have at least 1 myelosuppressive drug (74.8%) in the regimen compared with patients who received filgrastim in 2003 (70.0%, P = 0.013), but a greater proportion of filgrastim patients in 2003 (19.4%) had advanced-stage disease compared with pegfilgrastim patients (14.8%, P = 0.005). More patients who received filgrastim in 2003 (36.2%) had a cancer other than breast cancer or non-Hodgkin’s lymphoma compared with those who received pegfilgrastim (29.5%, P = 0.001). A total of 94 of 1,451 patients (6.5%) who received filgrastim experienced FN compared with 67 of 1,412 patients (4.7%) for pegfilgrastim. The odds ratio of developing FN among patients who received filgrastim versus pegfilgrastim was 1.41 (95% confidence interval, 1.02-1.96; P = 0.040) after adjusting for patient and chemotherapy regimen characteristics.

CONCLUSION: In this retrospective study of patients treated in 99 community oncology practices, patients who received filgrastim often initiated treatment later than recommended and received fewer days per cycle than demonstrated to be effective in randomized controlled trials. Pegfilgrastim was generally initiated earlier within the course of chemotherapy compared with filgrastim, and because of its sustained duration of action, only a single injection was required. In these patients treated with a heterogeneous group of chemotherapy regimens with a broad range of risk of FN, overall, an absolute 1.8% increase in the incidence of developing FN was observed in patients who received filgrastim compared with patients who received pegfilgrastim, (absolute rates of 6.5% and 4.7%, respectively).

KEYWORDS: Adult medical oncology, Outcomes research, Growth factors, Supportive care, Febrile neutropenia, Community practice, Patient management

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A number of initiatives are under way to begin to measure and improve the quality of cancer care, including the American Society of Clinical Oncology’s (ASCO’s) Quality Oncology Practice Initiative,1 the National Initiative for Cancer Care Quality (NICCQ),2 and the Oncology Demonstration Project sponsored by the Centers for Medicare and Medicaid Services.3 In addition to improving the quality of care associated with the diagnosis, staging, and cancer-related therapy, an equally important priority is to ensure that patients receive appropriate supportive care to manage both disease symptoms and treatment-related toxicity.4,6

Neutropenia, a marked decline in infection-fighting white blood cells, is a frequent, often serious, and sometimes fatal complication of myelosuppressive chemotherapy, which may result in chemotherapy dose reductions or delays.7,8 In some malignancies, this may result in a poorer response to treatment and decreased survival.7,9-11 In the United States, an estimated 60,000 patients a year are hospitalized for febrile neutropenia (FN) and neutropenia-related infections. The estimated average cost of an FN hospitalization in the United States is $13,400.12

By promoting hematopoietic recovery after chemotherapy, colony-stimulating factors (CSFs) reduce the incidence, duration, and severity of chemotherapy-induced neutropenia, and associated complications.13-16 Pegfilgrastim (Neulasta) was approved by the U.S. Food and Drug Administration (FDA) in January 2002 to decrease the incidence of infection, as manifested by FN in patients with nonmyeloid malignancies receiving myelosuppressive anticancer drugs associated with a clinically significant incidence of FN.20 The recommended dosage of pegfilgrastim is a single subcutaneous (SC) injection of 6 mg administered once per chemotherapy cycle. Pegfilgrastim should not be administered in the period between 14 days before and 24 hours after administration of cytotoxic chemotherapy because of the potential for an increase in sensitivity of rapidly dividing myeloid cells to cytotoxic chemotherapy.

Filgrastim (Neupogen) was approved by the FDA 11 years earlier, in February 1991, to decrease the incidence of infection, as manifested by FN, in patients with nonmyeloid malignancies receiving myelosuppressive chemotherapy. Filgrastim was subsequently approved by the FDA for a broader range of indications that include patients with acute myeloid leukemia receiving induction or consolidation chemotherapy, cancer patients receiving bone marrow transplant, patients undergoing peripheral blood progenitor cell collection and therapy, and patients with severe chronic neutropenia.21 The FDA-approved label states that filgrastim should be administered no earlier than 24 hours after the administration of cytotoxic chemotherapy and continued daily for up to 2 weeks, until the absolute neutrophil count (ANC) has reached 10,000/mm3. The duration of filgrastim therapy needed to attenuate chemotherapy-induced neutropenia may be dependent on the myelosuppressive potential of the chemotherapy regimen employed. In the registrational clinical trials that were the basis for FDA approval for filgrastim, a median of 11 days of injections was required to achieve neutrophil recovery, defined as postnadir ANC count exceeding 10.0 x 10⁹/L.15,17,22 In randomized controlled trials, a single dose of pegfilgrastim had efficacy comparable to 10 to 11 days of filgrastim in reducing the incidence of grade IV neutropenia, defined as ANC <0.5 x 10⁹/L.16,19

A recent population-based study in older breast cancer patients reported substantial regional variation in filgrastim use.23 Likewise, prior studies have found substantial variation in physicians' self-reported use of CSFs for prophylaxis of FN.24 Additionally, prescribing patterns (i.e., the timing of initiation and duration of use) for filgrastim have been shown to vary from that used in the clinical trials in several community practice studies.25-27 It is not known if these studies are representative of U.S. prescribing patterns for filgrastim generally or if prescribing patterns changed following the commercial approval of pegfilgrastim in January 2002. Therefore, we conducted this retrospective cohort study to evaluate prescribing patterns of CSFs of filgrastim and pegfilgrastim and to assess neutropenia-related outcomes in 99 oncology practices located throughout the United States. We hypothesized that, given the need for multiple daily injections, prescribing patterns for filgrastim would vary significantly from the 10 to 14 days per cycle used in the clinical trials and, therefore, the use of pegfilgrastim with its once per chemotherapy cycle administration would result in improved patient outcomes in community practice.

### Methods

#### Study Sample

A 2-stage sampling procedure was used to identify a retrospective cohort of adult patients (≥18 years) with breast, lung, ovarian, or colon cancer or lymphoma (Hodgkin’s and non-Hodgkin’s) who initiated treatment with chemotherapy and were new users28 of filgrastim in 2001 (prior to the FDA approval of pegfilgrastim in January 2002) or filgrastim or pegfilgrastim in 2003 (Figure 1).

Oncology practices were selected using stratified random sampling from a commercial database owned by IMS Health that contains information on prescription drug distribution by drug category within the United States.29 A probability sample was identified from 8 of 10 strata defined by volume of chemotherapy purchases in 2003. Practices were considered ineligible if they were a government affiliate, treated <150 patients/year with chemotherapy, or were unable to identify a sample of patients. Practices that declined, did not respond, or were determined to be ineligible were replaced with another randomly selected practice (n = 1,353) until the desired sample size (n = 100) was obtained. One practice subsequently decided not to participate, resulting in a final sample of 99 practices.

The 99 practices that agreed to participate identified a consecutive sample of eligible patients using 1 of the following data sources: pharmacy records, billing records, appointment data sources: pharmacy records, billing records, appointment
Of these 1,455 patients, 1,031 (71%) received only filgrastim, while 424 (29%) of patients in the filgrastim group received at least 1 subsequent cycle of pegfilgrastim (a total of 580 patients received both filgrastim and pegfilgrastim). The intent-to-treat analysis assigned patients to the first CSF the patients received; therefore, the 424 patients receiving both were assigned to the filgrastim group.

A maximum of 12 patients/site were allowed in 2001 and 100 patients/site in 2003.

Of these patients in the pegfilgrastim group, 1,922 (92%) received only pegfilgrastim, while 156 (8%) received at least 1 subsequent cycle of filgrastim (a total of 580 patients received both filgrastim and pegfilgrastim). The intent-to-treat analysis assigned patients to the first CSF the patients received; therefore, the 156 patients receiving both were assigned to the pegfilgrastim group.

* Eligible patients were treated with chemotherapy for breast, lung, ovarian, or colon cancer or lymphoma and were new users of filgrastim in 2001 (prior to the FDA approval of pegfilgrastim in January 2002) or filgrastim or pegfilgrastim in 2003. Patients could not be enrolled in a clinical trial that included a CSF (including sargramostim). A maximum of 12 patients/site were allowed in 2001 and 100 patients/site in 2003.

† Of these 1,455 patients, 1,031 (71%) received only filgrastim, while 424 (29%) of patients in the filgrastim group received at least 1 subsequent cycle of pegfilgrastim (a total of 580 patients received both filgrastim and pegfilgrastim). The intent-to-treat analysis assigned patients to the first CSF the patients received; therefore, the 424 patients receiving both were assigned to the filgrastim group.

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§ To understand the effect of pegfilgrastim and filgrastim on the development of FN, analyses were limited to patients who received chemotherapy regimens that were administered every 3 to 4 weeks and who received a CSF prior to developing FN. Patients who were receiving daily or weekly chemotherapy were excluded, since they would generally not be at risk for FN, as well as patients receiving biweekly chemotherapy, as this requires CSF support.

CSF = colony stimulating factor; FDA = U.S. Food and Drug Administration; FN = febrile neutropenia.
books, or chemotherapy administration records. Patients were ineligible if they were enrolled in a clinical trial that included a CSF or if they were receiving sargramostim. For patients treated in 2001, the first 3 consecutive patients meeting the study eligibility criteria who received filgrastim at each practice in each calendar quarter were included in the study, for a total of up to 12 patients per practice (n=829). For patients treated in 2003, each practice identified the first 25 consecutive patients treated with chemotherapy beginning with the first day of each calendar quarter, for a total of up to 100 patients per practice. Among these patients, those who received filgrastim or pegfilgrastim and every third patient not treated with a CSF were then selected for the study (n = 5,319). Of these, 1,031 received only filgrastim, 1,922 received only pegfilgrastim, 580 received both filgrastim and pegfilgrastim, and 1,786 never received a CSF.

### Data Collection Procedures

Trained research staff abstracted patients’ medical records from May to September 2004 for data on patient characteristics, tumor characteristics, details of chemotherapy and CSF use, laboratory data, episodes of FN, and hospitalizations for up to 8 cycles of chemotherapy. Presence of comorbid conditions was captured using a modified Charlson index that included the following: peripheral vascular disease, myocardial infarction, congestive heart failure, cerebrovascular disease, chronic pulmonary disease, renal disease, human immunodeficiency virus, diabetes mellitus, liver disease, connective tissue disease, dementia, and peptic ulcer disease. All data collection procedures complied with the Health Insurance Portability and Accountability Act (HIPAA) regulations, and the study protocol was determined to be exempt from review by the Western Institutional Review Board.

### Statistical Analyses

Patients’ chemotherapy treatment was characterized according to the number of chemotherapy drugs in the regimen, the planned cycle length, and whether the regimen included at least 1 of the following drugs associated with myelosuppression: cladribine, cytarabine, cyclophosphamide, docetaxel, fludarabine, ifosfamide, irinotecan, methotrexate, or topotecan. To describe the variation in use of CSFs, it was determined whether therapy was initiated before or after FN, the cycle initiated (i.e., the first cycle of chemotherapy in which a CSF was administered), the day initiated in the cycle of initiation (i.e., the first day during the cycle of chemotherapy in which a CSF was administered) and the mean day initiated in all subsequent cycles of use (i.e., the average of the first day of administration in subsequent cycles) (See Table 1 for definitions of key terms). Additionally, for filgrastim, the number of days of use was also determined (by definition, pegfilgrastim patients received only a single dose per course of chemotherapy).

### Table 1 Definition of Key Terms

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Advanced disease stage</td>
<td>Cancer documented to have spread beyond the original tumor and lymph nodes, i.e., metastases present</td>
</tr>
<tr>
<td>ANC</td>
<td>Absolute neutrophil count; neutrophils are the blood cells responsible in fighting infection</td>
</tr>
<tr>
<td>ASCO guidelines for CSF therapy*</td>
<td>Primary prophylaxis with G-CSFs is recommended for decreasing the risk of FN in patients who have a high risk of FN based on age, medical history, disease characteristics, and myelotoxicity of the chemotherapy regimen (risk of FN is approximately 20% or higher)</td>
</tr>
<tr>
<td>Cycle of CSF initiation</td>
<td>The first cycle of chemotherapy in which a CSF was administered</td>
</tr>
<tr>
<td>Day of initiation</td>
<td>The first day during the cycle of chemotherapy in which a CSF was administered</td>
</tr>
<tr>
<td>Subsequent cycles</td>
<td>Cycles of chemotherapy following the cycle of CSF initiation</td>
</tr>
<tr>
<td>Mean days of administration in subsequent cycles</td>
<td>The average number of days a CSF was administered in subsequent cycles</td>
</tr>
<tr>
<td>Febrile neutropenia (FN)</td>
<td>Fever in the presence of neutropenia, where fever is defined as a single oral temperature of ≥38.3°C (100.4°F), or ≥38.0°C (100.4°F) for ≥1 hour†</td>
</tr>
<tr>
<td>Grade I neutropenia</td>
<td>Absolute neutrophil count ≥1.5 to &lt;2.0 (x10⁹/L)‡</td>
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<tr>
<td>Grade II neutropenia</td>
<td>Absolute neutrophil count ≥2.0 to &lt;3.0 (x10⁹/L)‡</td>
</tr>
<tr>
<td>Grade III neutropenia</td>
<td>Absolute neutrophil count ≥3.0 to &lt;5.0 (x10⁹/L)‡</td>
</tr>
<tr>
<td>Grade IV neutropenia</td>
<td>Absolute neutrophil count &lt;0.5 (x10⁹/L)†</td>
</tr>
<tr>
<td>Myelosuppressive chemotherapy drugs</td>
<td>Examples include cladribine, cytarabine, cyclophosphamide, docetaxel, fludarabine, ifosfamide, irinotecan, methotrexate, or topotecan</td>
</tr>
<tr>
<td>NCCN guidelines for CSF therapy§</td>
<td>Myeloid growth factors are recommended in first and in subsequent chemotherapy cycles for patients receiving chemotherapy regimens with a risk of FN &gt;20%</td>
</tr>
<tr>
<td>Neutrophil recovery</td>
<td>Post-nadir absolute neutrophil count exceeds 10.0 x 10⁹/L</td>
</tr>
<tr>
<td>Nonmyeloid malignancies</td>
<td>All cancers exclusive of those that arise from myeloid cells (e.g., leukemia); examples include breast cancer, lung cancer, and lymphoma</td>
</tr>
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</table>

ANC = absolute neutrophil count; ASCO = American Society of Clinical Oncology; CSF = colony-stimulating factor; G-CSF = granulocyte-colony-stimulating factor;
Patients were considered to have experienced FN if there was documentation on any of the following in their medical records in any cycles of chemotherapy reviewed (initial and subsequent data): (1) FN, (2) temperature of ≥38.3°C with documentation of neutropenia or an absolute neutrophil count (ANC) <1.0 x 10^9/L on the same day, or (3) hospitalization for FN.32

Since we wanted to understand the effect of pegfilgrastim and filgrastim on the development of FN, analyses were limited to patients who received chemotherapy regimens that were administered every 3 to 4 weeks and received a CSF prior to developing FN. Patients who were receiving daily or weekly chemotherapy were excluded since they would generally not be at risk for FN, as were patients receiving biweekly chemotherapy, since this requires CSF support.33 In addition, since we were interested in comparing the effectiveness of filgrastim with pegfilgrastim when used to prevent FN, we excluded patients who had their first episode of FN prior to receiving any CSF.

