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JMCP publishes peer-reviewed original research manuscripts, subject reviews, and other content intended to advance the use of the scientific method, including the interpretation of research findings in managed care pharmacy. JMCP is dedicated to improving the quality of care delivered to patients served by managed care pharmacy by providing its readers with the results of scientific investigation and evaluation of clinical, health, service, and economic outcomes of pharmacy services and pharmaceutical interventions, including formulary management. JMCP strives to engage and serve professionals in pharmacy, medicine, nursing, and related fields to optimize the value of pharmaceutical products and pharmacy services delivered to patients. JMCP employs extensive bias-management procedures intended to ensure the integrity and reliability of published work.

EDITORIAL MISSION

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Fractals are all around us, but what are they? The word “fractal” is derived from the Latin fractus, meaning broken or fragmented. A fractal is an object that can be divided into sections, each of which resembles a reduced-size copy of the whole—a property called self-similarity. Rivers are good examples of natural fractals because of their intricate tributaries. Other examples include trees, ferns, snowflakes, and networks of blood vessels and bronchial tubes.

The potential practical applications of fractals are numerous. Fields such as physics, chemistry, medicine, pharmacy, and even stock market fluctuation analysis have begun to use fractal formulations. To read about possible applications of fractal mathematics for medical cost and event forecasting and management, see Fairman and Rucker's editorial on pages 351-358 of this issue.

The mathematics behind fractals began to take shape in the 17th century when mathematician and philosopher Gottfried Leibniz (1646-1716) studied recurring self-similarity. During the following 300 years, other mathematicians such as Karl Weierstrass (1815-1897), Helge von Koch (1870-1924), and Gaston Julia (1893-1978) further explored fractal geometry. In the 1960s, Benoît Mandelbrot (1924-) investigated self-similarity in papers such as How Long Is the Coast of Britain