We identified 580 patients who received both filgrastim and pegfilgrastim in 2003. These were patients who started on 1 CSF type and then switched to the other. Among patients who received both CSFs in 2003, approximately 73% patients (n = 424) received filgrastim first, then were switched to pegfilgrastim. Similarly, among both users, approximately 27% (n = 156) received pegfilgrastim first, then were switched to filgrastim. For patients who received both filgrastim and pegfilgrastim, we used an intent-to-treat analysis34 in which patients were assigned to whichever CSF treatment group they received first. Thus, our analytic sample included 583 patients treated with filgrastim in 2001, 868 patients treated with filgrastim in 2003, and 1,412 patients treated with pegfilgrastim in 2003.

Multivariable logistic regression was used to estimate the odds of developing FN in patients who received filgrastim as compared with pegfilgrastim, adjusting for their patient and chemotherapy characteristics. Interaction effects were also tested for among variables that might have a synergistic effect on the risk of developing FN (e.g., age and comorbidity). As the coefficients remained stable and the main results did not differ, only the results of our final model are reported.

Because factors that affect a patient’s underlying risk of FN (e.g., chemotherapy or patient characteristics such as age or comorbid conditions) may have influenced the physician’s decision to use filgrastim versus pegfilgrastim, we performed a sensitivity analysis using a propensity score approach. We used the inverse probability of treatment-weighted estimator method35 to examine the effect of receiving filgrastim or pegfilgrastim on the risk of FN for the cohort of patients treated in 2003 (in 2001, all patients were treated with filgrastim). The propensity score was estimated using a logistic regression model of the probability of receiving pegfilgrastim versus filgrastim that included all of the patient and treatment characteristics.

Because of the potential misclassification of subjects who received both filgrastim and pegfilgrastim using an intent-to-treat approach, logistic regression was also performed after excluding patients who received both CSFs. Additionally, in order to evaluate for the effects of clustering within practices, the regression analysis was repeated using the robust variance estimation method described by Liang and Zeger that uses a generalized estimating equation (GEE) approach to account for possible correlation among data, e.g., within the same practice, in order to improve the efficiency of the estimation, e.g., of treatment effect.36 By assuming only a functional form of marginal distribution, this method avoids the need for specifying multivariate distributions of the correlated data. GEEs have also been shown to provide consistent and asymptotically normal estimates even when correlation/covariance structures are misspecified.

Analyses were conducted using SAS version V8.2 (Cary, NC). The \( \chi^2 \) test was used to test for significant differences in categorical variables and the F test for continuous variables for descriptive comparisons. All statistical tests were 2-sided.

Results

Patient Characteristics and Patterns of Care

Patient characteristics and the chemotherapy and CSF regimens are summarized in Table 2. More patients who received filgrastim in 2003 (36.2%) had a cancer other than breast cancer or non-Hodgkin’s lymphoma compared with those who received pegfilgrastim (29.5%, \( P = 0.001 \)). In addition, patients who received filgrastim in 2003 (19.4%) were more likely to have received advanced cancer compared with 14.8% for pegfilgrastim in 2003 (\( P = 0.005 \)). No differences in the mean number of chemotherapy cycles planned or mean number of drugs in the regimen were observed over time or with choice of CSF However, patients who received pegfilgrastim were more likely to have at least 1 myelosuppressive drug in their chemotherapy regimen (74.8%) compared with patients who received filgrastim in 2003 (70.0%, \( P = 0.013 \)).

Patients who received pegfilgrastim generally initiated treatment earlier within the course of chemotherapy compared with those receiving filgrastim (Table 2). In the first cycle in which a CSF was used, 38% of patients treated with filgrastim in 2001 received it within 3 days of chemotherapy administration, 24% within 4 to 9 days, and 38% on day 10 or later (Figure 2). In contrast, in 2003, the proportion of patients treated with filgrastim who started it on day 10 or later in the first cycle of usage increased to 52%. In subsequent cycles, the proportion of patients who initiated filgrastim within 3 days of chemotherapy administration was 39% in 2001, declining to 21% in 2003. In contrast, 86% of patients treated with pegfilgrastim received treatment within 3 days of chemotherapy in the first cycle of use, and 78% received pegfilgrastim within 3 days in subsequent cycles.

Mean days of filgrastim used also declined between 2001 and 2003. Filgrastim was administered for a mean (SD) of 5.2
### Observational Study of the Prevalence of Febrile Neutropenia in Patients Who Received Filgrastim or Pegfilgrastim Associated With 3-4 Week Chemotherapy Regimens in Community Oncology Practices

#### Patients Receiving Chemotherapy Every 3 to 4 Weeks Who Initiated Colony-Stimulating Factors Prior to Developing Febrile Neutropenia: Patient Characteristics and Patterns of Care (N=2,863)

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>2001 Filgrastim n=583</th>
<th>2003 Filgrastim n=868</th>
<th>2003 Pegfilgrastim n=1,412</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥65</td>
<td>218 (37.4)</td>
<td>334 (38.5)</td>
<td>520 (36.8)</td>
<td>0.812</td>
</tr>
<tr>
<td>&lt;65</td>
<td>365 (62.6)</td>
<td>534 (61.5)</td>
<td>892 (63.2)</td>
<td>0.429</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>132 (22.6)</td>
<td>205 (23.6)</td>
<td>312 (22.1)</td>
<td>0.790</td>
</tr>
<tr>
<td>Female</td>
<td>451 (77.4)</td>
<td>663 (76.4)</td>
<td>1,100 (77.9)</td>
<td>0.400</td>
</tr>
<tr>
<td>Tumor</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast</td>
<td>301 (51.6)</td>
<td>418 (48.2)</td>
<td>747 (52.9)</td>
<td>0.770</td>
</tr>
<tr>
<td>Lung</td>
<td>120 (20.6)</td>
<td>208 (24.0)</td>
<td>300 (21.2)</td>
<td>0.771*</td>
</tr>
<tr>
<td>NHL</td>
<td>106 (18.2)</td>
<td>136 (15.7)</td>
<td>248 (17.6)</td>
<td>0.001*</td>
</tr>
<tr>
<td>Other†</td>
<td>56 (9.6)</td>
<td>106 (12.2)</td>
<td>117 (8.3)</td>
<td></td>
</tr>
<tr>
<td>Disease stage</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Advanced</td>
<td>88 (15.1)</td>
<td>168 (19.4)</td>
<td>209 (14.8)</td>
<td>0.867</td>
</tr>
<tr>
<td>Comorbid conditions</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>602 (69.4)</td>
<td>1,021 (72.3)</td>
<td>747 (52.9)</td>
<td>0.027</td>
</tr>
<tr>
<td>1</td>
<td>185 (21.3)</td>
<td>290 (20.5)</td>
<td>520 (36.8)</td>
<td>0.135</td>
</tr>
<tr>
<td>2+</td>
<td>60 (10.3)</td>
<td>81 (9.3)</td>
<td>747 (52.9)</td>
<td>0.203</td>
</tr>
<tr>
<td>Serum albumin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;3.5 g/dL</td>
<td>58 (9.9)</td>
<td>106 (12.2)</td>
<td>158 (11.2)</td>
<td>0.417</td>
</tr>
<tr>
<td>Anemia</td>
<td>24 (4.1)</td>
<td>28 (3.2)</td>
<td>51 (3.6)</td>
<td>0.590</td>
</tr>
<tr>
<td>Baseline ANC</td>
<td>8 (1.4)</td>
<td>11 (1.3)</td>
<td>14 (1.0)</td>
<td>0.459</td>
</tr>
<tr>
<td>Fehbre neutropenia</td>
<td>31 (5.3)</td>
<td>63 (7.3)</td>
<td>67 (4.7)</td>
<td>0.591</td>
</tr>
</tbody>
</table>

#### Patterns of Care, Mean [SD] Except Where Noted

<table>
<thead>
<tr>
<th>Characteristics of chemotherapy regimen</th>
<th>2001 Filgrastim</th>
<th>2003 Filgrastim</th>
<th>2003 Pegfilgrastim</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of cycles planned</td>
<td>4.9 [1.6]</td>
<td>5.0 [1.4]</td>
<td>5.1 [1.5]</td>
<td>0.098</td>
</tr>
<tr>
<td>Number of chemotherapy drugs in regimen</td>
<td>2.3 [0.6]</td>
<td>2.3 [0.8]</td>
<td>2.3 [0.6]</td>
<td>0.039</td>
</tr>
<tr>
<td>At least 1 myelosuppressive drug in regimen, n (%)†‡</td>
<td>424 (72.7)</td>
<td>608 (70.0)</td>
<td>1,056 (74.8)</td>
<td>0.339</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Colony-stimulating factors (CSF)</th>
<th>2001 Filgrastim</th>
<th>2003 Filgrastim</th>
<th>2003 Pegfilgrastim</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSF initiation, n (%)</td>
<td>0.004</td>
<td>0.018</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>322 (55.2)</td>
<td>537 (61.9)</td>
<td>848 (60.1)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>134 (23.0)</td>
<td>180 (20.7)</td>
<td>344 (24.4)</td>
<td></td>
</tr>
<tr>
<td>3+</td>
<td>127 (21.8)</td>
<td>151 (17.4)</td>
<td>220 (15.6)</td>
<td></td>
</tr>
<tr>
<td>Day of initiation in first cycle of use§</td>
<td>7.7 [6.5]</td>
<td>9.6 [6.2]</td>
<td>2.4 [3.2]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Day of initiation in subsequent cycles of use§</td>
<td>4.9 [4.6]</td>
<td>6.4 [6.4]</td>
<td>1.9 [3.0]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Days of administration in first cycle of use§</td>
<td>5.2 [3.5]</td>
<td>3.7 [2.8]</td>
<td>1.0 [0.0]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Days of administration in subsequent cycles of use§</td>
<td>6.0 [3.5]</td>
<td>4.6 [3.2]</td>
<td>1.0 [0.0]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Number of patients receiving CSFs in ≥2 subsequent cycles</td>
<td>457 (78.4)</td>
<td>489 (56.3)</td>
<td>1,234 (87.4)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Of the 868 filgrastim users in 2003, 318 (36.6%) received 1 or more subsequent cycles of pegfilgrastim and of the 1,412 pegfilgrastim users in 2003, 97 (6.9%) received 1 or more subsequent cycles of filgrastim in this intent-to-treat analysis.

P values are presented for pegfilgrastim 2003 versus filgrastim 2001 (peg 2003 vs. fil 2001) and pegfilgrastim 2003 versus filgrastim 2003 (peg 2003 vs. fil 2003). Comparisons of days of administration are made only between filgrastim 2001 and filgrastim 2003.

The $\chi^2$ test was used to test for significant differences in categorical variables and the F test for continuous variables. All statistical tests were 2-sided.

* P values for comparing incidence of breast cancer or NHL versus other tumor types.
† Other* included colon cancer, ovarian cancer, and Hodgkin's lymphoma.
‡ Myelosuppressive drug included cladribine, cytarabine, cyclophosphamide, doxorubicin, ifosfamide, irinotecan, mechlorethamine, methotrexate, or topotecan.
§ Day of initiation refers to the first day during the cycle of chemotherapy, cycle of initiation refers to the first cycle of chemotherapy in which a CSF was administered.
|| Days of administration was calculated for filgrastim but not pegfilgrastim since the latter requires just 1 injection per cycle.
ANC = absolute neutrophil count; NHL = non-Hodgkin's lymphoma.
Observational Study of the Prevalence of Febrile Neutropenia in Patients Who Received Filgrastim or Pegfilgrastim Associated With 3-4 Week Chemotherapy Regimens in Community Oncology Practices

FIGURE 2 The Day of Colony-Stimulating Factor (CSF) Initiation Within the Initial and Subsequent Chemotherapy Cycles for Filgrastim in 2001 and 2003 and Pegfilgrastim in 2003

(±3.5) days in 2001 compared with 3.7 (±2.8) days in 2003 (P <0.001) in the first cycle of usage, and 6.0 (±3.5) days versus 4.6 (±3.2) days in 2001 and 2003, respectively, in subsequent cycles of use (P <0.001) (Table 2). The proportion of patients receiving ≥8 days of filgrastim was only 9% in the first cycle and subsequent cycles of use in 2003, compared with 22% and 21% in 2001 (Figure 3).

Patient Outcomes

More chemotherapy drugs in the regimen and the presence of at least 1 myelosuppressive drug were associated with a higher incidence of FN (Table 3). A low baseline serum albumin was the only patient characteristic that was significantly associated with the incidence of FN (P = 0.011).

The incidence of FN varied with the CSF received. Patients who received filgrastim had a higher incidence of FN compared with patients who received pegfilgrastim (6.5% vs. 4.7%, respectively; P = 0.044). Adjusting for patient and chemotherapy regimen characteristics, patients receiving filgrastim had an approximately 40% increase in the odds of developing FN compared with patients who received pegfilgrastim (odds ratio [OR], 1.41; 95% confidence interval [CI], 1.02-1.96) (Table 4). Using a propensity score method instead of multivariate logistic regression to adjust for patient and chemotherapy regimen characteristics that predicted use of pegfilgrastim and filgrastim, the OR for developing FN in patients who received filgrastim as compared with pegfilgrastim was 1.52 (95% CI, 1.18-1.96). Excluding patients who received both pegfilgrastim and filgrastim from the analysis resulted in a modest increase in the OR for developing FN with filgrastim as compared with pegfilgrastim (OR, 1.59; 95% CI, 1.10-2.31).

Additional analysis accounting for clustering (within a given practice) yielded similar results. Adjusting for patient and chemotherapy regimen characteristics, patients receiving filgrastim were 40% more likely to experience FN than patients who received pegfilgrastim under both compound-symmetry assumption of within-cluster association (OR, 1.39; 95% CI, 1.01-1.90; P = 0.04) and independent within-cluster assumption.
(OR, 1.41; 95% CI, 1.03-1.93; \( P = 0.03 \)), using a robust variance estimation method.\(^{36} \)

### Discussion

The objective of this study was to examine patterns of care and neutropenia-related outcomes associated with pegfilgrastim and filgrastim in oncology practices throughout the United States. In this retrospective cohort study, use of filgrastim in community practices varied significantly from its use in the registrational clinical trials, where it was always scheduled to be administered a day after the last dose of chemotherapy for a duration of 9 to 14 days.\(^{15,17,22} \) Patients treated with filgrastim in these community oncology practices initiated treatment later within a chemotherapy cycle (for both the initial and subsequent cycles of use) and received shorter courses of therapy. In contrast, pegfilgrastim was initiated earlier than filgrastim in both the initial and subsequent cycles of use.

These findings are similar to other studies that have described the marked variation in the use of filgrastim.\(^{25-27} \) Bennett et al. surveyed U.S. oncologists regarding the use of CSFs in 1994 and 1997.\(^{24} \) They found that physicians reported using a wide variety of criteria for starting and stopping CSFs. In addition, 30% reported initiating CSF late in the cycle to treat febrile neutropenia. In a retrospective cohort study of patients with non-Hodgkin’s lymphoma, Lyman and colleagues found that among the 29.3% of patients who started a CSF in the first cycle of chemotherapy, more than half had it initiated later (more than 5 days after the start of chemotherapy) in the cycle, presumably in response to neutropenia, and more than half were treated for less than 7 days.\(^{37} \) In a similar study in breast cancer patients, the median day of CSF initiation after receiving the first cycle of chemotherapy among patients who received it was 10 days.\(^{38} \)

When using filgrastim, physicians appear to have a “watch and wait” approach to the management of chemotherapy-induced neutropenia, initiating therapy in response to a low white blood cell nadir, particularly in those patients who would not necessarily be considered for CSF therapy (e.g., a chemotherapy regimen with an expected risk of FN <20% and no other risk factors) according to ASCO\(^{33} \) or National Comprehensive Cancer Network (NCCN)\(^{39} \) guidelines. In contrast, our study indicated that pegfilgrastim was administered using a more proactive approach, with treatment initiated in the first cycle of chemotherapy in more than half of the patients and within
Observational Study of the Prevalence of Febrile Neutropenia in Patients Who Received Filgrastim or Pegfilgrastim Associated With 3-4 Week Chemotherapy Regimens in Community Oncology Practices

### TABLE 3  Incidence of Febrile Neutropenia by Patient and Chemotherapy Characteristics and Colony-Stimulating Factors Received (N=2,863)

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>Incidence of Febrile Neutropenia, n (%)</th>
<th>N (Denominator)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65</td>
<td>99 (5.5)</td>
<td>1,791</td>
<td>0.773</td>
</tr>
<tr>
<td>≥65</td>
<td>62 (5.8)</td>
<td>1,072</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>45 (6.9)</td>
<td>649</td>
<td>0.099</td>
</tr>
<tr>
<td>Female</td>
<td>116 (5.2)</td>
<td>2,214</td>
<td></td>
</tr>
<tr>
<td>Stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Limited or unknown</td>
<td>139 (5.8)</td>
<td>2,398</td>
<td>0.361</td>
</tr>
<tr>
<td>Advanced</td>
<td>22 (4.7)</td>
<td>465</td>
<td></td>
</tr>
<tr>
<td>Comorbid conditions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>105 (5.1)</td>
<td>2,045</td>
<td>0.144</td>
</tr>
<tr>
<td>1</td>
<td>37 (6.4)</td>
<td>576</td>
<td></td>
</tr>
<tr>
<td>≥2</td>
<td>19 (7.9)</td>
<td>242</td>
<td></td>
</tr>
<tr>
<td>Baseline serum albumin*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;3.5 g/dL</td>
<td>28 (8.7)</td>
<td>322</td>
<td>0.011</td>
</tr>
<tr>
<td>≥3.5 g/dL</td>
<td>133 (5.2)</td>
<td>2,541</td>
<td></td>
</tr>
<tr>
<td>Baseline anemia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin &lt;10.0 g/dL</td>
<td>10 (9.7)</td>
<td>103</td>
<td>0.067</td>
</tr>
<tr>
<td>Hemoglobin ≥10.0 g/dL</td>
<td>151 (5.5)</td>
<td>2,760</td>
<td></td>
</tr>
<tr>
<td>Baseline ANC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1.5 x 10^9/L</td>
<td>4 (12.1)</td>
<td>33</td>
<td>0.103</td>
</tr>
<tr>
<td>≥1.5 x 10^9/L</td>
<td>157 (5.5)</td>
<td>2,830</td>
<td></td>
</tr>
<tr>
<td>Characteristics of chemotherapy regimen</td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Number of chemotherapy drugs in regimen†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>8 (3.5)</td>
<td>227</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>60 (3.7)</td>
<td>1,642</td>
<td></td>
</tr>
<tr>
<td>≥3</td>
<td>93 (9.4)</td>
<td>994</td>
<td></td>
</tr>
<tr>
<td>At least 1 myelosuppressive drug in regimen‡</td>
<td></td>
<td></td>
<td>0.0001</td>
</tr>
<tr>
<td>No</td>
<td>26 (3.4)</td>
<td>775</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>135 (6.5)</td>
<td>2,088</td>
<td></td>
</tr>
<tr>
<td>CSF received*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pegfilgrastim</td>
<td>67 (4.7)</td>
<td>1,412</td>
<td>0.0448</td>
</tr>
<tr>
<td>Filgrastim</td>
<td>94 (6.5)</td>
<td>1,451</td>
<td></td>
</tr>
<tr>
<td>2001</td>
<td>31 (5.3)</td>
<td>583</td>
<td></td>
</tr>
<tr>
<td>2003</td>
<td>63 (7.3)</td>
<td>868</td>
<td></td>
</tr>
</tbody>
</table>

Filgrastim patients in 2001 and 2003; pegfilgrastim patients in 2003. The denominator is the number of patients with a particular patient, chemotherapy, or CSF characteristic. Incidence of febrile neutropenia refers to any febrile neutropenia event in the initial and subsequent cycles of chemotherapy reviewed. The total number of febrile neutropenia events in this entire sample is 161. The χ² test was used to test for significant differences in categorical variables and the F test for continuous variables. All statistical tests were 2-sided. * P <0.05 † P <0.001 ‡ P <0.01 § P value for pegfilgrastim vs filgrastim (2001 and 2003). ANC = absolute neutrophil count; CSF = colony-stimulating factor.

### TABLE 4  Odds of Febrile Neutropenia Occurrence With Use of Filgrastim Compared With Pegfilgrastim Adjusted for Patient and Chemotherapy Characteristics

<table>
<thead>
<tr>
<th>CSF received</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Filgrastim</td>
<td>1.41</td>
<td>1.02-1.96</td>
<td>0.040</td>
</tr>
<tr>
<td>Pegfilgrastim</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Incidence of febrile neutropenia refers to any febrile neutropenia event in the initial and subsequent cycles of chemotherapy reviewed. * Overall, 34% of patients had documentation that showed that they did not have metastases and were of limited stage (physicians often document “metastatic disease” in the medical chart but do not necessarily document the actual stage of disease). † OR estimate based on every 1-unit increase, i.e., 1 more drug in regimen. ANC = absolute neutrophil count; CI = confidence interval; CSF = colony-stimulating factor.

3 days of chemotherapy 86% of the time. The burden of daily injections with filgrastim may represent a potential barrier to patients receiving all of the recommended injections of filgrastim or may have prompted physicians to recommend shorter courses of therapy.

NCCN and ASCO guidelines recommend primary prophylaxis with a CSF in the first chemotherapy cycle and in
subsequent cycles for patients receiving chemotherapy regimens with a moderate to high risk (20% or greater) of FN.\textsuperscript{33,39} Additionally, in patients who are not necessarily candidates for primary prophylaxis, the guidelines also recommend use of CSF alter FN develops or when neutropenia could result in chemotherapy dose delays or dose reductions in patients treated with curative intent. Primary prophylaxis with a CSF has been demonstrated to reduce the relative risk of FN by approximately 50%.\textsuperscript{8} Randomized controlled trials have shown pegfilgrastim to be of similar efficacy to filgrastim.\textsuperscript{16,19} However, we found that, among patients treated with a heterogeneous group of chemotherapy regimens with a broad range of risk of FN in community oncology practices, an overall 1.8 percentage point increase in the incidence of developing FN was observed in patients who received filgrastim compared with patients who received pegfilgrastim, (absolute rates of 6.5% and 4.7%, respectively) resulting in a 40% increase in the odds of FN. Thus, overall, for every 56 patients treated in community settings with pegfilgrastim instead of filgrastim, 1 additional case of FN would be avoided. Thus, the absolute risk reduction associated with the use of pegfilgrastim as compared with filgrastim would range from approximately 2\% for a regimen with a 10\% risk of FN, 4\% for a regimen with a 20\% risk of FN to 12\% for a regimen with a 60\% risk of FN. However, it is worth noting that clinical guidelines recommend consideration of prophylaxis with a CSF when the risk of FN associated with a chemotherapy regimen is less than 20\% when patient characteristics place them at increased risk of dying as a result of FN or to avoid dose reduction and delays in patients treated with curative intent and not solely based upon avoidance of FN alone.\textsuperscript{33,39}

**Limitations**

Several limitations should be considered when interpreting the results of this study. First, while probability sampling was used to select the participating oncology practices, the substantial nonresponse rate could limit the generalizability of our results. Second, data for this study were obtained by abstracting patients’ charts and, therefore, are dependent upon the accuracy and completeness of medical record documentation. Thus, we have probably underestimated the true incidence of FN since patients who sought care in settings where care was not documented in their oncologist's chart (i.e., emergency room) are not reported. Third, our methodology may also have led to underestimation of the number of days of filgrastim use if this was not reliably documented or if patients received filgrastim outside of their oncologist’s office, including self-administration of growth factors at home. Filgrastim is distributed by community pharmacies, mail order, and specialty pharmacies.

Fourth, differences in patient treatment and factors associated with risk of FN that influenced physician selection of pegfilgrastim over filgrastim could have influenced our results. For example, the most important predictor of FN is the risk associated with the chemotherapy regimen, and patients who received pegfilgrastim were more likely to be treated with myelosuppressive chemotherapy regimens so our results may underestimate the impact of pegfilgrastim on patient outcomes. On the other hand, there were minimal differences in patient characteristics; for example, more patients treated with filgrastim in 2003 had a higher proportion of advanced stage cancer compared with pegfilgrastim in 2003. However, all of these factors were adjusted for in the multivariate logistic regression analysis used in this study.

Lastly, these analyses are limited to a comparison of the outcomes of the pegfilgrastim and filgrastim and do not include chemotherapy patients who did not receive a CSF agent. This study was not intended to answer the question about the how and when CSF agents are used in chemotherapy patients with breast, lung, ovarian, or colon cancer or lymphoma.

**Conclusion**

Despite comparable efficacy in clinical trials,\textsuperscript{16,19} we found that pegfilgrastim was associated with a lower incidence of FN compared with filgrastim in patients with breast, lung, ovarian, or colon cancer or lymphoma (Hodgkin's and non-Hodgkin's lymphoma) treated with chemotherapy in community practice. Difference in effectiveness of the 2 drugs may be related to how the drugs were actually used in clinical practice in contrast with their administration under optimal circumstances in clinical trials. These findings underscore the need for observational research to evaluate the effectiveness of therapy in heterogeneous patient populations treated in community practices. While all new U.S. pharmaceutical therapies undergo rigorous evaluation to demonstrate their safety and efficacy during the FDA approval process, variations in actual use and the diversity of patient populations may have a small but measurable impact on the effectiveness of medications.\textsuperscript{40}

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Morrison served as principal author of the study. Study concept and design were contributed primarily by Morrison and Malin, with input from the coauthors. Data collection was the work of Hershman and Malin; data interpretation was primarily the work of Morrison, Malin, and Ding, with input from the coauthors. Statistical support was provided by Amgen, Inc. Writing of the manuscript and its revision were primarily the work of Morrison, Malin, and Ding, with input from the coauthors.

REFERENCES
Administrative Claims Analysis of Utilization and Costs of Care in Health Plan Members With Atopic Dermatitis Who Had Prior Use of a Topical Corticosteroid and Who Initiate Therapy With Pimecrolimus or Tacrolimus

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ABSTRACT

BACKGROUND: In the United States, pimecrolimus cream and tacrolimus ointment are approved as second-line therapy for short-term and intermittent noncontinuous long-term treatment of atopic dermatitis (AD) in nonimmunocompromised patients aged 2 years or older who have failed to respond adequately to other topical prescription treatments (e.g., topical corticosteroids), or when those treatments are not advisable; pimecrolimus is indicated for mild-to-moderate AD and tacrolimus for moderate-to-severe AD. Comparative data on the effects of pimecrolimus versus tacrolimus on AD-related health care utilization and costs among similar patients seen in typical clinical practice are currently unavailable.

OBJECTIVE: To compare utilization and costs of AD-related medical care in health plan members with AD who had prior use of a topical corticosteroid and who subsequently initiate therapy with pimecrolimus cream or tacrolimus ointment.

METHODS: This was an observational, retrospective study using an administrative claims database with dates of service from August 1, 2000, through October 31, 2003, and representing approximately 2.5 million members in health maintenance organizations, preferred provider organizations, and Medicare and Medicaid plans mostly located in the cities of Chicago, Kansas City, and Phoenix and in the states of Kentucky, Florida, and Texas. The study sample included all members with 1 or more pharmacy claims for a topical corticosteroid and a diagnosis of AD (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] code 691.0X [excluding 691.0X), or 692.XX (excluding 692.0X-692.8X]) who subsequently had 1 or more pharmacy claims for pimecrolimus or tacrolimus. AD-related utilization and medical care costs (plan payments plus member cost share) over 12 months of follow-up were compared between the pimecrolimus and tacrolimus groups. Because information on disease severity was not available in the administrative claims data, propensity matching was used to control for differences between groups in baseline demographic and clinical characteristics and pretreatment utilization of AD-related medical care services.

RESULTS: Before matching, compared with the tacrolimus group (n = 197), members in the pimecrolimus group (n = 197) were older (mean age of 38 vs. 32 years, P = 0.022), had fewer topical corticosteroid pharmacy claims (mean 2.08 vs. 3.01, P = 0.002), and had fewer grams of corticosteroids dispensed (mean 132 vs. 193, P = 0.029) in the 12 months prior to treatment. After matching, there were 157 members in each group with no statistically significant differences in pretreatment characteristics. During the 12-month follow-up period, the mean (median) number of pharmacy claims was 1.0 (1.0) for pimecrolimus versus 2.0 (1.0) for tacrolimus and the mean (median) number of prescription refills was 102 (60) and 105 (60), respectively. Members in the pimecrolimus group had a lower average number of prescriptions for any topical corticosteroids (1.37 vs. 2.04, P = 0.021) and for high-potency topical corticosteroids (0.61 vs. 1.04, P = 0.023) and were less likely to initiate alternative therapy (5% vs. 17%, P <0.001) or receive antistaphylococcal antibiotics (16% vs. 27%, P = 0.014). Members in the pimecrolimus group had lower average (median) AD-related expenditures (75% to 78% attributable to AD drug cost) compared with matched tacrolimus members ($263 [$270] vs. $361 [$398], P = 0.012).

CONCLUSIONS: In health plan members with AD who had previously received at least 1 topical corticosteroid prescription, the customary use of pimecrolimus or tacrolimus was 1 to 2 prescriptions in 12 months of follow-up and only a median of 60 grams of topical medication. The difference in AD-related utilization and costs between pimecrolimus and tacrolimus was small, less than $100 per year, but favored pimecrolimus. Further research using validated measures of disease severity to control for potential confounding is needed to confirm the results of this observational study.

KEYWORDS: Atopic dermatitis, Pimecrolimus, Tacrolimus, Retrospective claims analysis, Costs

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What is already known about this subject

• A pooled analysis of 413 adults and 650 pediatric patients participating in 3 randomized studies found that tacrolimus compared with pimecrolimus was more effective based on (1) Investigator Global Atopic Dermatitis Assessment (IGADA), (2) improvement in percentage of total body surface area affected, and (3) improvement in itch scores; tacrolimus and pimecrolimus had comparable tolerability.

What this study adds

• Using propensity matching to control for differences between groups in baseline demographic and clinical characteristics and pretreatment utilization of AD-related medical care services in the absence of explicit classification of disease severity, the present study suggests that in real-world clinical practice, use of pimecrolimus may be associated with fewer pharmacy claims for topical corticosteroids, less utilization of antistaphylococcal antibiotics, and small but lower total costs of AD-related medical care (75% attributable to AD drug cost) compared with tacrolimus.

A topic dermatitis (AD) is a chronic or relapsing skin disease characterized by itching, redness, and inflammation, with a predilection for the face and extensor surfaces of the extremities in young children and the flexural folds in older children and adults.1 Although AD typically presents in infancy...
or early childhood and resolves with advancing age, it may persist into adulthood or commence at that time of life. In industrialized countries, the lifetime prevalence of AD is 10% to 20%.

Topical corticosteroids and moisturizing therapy have long been the mainstay of pharmacological treatment for AD. Although effective, prolonged use of steroids may lead to skin atrophy, hyperpigmentation, and, rarely, suppression of the hypothalamic-pituitary-adrenal axis. These effects may require the use of alternative topical agents.

Pimecrolimus cream and tacrolimus ointment are topical calcineurin inhibitors that are indicated for the short-term and intermittent long-term treatment of AD in immunocompetent patients aged 2 years or older who have failed to respond adequately to topical corticosteroids or who have been advised not to take topical corticosteroids (e.g., due to concerns regarding hyperpigmentation on head and neck areas). The 0.03% strength tacrolimus ointment is recommended for children aged 2 to 15 years and the 0.1% strength is recommended for adults.

Randomized, blinded, vehicle-controlled trials have shown that pimecrolimus and tacrolimus are more effective than placebo vehicle in treatment of AD. They are minimally absorbed and do not produce the adverse effects on the skin that are frequently seen with topical corticosteroids. While the 2 drugs have a similar mechanism of action, they differ in their pharmacological profiles, with pimecrolimus characterized by less skin permeation and systemic immunoreactions than for tacrolimus. Tacrolimus was approved by the U.S. Food and Drug Administration (FDA) in December 2000 and became available in the U.S. market in January 2001; pimecrolimus was approved by the FDA in December 2001 and became available in the U.S. market in March 2002. Importantly, whereas pimecrolimus is indicated for mild-to-moderate AD, tacrolimus is indicated for moderate-to-severe AD. The FDA has mandated a warning of a potential cancer risk from long-term use of topical immunosuppressant calcineurin inhibitors on the basis of animal studies, case reports, and mechanism of action, although a definitive causal link between use of these drugs and cancer has not been established.

In a meta-analysis of 16 noncomparative trials (9 tacrolimus and 7 pimecrolimus) involving a total of 5,301 patients (2,106 for tacrolimus and 1,225 for pimecrolimus), Iskedjian and colleagues reported similar clinical success rates for pimecrolimus and tacrolimus. The populations examined in the trials of pimecrolimus and tacrolimus differed, however, with trials of tacrolimus trials enrolling patients with more severe disease, which may have biased the comparison. Head-to-head comparative clinical studies of pimecrolimus and tacrolimus have had contradictory findings. In a randomized, investigator-blinded study of pimecrolimus (n = 71) and tacrolimus ointment (n = 70) in pediatric patients with moderate AD, Kempers and colleagues reported that efficacy based on the Investigator Global Atopic Dermatitis Assessment (IGADA) score was not statistically different between groups. However, patients receiving pimecrolimus had less frequent adverse skin reactions lasting more than 30 minutes and were more likely to rate ease of application as excellent or very good.

More recently, in a pooled analysis of the results of 3 randomized comparative studies of pimecrolimus versus tacrolimus involving 413 adult and 650 pediatric patients, Paller and colleagues reported that tacrolimus was more effective than pimecrolimus, based on improvement from baseline to 6 weeks or the end of the study in Eczema Area Severity Index (EASI) (52.8% vs. 39.1%, respectively; P < 0.001). IGADA scores (treatment success 62.1% vs. 49.8%, P < 0.001), and percentage of total body surface area affected (53.6% vs. 41.0%, P < 0.001). The least squares mean itch scores at baseline were 5.6 in both groups, and tacrolimus patients had lower least squares mean itch scores (2.6) at the end of the study (6 weeks) versus 3.3 for pimecrolimus, P < 0.001. The safety profiles of the 2 drugs were similar. Although a recent budgetary analysis reported that the addition of pimecrolimus as a treatment would have a minimal impact on AD-related costs for a health plan, and a recent cost-effectiveness analysis suggested that pimecrolimus is a cost-effective alternative for patients with AD, neither of these studies considered tacrolimus.

Although results from clinical trials suggest that there may be differences in efficacy, safety, and tolerability of pimecrolimus and tacrolimus, data on the differences in utilization and costs of AD-related medical care for patients receiving these 2 drugs in typical clinical practice are unavailable. We therefore conducted a retrospective observational health insurance claims-based study to compare AD-related utilization costs in health plan members receiving pimecrolimus or tacrolimus within 1 year following first prescription of either of these agents.

Methods

Study Design

This was a retrospective observational study comparing the utilization and costs of AD-related medical care among AD patients who had received at least 1 prescription for a topical corticosteroid and who subsequently initiated either pimecrolimus or tacrolimus. Data were obtained from a large administrative claims dataset. Utilization and costs during the 12 months following the first pharmacy claim for either of these agents were compared using propensity score matching to compare AD-related utilization costs in health plan members receiving pimecrolimus or tacrolimus within 1 year following first prescription of either of these agents.
Data Source

Data for this study were obtained from a Health Insurance Portability and Accountability Act (HIPAA)-compliant, limited dataset containing enrollment data as well as facility, professional service, and outpatient pharmacy claims for approximately 2.5 million members enrolled in a health maintenance organization (HMO), preferred provider organization, and Medicare and Medicaid plans mostly located in the cities of Chicago, Kansas City, and Phoenix and in the states of Kentucky, Florida, and Texas. Age, sex, U.S. Census region, and dates of benefit eligibility were generally available for all members. Data available for each outpatient pharmacy claim included the drug dispensed (in National Drug Code [NDC] format), the dispensing date, and the quantity and number of therapy days dispensed. Data available for each facility or professional service claim (“medical claim”) included dates of service and International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis codes; severity of AD was not ascertainable based on diagnosis codes. Facility claims also included ICD-9-CM procedure codes, revenue codes, and discharge status, while professional service claims also include Health Care Common Procedure Coding and Current Procedural Terminology procedure codes. Most claims also included information on paid amounts (plan payment and member cost share). Claims for an individual member were linkable using a unique encrypted patient identifier. This study included claims spanning the period from August 1, 2000, to October 31, 2003 (“study period”).

Study Sample

To identify the study sample, we selected all members in the database with 1 or more pharmacy claims for a topical corticosteroid between August 1, 2000, and October 31, 2002. The date of the first pharmacy claim for a topical corticosteroid was designated the “steroid start date.” From these members, we selected those with 1 or more pharmacy claims for pimecrolimus or tacrolimus between August 1, 2001, and October 31, 2002, and after the steroid start date. The date of the first pharmacy claim for either pimecrolimus or tacrolimus was designated the “index date.” The 12-month period prior to the index date was designated the “pretreatment period.” The 12-month period subsequent to the index date was designated the “follow-up period.”

Members meeting the above criteria were then stratified into treatment groups (pimecrolimus or tacrolimus) based on the study medication received on the index date; those with pharmacy claims for both pimecrolimus and tacrolimus on the index date were excluded. Other exclusion criteria were as follows:

1. Fewer than 12 months of continuous eligibility for drug and medical benefits during preindex and postindex periods
2. Less than 1 medical claim with a diagnosis (primary or secondary) of AD (ICD-9-CM 691.XX, excluding 691.0X, or 692.XX, excluding 692.0X-692.8X) during the pretreatment period
3. One or more medical claims with a diagnosis of diaper rash, contact dermatitis, or dermatitis due to substances taken internally (ICD-9-CM 691.0X, 692.0X-692.8X, 693.XX) during the pretreatment period
4. Age less than 2 years as of the index date

Because we required 12 months of continuous enrollment prior to the first prescription for pimecrolimus or tacrolimus, the “washout” period for these drugs was 12 months.

Patient Characteristics

Information on age, sex, U.S. Census region, and plan type was obtained from enrollment files for each member. Medical claims during the pretreatment period were scanned to identify members with 1 or more encounters for other inflammatory conditions of the skin and subcutaneous tissue (ICD-9-CM 690.XX-698.XX, excluding codes for AD described above), staphylococcal infection of the skin and subcutaneous tissue (ICD-9-CM 041.1X and 680.XX-709.XX), and nonspecific dermatitis (ICD-9-CM 692.9X).

Measures of Utilization and Costs

For each member, we calculated several measures of utilization and costs during the 12-month pretreatment and follow-up periods. Utilization measures included the total number of pharmacy claims and grams of low-potency topical corticosteroids (e.g., hydrocortisone cream or ointment 1.0% or 2.5%, fluocinolone acetonide cream 0.01%), medium-potency topical corticosteroids (e.g., triamcinolone acetonide cream or ointment 0.025% or 0.1%, betamethasone valerate cream or ointment 0.1%), and high-potency topical corticosteroids (e.g., clobetasol propionate cream or ointment 0.05%, fluocinonide cream or ointment 0.05%) during the pretreatment and follow-up periods. Costs measures included the cost of AD-related visits plus the cost of AD-related medications during the pretreatment and follow-up periods. We also identified members who had pharmacy claims for antihistamines, systemic immunosuppressives, or antistaphylococcal antibiotics during the pretreatment and follow-up periods as well as those who had pharmacy claims for the alternative study medication during the follow-up period.
cost for each claim was defined as the sum of plan payment and member cost share (i.e., allowable charge). In calculating measures of utilization and costs, office visits occurring on the index date were assigned to the pretreatment period, while pharmacy claims occurring on the index date were assigned to the follow-up period.

Statistical Analyses

Demographic characteristics, as well as measures of utilization and costs of AD-related medical care during the pretreatment and follow-up periods, were compared between the treatment groups using chi-square tests for categorical variables and the Student t test for continuous variables. To control for differences between groups in baseline characteristics, we also compared measures of utilization and costs during follow-up among propensity-matched members in the pimecrolimus and tacrolimus groups.38,39 Propensity scores were calculated for all members by estimating a logistic regression model with treatment group as the dependent variable and selected patient demographic characteristics and pretreatment measures of AD-related utilization as independent variables. The latter included age, sex, region, plan type, pretreatment diagnosis of other inflammatory skin condition, pretreatment claims for antistaphylococcal antibiotics, antihistamines, or systemic immunosuppressive medications, numbers of pretreatment AD-related specialist and generalist visits, and numbers of pretreatment steroid claims. The propensity score for each member was defined as the predicted probability (range: 0.0-1.0) of receiving pimecrolimus conditioned on the observed values of the other characteristics. Matched pairs of pimecrolimus and tacrolimus members were identified using a greedy matching technique so that the maximum difference in propensity score between paired members was 0.1.40 Because tacrolimus is available in 2 dosage forms (0.03% and 0.1%) and clinical effectiveness might differ by formulation, we conducted a secondary analysis in which we compared members receiving pimecrolimus with matched members receiving tacrolimus 0.1%. All analyses were conducted using SAS Proprietary Software, Release 9.1 (Cary, NC).

Results

Study Sample

We identified 17,341 members who had 1 or more pharmacy claims for a topical corticosteroid between August 1, 2000, and October 31, 2002 (see Figure). Of these, 1,502 had a pharmacy claim for pimecrolimus or tacrolimus between August 1, 2001, and October 31, 2002. These 1,502 members included 832 who had claims for pimecrolimus on the index date and 662 who had claims for tacrolimus on the index date, as well as 8 members who had claims for both tacrolimus and pimecrolimus on the index date and who were therefore excluded from the analysis. In the pimecrolimus group, 496 (60%) were excluded because they did not have a pharmacy claim for topical steroids prior to

![Flowchart](https://example.com/flowchart.png)

**FIGURE** Flowchart of Study Subjects

- **Members With ≥1 Rx for TCS Between 8/1/2000-10/31/2002 (N = 17,341, 100%)**
- **Members With ≥1 Rx for PIM or TAC Between 8/1/2001-10/31/2002 (N = 1,502, 8.7%)**
- **Members With PIM Only on Index Date (n = 832; 4.8%)**
- **Members With TAC Only on Index Date (n = 662; 3.8%)**
- **Members With Steroid Start Date Prior to Index Date (n = 336; 1.9%)**
- **Members With Steroid Start Date Prior to Index Date (n = 303; 1.7%)**
- **Members in PIM Group With Diagnosis of AD Prior to Index Date (n = 216; 1.2%)**
- **Members in TAC Group With Diagnosis of AD Prior to Index Date (n = 203; 1.2%)**
- **Members in PIM Group With Age ≥2 Years on Index Date (n = 197; 1.1%)**
- **Members in TAC Group With Age ≥2 Years on Index Date (n = 197; 1.1%)**

**AD** = atopic dermatitis; **PIM** = pimecrolimus; **Rx** = pharmacy claim; **TAC** = tacrolimus; **TCS** = topical corticosteroid.
TABLE 1  Pretreatment Characteristics of Full and Propensity-Matched Samples of Pimecrolimus and Tacrolimus Patients*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Full Sample</th>
<th>Propensity-Matched Sample</th>
<th>P Value</th>
<th>Full Sample</th>
<th>Propensity-Matched Sample</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pimecrolimus</td>
<td>Tacrolimus</td>
<td></td>
<td>Pimecrolimus</td>
<td>Tacrolimus</td>
<td></td>
</tr>
<tr>
<td></td>
<td>N = 197</td>
<td>N = 197</td>
<td>P Value</td>
<td>N = 157</td>
<td>N = 157</td>
<td>P Value</td>
</tr>
<tr>
<td>Age, years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2-12</td>
<td>47 (24)</td>
<td>59 (30)</td>
<td>0.173</td>
<td>46 (29)</td>
<td>39 (25)</td>
<td>0.374</td>
</tr>
<tr>
<td>13-18</td>
<td>17 (9)</td>
<td>22 (11)</td>
<td>0.399</td>
<td>13 (8)</td>
<td>18 (11)</td>
<td>0.344</td>
</tr>
<tr>
<td>&gt;18</td>
<td>133 (68)</td>
<td>116 (59)</td>
<td>0.076</td>
<td>98 (62)</td>
<td>100 (64)</td>
<td>0.815</td>
</tr>
<tr>
<td>Mean [SD]</td>
<td>38 [25]</td>
<td>32 [23]</td>
<td>0.022</td>
<td>34 [24]</td>
<td>34 [23]</td>
<td>0.842</td>
</tr>
<tr>
<td>Male</td>
<td>80 (41)</td>
<td>76 (39)</td>
<td>0.680</td>
<td>63 (40)</td>
<td>59 (38)</td>
<td>0.643</td>
</tr>
<tr>
<td>South region</td>
<td>43 (22)</td>
<td>35 (18)</td>
<td>0.312</td>
<td>28 (18)</td>
<td>31 (20)</td>
<td>0.665</td>
</tr>
<tr>
<td>Health maintenance organization</td>
<td>108 (55)</td>
<td>132 (67)</td>
<td>0.013</td>
<td>98 (62)</td>
<td>102 (65)</td>
<td>0.639</td>
</tr>
<tr>
<td>Other inflammatory skin conditions</td>
<td>56 (28)</td>
<td>44 (22)</td>
<td>0.165</td>
<td>37 (24)</td>
<td>39 (25)</td>
<td>0.792</td>
</tr>
<tr>
<td>Antihistamine</td>
<td>103 (52)</td>
<td>102 (52)</td>
<td>0.920</td>
<td>77 (49)</td>
<td>75 (48)</td>
<td>0.821</td>
</tr>
<tr>
<td>Systemic immunosuppressants</td>
<td>27 (14)</td>
<td>31 (16)</td>
<td>0.570</td>
<td>21 (13)</td>
<td>23 (15)</td>
<td>0.745</td>
</tr>
<tr>
<td>Antistaphylococcal antibiotics</td>
<td>46 (23)</td>
<td>50 (25)</td>
<td>0.639</td>
<td>38 (24)</td>
<td>39 (25)</td>
<td>0.896</td>
</tr>
<tr>
<td>Nonspecific dermatitis</td>
<td>136 (69)</td>
<td>143 (73)</td>
<td>0.438</td>
<td>115 (73)</td>
<td>118 (75)</td>
<td>0.699</td>
</tr>
<tr>
<td>Topical corticosteroids, mean [SD]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of pharmacy claims</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low potency</td>
<td>0.14 [0.39]</td>
<td>0.39 [1.01]</td>
<td>0.002</td>
<td>0.17 [0.43]</td>
<td>0.15 [0.51]</td>
<td>0.718</td>
</tr>
<tr>
<td>Medium potency</td>
<td>0.92 [1.58]</td>
<td>1.14 [1.94]</td>
<td>0.232</td>
<td>1.00 [1.69]</td>
<td>0.92 [1.33]</td>
<td>0.657</td>
</tr>
<tr>
<td>High potency</td>
<td>1.02 [2.01]</td>
<td>1.48 [2.65]</td>
<td>0.050</td>
<td>1.08 [2.17]</td>
<td>1.20 [1.99]</td>
<td>0.607</td>
</tr>
<tr>
<td>Total</td>
<td>2.08 [2.45]</td>
<td>3.01 [3.27]</td>
<td>0.002</td>
<td>2.25 [2.65]</td>
<td>2.28 [2.11]</td>
<td>0.925</td>
</tr>
<tr>
<td>No. of grams</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low potency</td>
<td>5 [16]</td>
<td>28 [144]</td>
<td>0.025</td>
<td>6 [17]</td>
<td>5 [20]</td>
<td>0.856</td>
</tr>
<tr>
<td>Medium potency</td>
<td>78 [228]</td>
<td>88 [211]</td>
<td>0.657</td>
<td>73 [178]</td>
<td>69 [166]</td>
<td>0.858</td>
</tr>
<tr>
<td>High potency</td>
<td>49 [103]</td>
<td>77 [157]</td>
<td>0.037</td>
<td>52 [110]</td>
<td>63 [125]</td>
<td>0.399</td>
</tr>
<tr>
<td>Total</td>
<td>132 [249]</td>
<td>193 [300]</td>
<td>0.029</td>
<td>131 [213]</td>
<td>138 [208]</td>
<td>0.757</td>
</tr>
<tr>
<td>No. of AD-related visits, mean [SD]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonspecialist</td>
<td>0.63 [0.82]</td>
<td>0.87 [1.14]</td>
<td>0.020</td>
<td>0.72 [0.82]</td>
<td>0.70 [0.93]</td>
<td>0.847</td>
</tr>
<tr>
<td>All</td>
<td>1.81 [1.84]</td>
<td>2.05 [1.45]</td>
<td>0.162</td>
<td>1.90 [1.94]</td>
<td>1.87 [1.21]</td>
<td>0.889</td>
</tr>
<tr>
<td>AD-related costs, $, mean [SD]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medications</td>
<td>50 [95]</td>
<td>78 [148]</td>
<td>0.029</td>
<td>54 [101]</td>
<td>57 [103]</td>
<td>0.776</td>
</tr>
<tr>
<td>Visits</td>
<td>134 [268]</td>
<td>151 [242]</td>
<td>0.496</td>
<td>141 [292]</td>
<td>143 [222]</td>
<td>0.939</td>
</tr>
<tr>
<td>Total</td>
<td>184 [292]</td>
<td>229 [293]</td>
<td>0.127</td>
<td>195 [317]</td>
<td>201 [254]</td>
<td>0.865</td>
</tr>
</tbody>
</table>

* Values are no. (%) of patients unless otherwise indicated.
AD = atopic dermatitis.
Differences between groups in study outcomes during the care (mean $258 vs. $440, \( P < 0.001 \)) and were less likely to be enrolled in HMOs (55% vs. 67%, \( P = 0.013 \)). Members in the pimecrolimus group received fewer pharmacy claims for topical corticosteroids (mean 2.08 vs. 3.01, \( P = 0.002 \)) and fewer total grams of topical corticosteroids (mean 132 vs. 193, \( P = 0.029 \)) during the pretreatment period than did those in the tacrolimus group. They also had fewer pretreatment AD-related nonspecialist visits (mean 0.63 vs. 0.87, \( P = 0.020 \)) and lower pretreatment costs of AD-related pharmacy claims (mean $50 vs. $78, \( P = 0.029 \)). The 2 groups were similar in terms of sex, region, pretreatment diagnoses for other skin conditions, and use of antihistamines, systemic immunosuppressives, and antistaphylococcal antibiotics.

After propensity score matching, there were no statistically significant differences in pretreatment characteristics between groups. Mean age was 34 years in both the pimecrolimus and tacrolimus groups (\( P = 0.842 \)). Mean total pharmacy claims for topical corticosteroids during the pretreatment period were 2.25 and 2.28 in the pimecrolimus and tacrolimus groups, respectively (\( P = 0.925 \)). Mean total AD-related costs during the pretreatment period were $195 for the pimecrolimus group and $201 for the tacrolimus group (\( P = 0.865 \)).

Utilization and Costs During Follow-up

Measures of utilization and costs during follow-up for the full and propensity-matched samples are shown in Table 2. Before matching, members who received pimecrolimus had fewer total pharmacy claims for topical corticosteroids (mean 1.32 vs. 2.30, \( P < 0.001 \)) and fewer total grams of topical corticosteroids (mean 82 vs. 193, \( P = 0.015 \)) during follow-up than had members who received tacrolimus. Pimecrolimus members also were less likely to receive tacrolimus during follow-up than were tacrolimus members to receive pimecrolimus during follow-up (5% vs. 17%, \( P < 0.001 \)). Utilization of concomitant medications was similar in the 2 groups. Members receiving pimecrolimus had fewer total AD-related visits (mean 0.84 vs. 1.18, \( P = 0.024 \)) but not fewer AD-related specialist visits (mean 0.61 vs. 0.85, \( P = 0.054 \)). They also had lower total costs of AD-related medical care (mean $258 vs. $440, \( P < 0.001 \)), primarily due to lower costs of AD medications (mean $198 vs. $349, \( P < 0.001 \)).

Differences between groups in study outcomes during the follow-up were generally attenuated by propensity matching. Nevertheless, even after matching, members in the pimecrolimus group had fewer pharmacy claims for topical corticosteroids during follow-up than had those in the tacrolimus group (mean 1.37 vs. 2.04, \( P = 0.021 \)); this difference was largely due to fewer claims for high-potency topical corticosteroids among pimecrolimus members (mean 0.61 vs. 1.04, \( P = 0.023 \)). Fewer pimecrolimus members had pharmacy claims for antistaphylococcal antibiotics during follow-up than had the matched tacrolimus members (16% vs. 27%, \( P = 0.014 \)). Total AD-related costs during follow-up also were lower among propensity-matched members receiving pimecrolimus (mean $263 vs. $361, \( P = 0.012 \)).

Pimecrolimus Versus Tacrolimus 0.1%

Of the 197 members who met all criteria for inclusion and initiated therapy with tacrolimus, 144 (74%) received tacrolimus 0.1% on the index date. After matching these members to those receiving pimecrolimus, using propensity scores, we found that there were 122 matched pairs of pimecrolimus and tacrolimus 0.1% members. Results from this analysis (Tables 3 and 4) were generally similar to those comparing pimecrolimus with both formulations of tacrolimus. After matching, members receiving pimecrolimus on their index date had fewer pharmacy claims for high-potency topical corticosteroids during follow-up (mean 0.70 vs. 1.13, \( P = 0.047 \)), were less likely to switch therapy during follow-up (5% vs. 16%, \( P = 0.006 \)), and were less likely to have a pharmacy claim for an antistaphylococcal antibiotic during follow-up (mean 16% vs. 28%, \( P = 0.020 \)) than were those who received tacrolimus 0.1%. Total AD-related expenditures were not significantly different between the 2 groups in the 12-month follow-up period (mean $308 for pimecrolimus versus $376 for tacrolimus [\( P = 0.137 \)].

Discussion

We conducted a retrospective observational comparison of utilization and costs of AD-related medical care in health plan members with AD who received topical corticosteroids and subsequently initiated therapy with pimecrolimus or tacrolimus. After attempting to control for differences between groups using propensity matching on baseline clinical characteristics and pretreatment utilization of AD-related medical care, we found that pimecrolimus members had fewer pharmacy claims for topical corticosteroids, were less likely to switch therapy, were less likely to receive antistaphylococcal antibiotics, and had lower costs of AD-related medical care during follow-up than had corresponding tacrolimus members.

A recent pooled analysis of 413 adults and 650 pediatric patients participating in 3 randomized studies found that tacrolimus was more effective than pimecrolimus, based on a variety of measures. A randomized, investigator-blinded
Administrative Claims Analysis of Utilization and Costs of Care in Health Plan Members With Atopic Dermatitis Who Had Prior Use of a Topical Corticosteroid and Who Initiate Therapy With Pimecrolimus or Tacrolimus

### TABLE 2
Utilization and Costs of AD-Related Care During Follow-up for Full and Propensity-Matched Samples of Pimecrolimus and Tacrolimus Patients*

<table>
<thead>
<tr>
<th></th>
<th>Full Sample</th>
<th></th>
<th>Propensity-Matched Sample</th>
<th></th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pimecrolimus</td>
<td>Tacrolimus</td>
<td>Pimecrolimus</td>
<td>Tacrolimus</td>
<td></td>
</tr>
<tr>
<td></td>
<td>N = 197</td>
<td>N = 197</td>
<td>N = 157</td>
<td>N = 157</td>
<td></td>
</tr>
<tr>
<td>No. of pharmacy claims for study medication</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean [SD]</td>
<td>1.8 [1.4]</td>
<td>2.4 [2.4]</td>
<td>1.8 [1.5]</td>
<td>2.0 [1.6]</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>No. of grams of study medication</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>60</td>
<td>60</td>
<td>60</td>
<td>60</td>
<td></td>
</tr>
<tr>
<td>1 or more pharmacy claims for topical corticosteroids</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low potency</td>
<td>17 (9)</td>
<td>31 (16)</td>
<td>14 (9)</td>
<td>19 (12)</td>
<td>0.031</td>
</tr>
<tr>
<td>Medium potency</td>
<td>53 (27)</td>
<td>57 (29)</td>
<td>44 (28)</td>
<td>43 (27)</td>
<td>0.653</td>
</tr>
<tr>
<td>High potency</td>
<td>60 (30)</td>
<td>76 (39)</td>
<td>44 (28)</td>
<td>64 (41)</td>
<td>0.090</td>
</tr>
<tr>
<td>Total</td>
<td>108 (55)</td>
<td>125 (63)</td>
<td>84 (54)</td>
<td>97 (62)</td>
<td>0.081</td>
</tr>
<tr>
<td>No. of grams of topical corticosteroids, mean [SD]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low potency</td>
<td>0.14 [0.59]</td>
<td>0.40 [1.77]</td>
<td>0.13 [0.52]</td>
<td>0.32 [1.77]</td>
<td>0.052</td>
</tr>
<tr>
<td>Medium potency</td>
<td>0.57 [1.36]</td>
<td>0.79 [1.86]</td>
<td>0.62 [1.43]</td>
<td>0.69 [1.50]</td>
<td>0.195</td>
</tr>
<tr>
<td>High potency</td>
<td>0.61 [1.24]</td>
<td>1.11 [2.29]</td>
<td>0.61 [1.31]</td>
<td>1.04 [1.94]</td>
<td>0.007</td>
</tr>
<tr>
<td>Total</td>
<td>1.32 [2.00]</td>
<td>2.30 [3.37]</td>
<td>1.37 [2.10]</td>
<td>2.04 [2.98]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No. of grams of topical corticosteroids, mean [SD]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low potency</td>
<td>5.9 [22.8]</td>
<td>68.0 [578.5]</td>
<td>5.9 [22.2]</td>
<td>62.5 [625.2]</td>
<td>0.133</td>
</tr>
<tr>
<td>Medium potency</td>
<td>41.9 [130.9]</td>
<td>59.0 [156.4]</td>
<td>47.3 [141.3]</td>
<td>47.9 [123.8]</td>
<td>0.241</td>
</tr>
<tr>
<td>High potency</td>
<td>34.3 [80.0]</td>
<td>65.9 [168.2]</td>
<td>35.6 [85.2]</td>
<td>60.5 [146.8]</td>
<td>0.018</td>
</tr>
<tr>
<td>Total</td>
<td>82.2 [162.1]</td>
<td>192.9 [615.0]</td>
<td>88.8 [171.0]</td>
<td>171.0 [649.1]</td>
<td>0.015</td>
</tr>
<tr>
<td>1 or more prescriptions for alternative study therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Antihistamine</td>
<td>9 (5)</td>
<td>33 (17)</td>
<td>8 (5)</td>
<td>27 (17)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Systemic immunosuppressants</td>
<td>23 (12)</td>
<td>28 (14)</td>
<td>20 (13)</td>
<td>21 (13)</td>
<td>0.453</td>
</tr>
<tr>
<td>Antistaphylococcal antibiotics</td>
<td>34 (17)</td>
<td>49 (25)</td>
<td>25 (16)</td>
<td>43 (27)</td>
<td>0.064</td>
</tr>
<tr>
<td>No of AD-related visits, mean [SD]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Specialist</td>
<td>0.61 [1.14]</td>
<td>0.85 [1.35]</td>
<td>0.59 [1.14]</td>
<td>0.81 [1.33]</td>
<td>0.364</td>
</tr>
<tr>
<td>Nonspecialist</td>
<td>0.24 [0.72]</td>
<td>0.33 [0.86]</td>
<td>0.22 [0.61]</td>
<td>0.19 [0.57]</td>
<td>0.594</td>
</tr>
<tr>
<td>All</td>
<td>0.84 [1.32]</td>
<td>1.18 [1.60]</td>
<td>0.82 [1.26]</td>
<td>1.00 [1.40]</td>
<td>0.024</td>
</tr>
<tr>
<td>AD-related costs, $, mean [SD]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medications</td>
<td>198 [202]</td>
<td>349 [462]</td>
<td>&lt;0.001</td>
<td>196 [200]</td>
<td>0.013</td>
</tr>
<tr>
<td>Visits</td>
<td>61 [148]</td>
<td>91 [214]</td>
<td>0.096</td>
<td>67 [163]</td>
<td>0.592</td>
</tr>
<tr>
<td>Total</td>
<td>258 [262]</td>
<td>440 [543]</td>
<td>&lt;0.001</td>
<td>263 [270]</td>
<td>0.013</td>
</tr>
</tbody>
</table>

* Values are no. (%) of patients unless otherwise indicated. AD = atopic dermatitis.
study of pimecrolimus and tacrolimus ointment 0.03% in 141 pediatric patients reported similar efficacy with pimecrolimus and tacrolimus but superior local tolerability and more favorable ratings of product characteristics with pimecrolimus. While we did not examine these specific outcomes in our study, it is possible that the differences in outcomes that we observed

---

**TABLE 3** Pretreatment Characteristics of Propensity-Matched Sample of Pimecrolimus and Tacrolimus 0.1% Patients*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Pimecrolimus</th>
<th>Tacrolimus 0.1%</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2-12</td>
<td>22 (18)</td>
<td>19 (16)</td>
<td>0.607</td>
</tr>
<tr>
<td>13-18</td>
<td>10 (8)</td>
<td>16 (13)</td>
<td>0.213</td>
</tr>
<tr>
<td>&gt;18</td>
<td>90 (74)</td>
<td>87 (71)</td>
<td>0.667</td>
</tr>
<tr>
<td>Mean [SD]</td>
<td>41 [24]</td>
<td>39 [22]</td>
<td>0.431</td>
</tr>
<tr>
<td>Male</td>
<td>48 (39)</td>
<td>44 (36)</td>
<td>0.597</td>
</tr>
<tr>
<td>South region</td>
<td>23 (19)</td>
<td>22 (18)</td>
<td>0.869</td>
</tr>
<tr>
<td>Health maintenance organization</td>
<td>76 (62)</td>
<td>75 (61)</td>
<td>0.895</td>
</tr>
<tr>
<td>Other inflammatory skin conditions</td>
<td>33 (27)</td>
<td>32 (26)</td>
<td>0.885</td>
</tr>
<tr>
<td>Antihistamine</td>
<td>58 (48)</td>
<td>57 (47)</td>
<td>0.898</td>
</tr>
<tr>
<td>Systemic immunosuppressants</td>
<td>19 (16)</td>
<td>19 (16)</td>
<td>1.000</td>
</tr>
<tr>
<td>Antistaphylococcal antibiotics</td>
<td>36 (30)</td>
<td>34 (28)</td>
<td>0.777</td>
</tr>
<tr>
<td>Nonspecific dermatitis</td>
<td>95 (78)</td>
<td>91 (75)</td>
<td>0.547</td>
</tr>
</tbody>
</table>

Topical corticosteroids, mean [SD]

<table>
<thead>
<tr>
<th>Condition</th>
<th>Pimecrolimus</th>
<th>Tacrolimus 0.1%</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low potency</td>
<td>0.15 [0.42]</td>
<td>0.18 [0.59]</td>
<td>0.617</td>
</tr>
<tr>
<td>Medium potency</td>
<td>1.04 [1.86]</td>
<td>0.87 [1.38]</td>
<td>0.414</td>
</tr>
<tr>
<td>High potency</td>
<td>1.35 [2.38]</td>
<td>1.39 [2.21]</td>
<td>0.889</td>
</tr>
<tr>
<td>Total</td>
<td>2.54 [2.88]</td>
<td>2.44 [2.48]</td>
<td>0.775</td>
</tr>
</tbody>
</table>

No. of grams

<table>
<thead>
<tr>
<th>Condition</th>
<th>Pimecrolimus</th>
<th>Tacrolimus 0.1%</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low potency</td>
<td>6 [19]</td>
<td>8 [26]</td>
<td>0.538</td>
</tr>
<tr>
<td>Medium potency</td>
<td>98 [279]</td>
<td>78 [198]</td>
<td>0.516</td>
</tr>
<tr>
<td>High potency</td>
<td>66 [121]</td>
<td>67 [117]</td>
<td>0.951</td>
</tr>
<tr>
<td>Total</td>
<td>170 [299]</td>
<td>152 [231]</td>
<td>0.611</td>
</tr>
</tbody>
</table>

No. of AD-related visits, mean [SD]

<table>
<thead>
<tr>
<th>Condition</th>
<th>Pimecrolimus</th>
<th>Tacrolimus 0.1%</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specialist</td>
<td>1.34 [2.07]</td>
<td>1.30 [1.24]</td>
<td>0.822</td>
</tr>
<tr>
<td>Nonspecialist</td>
<td>0.71 [0.87]</td>
<td>0.66 [0.82]</td>
<td>0.596</td>
</tr>
<tr>
<td>All</td>
<td>2.04 [2.01]</td>
<td>1.93 [1.25]</td>
<td>0.620</td>
</tr>
</tbody>
</table>

AD-related costs, $, mean [SD]

<table>
<thead>
<tr>
<th>Condition</th>
<th>Pimecrolimus</th>
<th>Tacrolimus 0.1%</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medications</td>
<td>65 [112]</td>
<td>57 [95]</td>
<td>0.512</td>
</tr>
<tr>
<td>Visits</td>
<td>159 [319]</td>
<td>149 [236]</td>
<td>0.768</td>
</tr>
<tr>
<td>Total</td>
<td>224 [346]</td>
<td>205 [265]</td>
<td>0.624</td>
</tr>
</tbody>
</table>

* Values are no. (%) of patients unless otherwise indicated. AD = atopic dermatitis.
were due to differences in tolerability and patient perceptions regarding product characteristics that have been reported elsewhere.33

**Limitations**

First and foremost, this was a retrospective, observational study using health insurance administrative claims data. Such studies
Administrative Claims Analysis of Utilization and Costs of Care in Health Plan Members With Atopic Dermatitis Who Had Prior Use of a Topical Corticosteroid and Who Initiate Therapy With Pimecrolimus or Tacrolimus

are useful for examining outcomes in “real world” settings where patient selection and treatment conditions are more inclusive than are typically done in tightly controlled randomized controlled trials. Because treatment with pimecrolimus or tacrolimus was not randomly assigned, it is possible that our findings were due to confounding factors that were not accounted for in our analyses. Of particular importance is the issue of disease severity. Pimecrolimus is approved for use in the United States in patients with mild-to-moderate AD, whereas tacrolimus is approved for use in patients with moderate-to-severe AD. One would expect, therefore, that members receiving pimecrolimus would have less severe disease than those receiving tacrolimus. Indeed, we found that members in the pimecrolimus group utilized less topical corticosteroid and had fewer visits in the pretreatment period than had those in the tacrolimus group. Also, members who received pimecrolimus were less likely to have received topical corticosteroids prior to therapy initiation. Although we attempted to control for these differences by selecting patients who received prior steroid therapy and by using propensity-score matching, we lacked information on disease severity and were unable to control for it directly in our analysis.

Second, since we required AD patients in this study to have received at least 1 prior pharmacy claim for a topical steroid, we may have excluded many patients who were using only over-the-counter (OTC) topical steroids because OTC topical steroid use was not measured. We also do not know the extent of OTC topical steroid use during the 12-month follow-up period.

Third, our sample size was relatively small, which precluded subgroup analyses based on baseline characteristics such as age, sex, level of pretreatment utilization of steroids, or dosage or intensity of treatment with pimecrolimus or tacrolimus.

Fourth, because our sample was drawn from members in a variety of health plans offered by a single large U.S. health benefits company, our findings may not be generalizable to patients in other countries, regions, or types of health plans.

Fifth, we did not evaluate a control group of AD patients who received only corticosteroids and neither tacrolimus nor pimecrolimus. Although this group of patients might have provided additional information about the value of tacrolimus or pimecrolimus compared with corticosteroids, it is likely that any comparison would be confounded because receipt of topical calcineurin inhibitors is very probably highly correlated with response to topical steroid therapy.

Conclusions

We found that compared with health plan members who used tacrolimus, members with AD who used pimecrolimus and had previously received at least 1 topical corticosteroid prescription received fewer pharmacy claims for topical corticosteroids, were less likely to receive antistaphylococcal antibiotics, and had lower total costs of AD-related medical care. Further research using validated measures of disease severity is needed to confirm the results of this observational study.

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author of the study. Study concept and design were contributed by Delea, Sung, Pinkston, and Gause. Data collection was the work of Makin, Hussein, Vanderpoel, and Sandman, data interpretation was primarily the work of Delea and Goldhale, with input from the coauthors. Writing of the manuscript was the work of Delea, Goldhale, Chang, and Jackson; its revision was primarily the work of Goldhale and Delea, with input from the coauthors.

REFERENCES

Opinions Regarding the Academy of Managed Care Pharmacy Dossier Submission Guidelines: Results of a Small Survey of Managed Care Organizations and Pharmaceutical Manufacturers

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ABSTRACT

BACKGROUND: In recent years, there has been more emphasis on determining the total value of a drug product, which includes safety and efficacy information and clinical and economic value relative to other therapies. The Academy of Managed Care Pharmacy (AMCP) Format for Formulary Submissions was intended as a tool to assist health care providers in evaluating and selecting drug products.

OBJECTIVE: The purpose of this research was to gain the perspectives of a sample of managed care organizations (MCOs) and pharmaceutical manufacturers regarding the AMCP Format submission and evaluation process, as well as their comments on possible future direction for these guidelines as an important part of the formulary decision-making process.

METHODS: A random sample of large (>1 million lives) and small (<1 million lives) MCOs was generated using telephone numbers from the National Directory of Managed Care Organizations’ database. Pharmaceutical manufacturer respondents were identified from the Pharmaceutical Research and Manufacturers of America (PhRMA) Foundation’s Health Outcomes Committee. Telephone interviews were conducted by 2 researchers between September 2004 and October 2005. Respondents from both pharmaceutical manufacturers and MCOs nationwide were familiar with the AMCP dossier preparation and review process, allowing us to compare perspectives from each group. The interview was designed to assess the following key areas: economic models, organizational burden, confidentiality, overall value, and future expectations.

RESULTS: Representatives from 20 MCOs and 7 pharmaceutical manufacturers completed the interview; 21 MCO representatives refused to participate, citing company policy. Nearly all (87.5%) of the MCO personnel contacted reviewed dossiers within their organization. However, MCO respondents indicated that only 40% of all drugs they reviewed included dossiers from the manufacturers. For drug evaluation at the level of the pharmacy and therapeutics committee, we found that drugs were compared with a variety of products, with 11 respondents reporting comparisons with a placebo, and all respondents reporting a comparison with at least 1 other branded product. On average, 53.5% of the dossiers MCOs received included budget-impact models, and 39.3% included cost-effectiveness analyses (CEAs) or cost-benefit analyses. Of the dossiers with economic models, less than half (46.2%) were deemed adequate. Nearly two thirds of MCO respondents reported that they modified the provided model with their own population statistics, as many respondents that manufacturers do not make models directly applicable to their health plan population.

The perspectives of the pharmaceutical manufacturers varied dramatically from the MCO respondents with regard to the inclusion of economic models. Five of the 7 respondents indicated that their companies always included an economic model in the submitted dossiers. One respondent indicated that 85% of company dossiers included models, and another reported that 50% of dossiers included CEA models. Both MCOs and pharmaceutical manufacturers commented that organizational burden was high, with 70% of both groups reporting the use of outside consultants to assist in the dossier process.

CONCLUSIONS: Overall, findings for this study suggest that awareness of the AMCP Format is high among MCOs and pharmaceutical manufacturers, but aligning objectives between the 2 organization types is necessary. Conceptually, proving a drug value beyond what the U.S. Food and Drug Administration requires is a reasonable request, something most respondents agreed on. However, less than half of all drugs reviewed had a dossier. In contrast to MCO respondents, pharmaceutical manufacturers appear to have a more positive outlook on the role of the AMCP Format in effectively communicating the value of a new drug product. Further steps need to be taken to improve acceptance and integration of the AMCP Format.

KEYWORDS: AMCP Format, Formulary decision making, Economic models

What is already known about this subject

• There is little known about how MCOs are receiving and incorporating the drug product dossiers. The experience of 1 MCO showed that it received dossiers in 58% of the requests, and pharmacoeconomic models were included in 68% of the dossiers received. However, most dossiers had limited utility because they were not unlocked interactive economic or budget-impact models that permitted use of MCO-specific data.

What this study adds

• This research provides perspectives on the AMCP Format from both MCO and pharmaceutical manufacturer representatives.

• Less than half of MCO respondents found the pharmacoeconomic (PE) models to be adequate. Two thirds of MCO respondents reported that they used the PE model provided with the dossier to examine the results using data from their own MCOs.

The formulary system is intended as a tool to assist health care providers in evaluating and selecting drug products. In the past, the evaluation of drugs by managed care organizations (MCOs) for inclusion on the formulary had a primary focus on safety and efficacy issues and a secondary focus on the overall cost-effectiveness of the product.

There has been a move in recent years to consider all available information in an evidence-based formulary system. In 1994, Regence BlueShield created a set of guidelines for reviewing and
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Evaluating drug products, which has since been espoused by the Academy of Managed Care Pharmacy (AMCP) and is currently considered the gold standard for evidence used by MCOs in evaluating drugs for the formulary, the main intentions of these guidelines are as follows: (1) decisions regarding a medication’s inclusion on a formulary will be based on the overall value that medication brings to a specific population, and (2) the value argument will be based on good scientific evidence, including pharmacoeconomic models as an integral part of formulary review.

The AMCP Format for Formulary Submissions guidelines encourage pharmaceutical manufacturers to submit a structured dossier that includes clinical and economic data from both published and unpublished studies and a disease-based economic model that predicts the product’s impact on health outcomes and economic consequences for the specific health plan. Because the guidelines are promoted as a template rather than a mandate, individual MCOs may implement them with modifications to fit their organizations, resulting in a wide variety of outcomes. The Format is now viewed as an industry standard, but little is known about how MCOs and drug companies are receiving and incorporating the guidelines. Of primary concern to many has been the length and preparation involved in the dossier format. Regence BlueShield reported that the time required for its staff members to prepare review summaries for the pharmacy and therapeutics (P&T) committee decreased over time as they became more experienced with the Format.

To date, few studies have specifically investigated the use of pharmacoeconomic models in formulary decision making. Watkins et al. used a case-study approach (CORE diabetes model) to show how the use of an economic model can affect formulary decisions. The model demonstrating the effects of exenatide versus comparators on long-term disease burden and costs was included as part of the formulary monograph. The pharmacy staff members of the health plan manipulated the model to project cost outcomes, and in this case, the decision to include the medication on the formulary partially owed to these results.

Earlier, Sullivan et al. reported the results of a roundtable discussion in 2004 involving 12 MCO representatives and pharmacy benefit managers (PBMs). The main findings from their discussion, which focused on P&T committee reactions to pharmacoeconomic models, included an emphasis on clinical meaningfulness over statistical significance and on increasing the transparency of models so that P&T committees could easily adapt the model for their plan population.

Olson et al. conducted a survey of 20 pharmacoeconomic researchers from U.S. pharmaceutical and biotechnology companies to better understand industry views of how MCO decision makers perceive economic models. Findings suggest that models do affect health policy decisions. Olson et al. also reported important findings regarding intellectual property and confidentiality. Eighty percent of their survey participants would not leave electronic copies of their models with MCOs for a variety of reasons. The 20% who did provide electronic copies required signed confidentiality agreements, reinforcing the importance of the role of confidentiality guidelines in dossier submissions.

Previous research has shown the growing importance of the role of pharmacoeconomics in drug research and development as well as in formulary decisions. Little research, however, has investigated the impact of the AMCP dossier in these areas or assessed both pharmaceutical firms and MCO views simultaneously. In the current study, we conducted phone interviews with 35 people from both pharmaceutical manufacturers and MCOs nationwide who are familiar with the AMCP dossier preparation and review. These interviews enabled us to compare perspectives from the respondents of each group. The interviews were designed to assess the following key areas: economic models, organizational burden, confidentiality, overall value, and future expectations. These research topics expanded on those used in previous studies of this nature.

This article reports on both the MCOs’ and pharmaceutical manufacturers’ responses for each key area and provides possible explanations for the discrepancies that were noted. We conclude by commenting on the policy implications of these findings and recommending future action to improve the nature of the AMCP guidelines in the formulary decision-making process.

**Methods**

**Interview**

A structured interview protocol and questions tailored for MCOs and pharmaceutical companies were developed and pilot tested for use in this project (see Tables 1 and 2). The interview protocol was designed to facilitate information exchange quickly to reduce respondent burden. Each interview lasted approximately 15 minutes. Respondents were asked to recall the past 6 months and comment on the review and formulary decision-making processes. Additionally, respondents were given the opportunity to provide open-ended commentary on the AMCP Format after answering the structured survey questions. Interview content and protocol were reviewed and approved by the appropriate human subjects review committee. Two investigators conducted the interviews using this protocol.

**Study Population**

Participants were contacted by phone between September 2004 and October 2005.

**MCOs.** A random sample of large (>1 million lives) and small (<1 million lives) MCOs was generated using phone numbers from the National Directory of Managed Care Organizations’ (NDMCO) database. NDMCO is a publicly available database that provides contact information and company profiles for MCOs. We attempted to sample from both large and small

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**TABLE 1 Managed Care Organization Survey**

1a) What is your position within the MCO?
- [ ] CEO
- [ ] Pharmacy Director
- [ ] Benefits Manager
- [ ] Other ________________

1b) Does your organization conduct its own formulary review, or is it contracted to another entity (such as a pharmaceutical benefit manager)?
- [ ] Conduct own formulary review  SKIP to 2
- [ ] Contract to another entity
  - If so, who? ________________

Although you’ve contracted, is your organization still involved in the evaluation of dossiers?
- [ ] Yes  SKIP to 2
- [ ] No  END INTERVIEW

2) Are you personally involved in dossier reviews?
- [ ] Yes  SKIP to 3.
- [ ] No  Ask for name, email, phone of the individual in the organization who is involved with the review. ________________

(END INTERVIEW)

3) Which of the following activities describes your role in the formulary selection process? (CHECK ALL THAT APPLY)
- [ ] Prepare some or all of the drug monograph
- [ ] Evaluate the submitted dossier
- [ ] Compile data from plan in therapeutic area for P&T committee use
- [ ] Develop pharmacoeconomic models for P&T use
- [ ] Present the staff recommendations
- [ ] Other (please specify) ________________

4) In the last 6 months, what are the drug classes of dossiers that you, the respondent, have been personally involved in reviewing?
- [ ] Cardiovascular
- [ ] Diabetes
- [ ] Pain
- [ ] Schizophrenia
- [ ] Depression
- [ ] Lifestyle
- [ ] Other (please specify) ________________

5) Approximately how many drugs have been reviewed over the last 6 months? __________
   (If respondent has difficulty coming up with number, probe with the following formatted choices:)
   - [ ] None
   - [ ] 1-3
   - [ ] 4-6
   - [ ] 7-9
   - [ ] 10 or more

5a) Please estimate the number of those reviewed in the last 6 months that included dossiers from manufacturers?
   (If respondent has difficulty coming up with number, probe with the following formatted choices:)
   - [ ] None
   - [ ] 1-3
   - [ ] 4-6
   - [ ] 7-9
   - [ ] 10 or more

5b) How many of these reviews have included an economic model that you considered adequate?
   - [ ] 100%
   - [ ] 75%
   - [ ] 50%
   - [ ] 25%
   - [ ] None

5c) How many of these included a budget impact model?
   - [ ] 100%
   - [ ] 75%
   - [ ] 50%
   - [ ] 25%
   - [ ] None

5d) How many of these included an incremental cost-effectiveness or cost-benefit ratio?
   - [ ] 100%
   - [ ] 75%
   - [ ] 50%
   - [ ] 25%
   - [ ] None

6) How many times in the last 6 months has your staff developed an original economic model specific to a formulary decision? __________
   (If respondent has difficulty coming up with number, probe with the following formatted choices:)
   - [ ] None
   - [ ] 1-3
   - [ ] 4-6
   - [ ] 7-9
   - [ ] 10 or more
   If None, GO to 6A.  If one or more, SKIP to 7.

6a) If not in the last 6 months, when is the last time you developed your own model for formulary decision making?
   - [ ] 6 months–one year ago
   - [ ] More than one year ago
   - [ ] Never

7) When thinking about the most recent dossier, did you modify the provided model for use with your own population?
   - [ ] Yes  If yes, what was the class of the drug that the last population modification was built for? ________________
   - [ ] No

8) When thinking about the most recent dossier, did you vary the assumptions of the model outside the bounds of the model that you have been given?
   - [ ] Yes  GO to 8a
   - [ ] No  SKIP to 9

8a) When thinking about the most recent dossier, which assumption made the most important difference?
   - [ ] Pricing
   - [ ] Market share
   - [ ] Probabilities of events
   - [ ] Quality-adjusted life-years
   - [ ] None of the above
companies, since organization size may affect the ways in which health plans evaluate and respond to dossier submissions. One hundred ninety-one pharmacy directors (or equivalent position) were contacted to complete the MCO telephone interview. A substantial number of telephone numbers were missing or inaccurate, 21 organizations refused to participate in the survey per company policy, and 64 pharmacy directors were unreachable. Nine (7 small, 2 large) MCO operators referred us directly to a PBM when we inquired about speaking to anyone involved in formulary decisions. There were no differences in company size between responders and nonresponders.

Pharmaceutical manufacturers. Members of the Pharmaceutical Research and Manufacturers of America (PhRMA) Foundation’s Health Outcomes Committee were contacted to participate in the survey of pharmaceutical manufacturers. This committee is made up primarily of directors of health outcomes departments of pharmaceutical companies and consists of approximately 15 members, all of whom have experience with multiple dossiers developed in accordance with dossier guidelines. These respondents are likely representative of a very knowledgeable and involved group of pharmaceutical manufacturers.

### Results

#### Respondent Information

MCOs. A total of 28 (18 small, 10 large) MCO representatives agreed to participate in the telephone interview. Four (3 small, 1 large) of the 28 respondents reported that their organizations contracted formulary decisions directly to a PBM, and these interviews were promptly ended. Three respondents (11%) reported that their organizations did not use dossiers, and 1 individual was not personally involved in the review process, thus reducing our final sample to 20 (14 small, 6 large). Therefore, our final sample was approximately 10% of the original 191 MCO representatives that we attempted to contact.

Fifteen of those interviewed (75%) held the position of pharmacy director, while the remaining 5 (25%) had similar titles (chief pharmacy officer, pharmacy manager, or vice president of pharmacy). The most common responsibilities of the MCO respondent included evaluating the submitted dossier, compiling data from the health plan for P&T committee use, and presenting staff recommendations at P&T meetings.

Pharmaceutical manufacturers. Seven pharmaceutical manufacturer interviews were completed. Four respondents were directors of health economics and outcomes research,
TABLE 2  Pharmaceutical Manufacturer Survey

1) What is your position within the company? _______________________

2) Are you personally involved in dossier preparation/submission?
   □ Yes        SKIP to 3.
   □ No        Please provide name, email, phone of the individual in the
               company who is involved with the preparation and submission
               of dossiers _______________________

(END INTERVIEW)

3) Which of the following activities describes your role in the dossier
   submission process? (CHECK ALL THAT APPLY)
   □ Request summary plan characteristics from MCO population
   □ Provide product description
   □ Prepare supporting clinical information
   □ Develop pharmaco economic models for P&T use
   □ Other (please specify) ______________________________________

4) In the last 6 months, what are the drug classes of dossiers that you, the
   respondent, have been personally involved in preparing/submitting?
   □ Cardiovascular
   □ Diabetes
   □ Pain
   □ Schizophrenia
   □ Depression
   □ Lifestyle
   □ Neurologic
   □ Oncology
   □ Respiratory
   □ Anti-infective
   □ Other (please specify) ______________________________________

5) Approximately how many drugs has your company submitted dossiers for
   over the last 6 months? _______
   (If respondent has difficulty coming up with number, probe with the
   following formatted choices:)
   □ None
   □ 1-3
   □ 4-6
   □ 7-9
   □ 10 or more

5a) How many of these dossier submissions included an economic model?
   □ 100%
   □ 75%
   □ 50%
   □ 25%
   □ None

5b) How many of these dossier submissions included a budget impact model?
   □ 100%
   □ 75%
   □ 50%
   □ 25%
   □ None

5c) How many of these dossier submissions included an incremental cost-
    effectiveness or cost-benefit ratio?
   □ 100%
   □ 75%
   □ 50%
   □ 25%
   □ None

5d) Are these models submitted in their entirety and in a format that can be
    manipulated by the MCO (versus just an example of the model within
    text?)
   □ Yes
   □ No

6) When thinking about the most recent dossier, did you tailor the model to
   the requesting organization’s population demographics?
   □ Yes
   □ If yes, what was the class of the drug that the last population
     modification was built for? _______________________
   □ No

7) Do you justify assumptions for the specific plan population?
   □ Yes
   □ No

8) When thinking about the most recent dossier submission, which
   assumption made the most important difference?
   □ Pricing
   □ Market share
   □ Probabilities of events
   □ Quality-adjusted life-years
   □ Combination of price and outcome
   □ None of the above

9) Do you provide comparator information on:
   □ Placebo?
   □ At least one branded product?
   □ If yes, how do you select the branded product?
     □ Branded product with greatest market share within class
     □ Cheapest branded product in class
     □ Branded product going generic soonest
     □ Other ______________________________________

10) Does your company provide both on-label and off-label data?
    □ Yes
    □ No

11) Do you build the models in house, or do you utilize consultants to assist
    in model-building?
    □ In house
    □ Consultants
    □ Both

11a) Approximately how many full-time employees (FTEs) have been involved
     in the preparation and submission of dossiers within the last 6 months?
     □ <1
     □ 1
     □ 2
     □ 3
     □ 4
     □ 5 or more

11b) Have you increased staff in the last 2 years to assist in dossier preparation/
     submission?
    □ Yes
    □ No

11c) Have you used outside experts or consultants to help you in preparation/
     submission?
    □ Yes
    □ No

(continued on next page)
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2 were senior directors of global health outcomes, and 1 was a global project leader/MCO liaison. All 7 respondents reported that their main involvement in the dossiers involved developing pharmacoeconomic models and collating and reviewing all sections of the document.

Key Interview Topics

Drug Product Reviews

MCOs. Awareness of the AMCP Format was high, with 21 of the 24 (87.5%) MCO personnel initially contacted having reviewed dossiers within their organizations. However, on average, respondents indicated that only 40% of all drugs reviewed by MCOs included dossiers from the manufacturer. Table 3 shows that, across all respondents, the drug classes of dossiers most commonly submitted and reviewed in the 6 months before the interview were (1) cardiovascular, (2) lifestyle (including erectile dysfunction, incontinence, dermatology, irritable bowel syndrome), (3) pain, and (4) antibiotics.

On average, 26.5 individual drugs were reviewed over the 6 months before the interview (small MCO = 23 drugs; large MCO = 36). There appeared to be 2 common approaches to formulary reviews at the P&T level. Individual drug candidates were either specifically evaluated at the time of request (most likely at product launch), or the drug was evaluated as part of a general therapeutic class review scheduled to incorporate the new U.S. Food and Drug Administration (FDA)-approved agent. This variation in P&T committee meetings to review drugs may explain the large variation in the number of drugs reviewed, with 7 (35%) respondents reporting less than a dozen products reviewed over the past 6 months, and 4 (20%) reporting more than 50 products. Our results were similar to those found by Sullivan, whose discussions also revealed variability in the frequency of P&T committee meetings.9

Pharmaceutical manufacturers. Pharmaceutical industry respondents reported that they submitted dossiers to MCOs for approximately 3.9 (range 2-6) individual drugs in the 6 months before the survey interview.

Drug Comparisons

MCOs. For drug evaluation at the P&T level, we found that drugs were compared with a variety of products, with 11 respondents reporting comparisons with a placebo, since few companies conduct head-to-head studies before product launch.11 Products in the same pharmacologic class or therapeutic class were always compared with the other branded products, with the majority of comparisons between

| TABLE 2 | Pharmaceutical Manufacturer Survey (continued) |
| 12) How much time are you given by the MCO to respond to a request for a dossier? | 16) To what extent do you expect the new guidelines to change the submission process? |
| - More than 4 months prior to product review | - Improve |
| - 2-4 months prior to product review | - Worsen |
| - 1-2 months prior to product review | - No change |
| - Less than 1 month | 17) Have you begun adapting the dossier for a Medicare population? |
| 13) Has the amount of notice improved over time? | - Yes |
| - Yes | - No |
| - No | 18) Has your company submitted dossiers to Medicaid? |
| 14) How often does your company meet the timeline? | - Yes (GO to 18a) |
| - 100% of the time | - No (SKIP to 19) |
| - 75% | 18a) Do you believe the dossier has been helpful in informing discussion/ negotiation with the state? |
| - 50% | - Yes |
| - 25% | - No |
| - Never | 18b) Do you anticipate a similar process with the Prescription Drug Plans? |
| 15) What assurances are provided to your company regarding the confidentiality of requested dossiers? (CHECK ALL THAT APPLY) | - Yes |
| - Only the MCO staff involved in reviewing are allowed access to the dossier | - No |
| - Only the MCO staff reviewing and P&T committee are allowed access to the dossier | 19) Do you expect that Prescription Drug Plans will begin requesting dossiers for their formulary reviews? |
| - The dossier will not be made public | - Yes |
| - No assurances are provided | - No |

MCO = managed care organization, P&T = pharmacy & therapeutics.
Development and Review of Economic Models

MCOs. On average, respondents reported that 53.5% of dossiers received included budget-impact models and 39.3% included cost-effectiveness analyses (CEAs) or cost-benefit analyses (CBAs). A recent study by Spooner et al. found that pharmacoeconomic models were included in 68% of the dossiers received. Table 4 shows that, of the dossiers with economic models, respondents from the current study believed that nearly half (46.2%), on average, contained adequate economic models.

There was a notable difference between small and large MCO respondents, with small plans reporting that 59.5% of dossiers contained an adequate economic model, and large plans reporting an adequate model only 9% of the time. The difference between large and small MCOs for the percentage of dossiers containing an adequate economic model might be a function of the level of expertise in evaluating such models. If smaller health plans are less familiar with economic models or lack the staff to assist in evaluation, they may be more likely to deem a model adequate, whereas a larger plan with more staff and/or experience may not regard it as such. Alternatively, the needs of smaller MCOs might be more modest in dossier reviews than those of the larger organizations. The capacity of MCOs to adequately interpret and use cost-effectiveness information is unknown. Smaller organizations might not have the resources available for staff training or might prefer contracting out to consultants, such as academic centers.

Fifteen (75%) MCO respondents reported being involved in some capacity with developing or evaluating the economic models currently on the formulary.

Most MCO respondents commented at the end of the interview that their primary focus was on clinical efficacy and safety when they made comparisons. If products were equal on these measures, the decision to adopt the medication was then based on financial considerations. Others indicated that formulary decisions rely heavily on rebate options known commonly as the “bid grid,” where adding another drug to a therapeutic class decreases the existing rebate structure. The “bid grid” is a tool to determine how the existing rebate structure for competitors’ products will change if the drug being considered is added to the formulary in that particular therapeutic class.

Our findings are similar to results from a focus group study by Delate et al. involving P&T committee members. Participants in the Delate study ranked the importance of factors for making drug coverage decisions using a 5-point scale (1 = not important, 5 = very important). Efficacy was ranked as the most important factor (mean = 4.9), followed by cost-effectiveness (4.4), cost (4.0), and safety (4.0).13

Pharmaceutical manufacturers. Pharmaceutical industry respondents reinforced the MCO results regarding drug comparisons. Five of the 7 companies responding indicated that their dossiers included comparator information with a placebo. All respondents reported providing comparisons with at least 1 branded product, which typically involved the product with the greatest market share within its class. Two of the 7 respondents (28.5%) reported that their companies provided information on all available comparators.
models, while 6 reported that they had a pharmacoeconomist on staff to assist in dossier reviews. In the 6 months before the interview, approximately 8 (40%) MCOs, on average, reported that they had developed original economic models specific to formulary decisions. It is difficult to assess the degree of sophistication involved in these models from interview responses alone. However, on the basis of additional comments from respondents, it appears that the complexity varied drastically from simple utilization or rebate models to more complex cost-effectiveness models.

Thirteen of 20 (65%) MCO respondents reported that they modified the provided model with their own population statistics, as many reported that manufacturers do not make models directly applicable to their health plan population (Table 4). Many commented that if the manufacturers tailored models to reflect situations specific to individual MCOs, it would make the models much more beneficial. These findings corroborated those of Sullivan et al., in which respondents urged transparency in economic models so P&T committees could easily input their plan demographics into the model.

Similarly, about one third (6 of 20) of respondents indicated that they commonly varied the assumptions of models that permitted such testing. The relatively small proportion who conducted these analyses may believe that small changes in an economic model will not have a major impact. Of those who did vary assumptions, they made the key drivers of the models the price of the products and the probability of events associated with treatment. None suggested that assumptions regarding quality-adjusted life-years (QALYs) were of critical importance to the model outcome.

Many MCO respondents complained during their interviews that models provided by drug companies were unnecessarily awkward and difficult to manipulate. Additionally, most commented during the interview that they would rather see simple and easy-to-follow models relevant to specific decisions. Another reason to provide less complicated models is that P&T committees comprise physicians and pharmacists who have not been trained to evaluate cost-effectiveness models. Most MCOs reported that economic models were commonly presented to the committee in a summary review format, with technical aspects omitted. Similarly, roundtable participants in the Sullivan study commented that economic models should be presented in a format comprehensible by P&T committee members. Specifically, they recommended emphasizing clinically meaningful findings over statistically significant results.

The perspectives of the pharmaceutical manufacturers interviewed varied dramatically from the MCO respondents with regard to the inclusion of economic models. Five of the respondents indicated that their companies always included an economic model in the submitted dossiers. Of the remaining 2 respondents, 1 indicated that 85% of their dossiers included models, and the other reported that 50% of their dossiers included CEA models.

Only 1 of the 7 pharmaceutical manufacturer respondents reported tailoring the model to the requesting health plan’s population. The majority (70%) of MCOs reported modifying the model in-house with their own population. Most pharmaceutical respondents reported basing models on national prevalence rates, while 1 individual was under the impression that MCOs preferred to not provide plan-specific information. On this subject specifically, there appears to be a clear disconnect between MCOs and pharmaceutical

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**TABLE 4** Summary of Responses on Economic Models

<table>
<thead>
<tr>
<th></th>
<th>Small MCO (n=14)</th>
<th>Large MCO (n=6)</th>
<th>All MCO (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Over past 6 months</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean number [SD] of drugs reviewed with dossiers</td>
<td>5.5 [4.3]</td>
<td>5.0 [3.4]</td>
<td>5.4 [4.0]</td>
</tr>
<tr>
<td>Mean percent [SD] with adequate model</td>
<td>59.5% [33.4%]</td>
<td>9.0% [12.5%]</td>
<td>46.2% [36.9%]</td>
</tr>
<tr>
<td>Mean percent [SD] with BI model</td>
<td>58.3% [33.7%]</td>
<td>40.0% [41.8%]</td>
<td>53.5% [35.7%]</td>
</tr>
<tr>
<td>Mean percent [SD] with CEA or CBA</td>
<td>44.6% [33.3%]</td>
<td>24.2% [42.6%]</td>
<td>39.3% [37.3%]</td>
</tr>
<tr>
<td>Mean number [SD] developing original model</td>
<td>9.0 [19.9]</td>
<td>4.6 [4.7]</td>
<td>7.8 [17.2]</td>
</tr>
<tr>
<td>Most recent dossier</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of MCOs that modified the model</td>
<td>10</td>
<td>3</td>
<td>13</td>
</tr>
<tr>
<td>No. of MCOs that varied assumptions</td>
<td>5</td>
<td>1</td>
<td>6</td>
</tr>
</tbody>
</table>

Note: For the question regarding the number of drugs including dossiers, data were based on 19 respondents, as one outlier (reporting reviewing 400+ drugs) was excluded. Columns do not total 100 because of multiple response possibilities. BI = budget impact; CEA = cost-effectiveness analysis; CBA = cost-benefit analysis; MCO = managed care organization.
manufacturers. Better communication from the MCOs regarding what is expected or desired will enable manufacturers to provide more specific and, hence, more valuable models. This was demonstrated in the Watkins study, in which effective communication between manufacturer and payer resulted in the decision to include exenatide on the formulary.

Only 3 pharmaceutical manufacturers’ respondents varied the assumptions of the provided model. Assumptions that made the most difference according to pharmaceutical manufacturers were a combination of pricing and outcome (i.e., probabilities of events or QALYs).

Organizational Burden
The additional burden on staff and financial resources continues to be a common complaint of the AMCP dossier format for both MCOs and pharmaceutical firms. MCOs. In this sample, the majority (16 of 20) reported having a pharmacy director involved in developing and evaluating economic models, while 13 of 20 reported P&T committee involvement. The average number of full-time equivalent (FTE) staff members involved in the dossiers in the past 6 months was 5.2. Only 5 of the MCOs reported hiring additional in-house staff within the past 2 years to assist in the dossier review, although 5 of 20 individuals (25%) mentioned, in open commentary, that more help was desired. Fourteen (70%) of the MCOs interviewed used outside experts to assist in dossier review in the previous 6 months. Fifty percent of the large companies indicated that they used outside consultants, while 71% of the small companies enlisted the aid of outside sources.

Pharmaceutical manufacturers. All 7 pharmaceutical company respondents reported building models both in-house as well as with the aid of outside consultants. An average of 1.43 FTEs were involved in developing and reviewing dossiers within the past 6 months. Only 1 of the pharmaceutical manufacturer respondents in our sample reported hiring additional company employees within the past 2 years to assist in the dossier submission process.

Dossier Timelines
MCOs. MCO respondents reported that the timelines related to requests for dossiers ranged anywhere from no deadline (3 of 20 respondents) to 6 months (1 of 20 respondents) before product review. Four of 20 respondents (20%) were not aware of an imposed deadline because they were not personally involved in dossier requests. On average, the MCO respondents who request dossiers reported that manufacturers met the MCO-imposed deadlines approximately 83% of the time.

Pharmaceutical manufacturers. Five of the 7 pharmaceutical company respondents were familiar with the timelines associated with requests. Similar to the MCOs, these pharmaceutical manufacturers reported that the deadlines imposed on dossier requests ranged from no deadline to 6 months before product review. Pharmaceutical manufacturers reported meeting the deadline about 95% of the time, which was slightly higher than the figures (84%) reported by MCOs. One pharmaceutical manufacturer respondent commented that the company proactively develops the principal components of the dossiers before product launch (as opposed to waiting for a request) and is therefore more likely to meet timelines.

Confidentiality
Dossier confidentiality is a great concern for pharmaceutical manufacturers, as they are often fearful their proprietary information will be made public. MCOs. Half (10 of 20) of the MCOs reported giving verbal assurances to the manufacturers regarding confidentiality, while the other half reported that no assurances were made.

Pharmaceutical manufacturers. Only 5 of the 7 respondents (71%) were familiar with the confidentiality issues associated with dossier submission. The perspectives of these 5 manufacturers were fairly consistent with the MCO reports on confidentiality. One of the pharmaceutical manufacturers reported that the company requires MCOs to sign a legal confidentiality agreement, but that was not the norm. Four pharmaceutical company representatives reported that they were given verbal assurances by the MCOs that the dossier would not be made public, and 1 reported that no assurances were made. Four of the 5 firms commented on the need for more clearly documented confidentiality guidelines.

Overall Value to Formulary Decisions
MCOs. MCO respondents held various opinions regarding the overall value of the AMCP dossier format. The majority of these opinions were expressed as open-ended comments at the end of the structured survey questions. Some have made the formal decision to include dossiers in their decision-making process, while others do not use them because they fail to see the value they provide, primarily because of perceived bias on the part of the pharmaceutical manufacturers.

In a recent article by Fullerton and Atherly, Regence BlueShield stated that, between January 1998 and June 2000, drugs with useful economic models were approved 75% of the time versus 54% for all drugs reviewed in that time period. Some of the major criticisms (in order of frequency) involve the applicability, length, complexity, and potential bias in models developed by pharmaceutical manufacturers as a key component of the dossier format. Many MCO respondents commented that the models were created to produce desired results, and their construction should be scrutinized. Other respondents reported that because the manufacturers have clearly biased views, their organizations do not give the economic model portion of the dossier reviews much weight in the formulary decision process. On this basis, one may assume that manufacturers with such information may hesitate to put much effort into models if they
believe they are likely to be overlooked or disregarded.

Pharmaceutical manufacturers. In general, pharmaceutical manufacturers felt that the AMCP Format provided an opportunity to convey the value of a product, including more latitude for economic analyses and arguments. Nearly all (95%) respondents in Olson’s survey of industry pharmaeconomists reported that an economic model played a role in improving product positioning on formularies at least once in their experience. The results from the study by Spooner et al. showed no relationship between dossier receipt and placement on the formulary.

In fact, products that included a dossier submission were less likely (0%) to be placed on the formulary at the second (preferred) copayment tier compared with those without a dossier (33%).

Expectations for the Future

Version 2.1 of the AMCP Format (which became available in April 2005) included changes encouraging clarity in presenting model results and a need to clearly differentiate between cost-effectiveness and budget-impact models. Three of the pharmaceutical manufacturers interviewed believe the new AMCP guidelines will improve the submission process, while the other 3 expected that the guidelines will not affect the current process. Since the Centers for Medicare and Medicaid Services have publicly stated their intention to develop a framework for formulary management based on existing national standards and guidelines (such as those established by AMCP), we asked participants about their expectations in this area. Five of the 7 respondents (71%) reported having already adapted the dossier for Medicaid, and 3 of these (60%) reported that the dossiers had been helpful in informing discussion and negotiation with Medicaid. All manufacturers interviewed believed that prescription drug plans (Medicare Advantage and PDPs) would begin requesting dossiers for their formulary reviews in the near future.

Discussion

It was our intention at the beginning of this project to determine the extent to which the AMCP Format was being used within MCOs and drug companies and what impact the dossiers might have on formulary decisions. The data gathered provide important descriptive information on the similarities and differences in perceptions of the respondents who represented the 2 organization types. In addition to giving specific survey responses to structured questions, many interviewees provided comments regarding their overall perspective of the AMCP dossier process.

Overall, findings for this study suggest that awareness of the AMCP Format is high among persons in MCOs with drug formulary decision-making responsibility and among employees of pharmaceutical manufacturers involved in preparing product dossiers, but it is necessary to align objectives between the 2 organization types. Conceptually, proving the value of a drug beyond what the FDA requires is a reasonable request; this was agreed on by almost all respondents in one form or another. However, less than half of all drugs reviewed had a dossier. In contrast to the MCO respondents, pharmaceutical manufacturer respondents appear to have a more positive outlook on the role of the AMCP Format in effectively communicating the value of a new drug product. Further steps need to be taken to improve acceptance and integration of the AMCP Format into the formulary decision-making process.

The different perceptions of the manufacturers and MCOs seem most acute in the use of the Format’s economic model. Although safety and efficacy information is more widely accepted by MCOs, many of them have attitudes of distrust and skepticism with the economic analysis portion. It appears that there are 2 different pharmaceutical company perspectives—1 that provides a modifiable model for MCOs to adjust as they see fit, and 1 that provides all the answers with a very specific, tailored model. The latter may reflect the belief that the MCOs will not adjust model parameters or might not have staff capable of developing plan-specific data and of appropriately altering the model parameters.

Our evaluation supports past research that suggests that although many pharmaceutical companies submit dossiers to P&T committees, very few follow the AMCP Format rigorously; most often omit the economic model. While Olson found that MCOs sought model simplicity, ability to customize the model, and transparency, it appears that submissions addressed in our research are still lacking in these elements, at least in the perception of the MCOs surveyed. Just more than half of the pharmaceutical company respondents reported including the entire model in the dossier, while others included only a summary but offered the model in its entirety on request.

The usefulness of the economic model becomes a key point as Medicaid pharmacy managers gain more experience with their use in formulary decision making because their interests may be different from those of large MCOs. Most important, Medicaid agencies may have even more acute staff capacity constraints that affect their ability to analyze a model in detail. Models for Medicaid agencies may need to focus on special populations, although this may be a rather steep challenge for pharmaceutical companies because of limited data for populating key elements of the model.

On the basis of our findings, we make the following recommendations:

1. MCOs and pharmaceutical manufacturers engage in continuous communication. MCOs must take a proactive role in initiating dossier requests from pharmaceutical manufacturers. Additionally, MCOs must be willing to provide feedback regarding the perceived shortcomings of the dossier submissions to permit pharmaceutical manufacturers to better meet MCOs’ expectations.
2. MCOs need to devote additional resources to evaluating drug dossiers. MCOs need to employ reviewers who have the capability to discern potential model biases as well as the appropriateness of the model in their member populations. Economic models could provide insight into other business processes and policies, but it’s not clear that MCOs have the necessary staff capacity to maximize these opportunities.

3. Pharmaceutical manufacturers need to adopt a perspective of transparency, consistency, and flexibility in their modeling efforts. The principal purpose of the dossier is to determine the drug’s place in treatment, and manufacturers need to consider the dossier as part of a broader strategy toward appropriate therapeutic decision making in general.

4. Because many MCOs now forbid sharing the information discussed in our interview, AMCP needs to promote an anonymous reporting system for both MCOs and pharmaceutical manufacturers to discuss the usefulness of the Format in their efforts to continue to refine their development and evaluation processes.

Such actions would allow the AMCP Format to function as intended—providing increased access to information about new drugs, facilitating the formula decision-making process, and generating higher levels of confidence in the decisions made.

Limitations

The first and main limitation of this study was the small sample size, which makes it difficult to generalize our findings. Nevertheless, our data provide information on how the guidelines are being used and integrated, which is an area that needs additional research. Second, because our pharmaceutical manufacturer respondents were chosen from the PhRMA Foundation’s Health Outcomes Committee and were therefore very knowledgeable and involved, these respondents may not reflect pharmaceutical manufacturers as a whole. This fact may also make it more difficult to compare their answers with those of MCO respondents, who were selected at random. Third, we did not assess the perspective of the PBMs, which would have provided additional insight into the use of the AMCP Format in formula decisions in the United States.

Fourth, it is possible that individuals who participated in the interview were “gaming” their answers or were not entirely forthcoming about their practices. We attempted to minimize this possibility by developing questions that would require the individual to have prior knowledge of terms and concepts to respond appropriately. A fifth limitation of this study design is that it was retrospective in nature and relied on the respondents’ recall.

Sixth, selection bias must be considered, since those who volunteered their time to participate in the interview process could have been more likely to praise or criticize the dossier process. We anticipate that the ability to gather future survey information on this topic will become more difficult since many MCOs and PBMs now have policies and procedures that prohibit sharing this type of information. Therefore, our data are valuable, especially if future studies of this nature are not well received.

Conclusions

Findings from our current research assess perceptions regarding the AMCP Format and give us insight into possible process improvements. As evidenced by open-ended comments from survey respondents, the current research reinforces the need for increased staffing and training, improved collaboration with individuals and companies experienced in pharmacoeconomic modeling, and improvements in model consistency, transparency, and flexibility. Additionally, our findings suggest the need for greater communication between model developers and users so they have similar expectations.

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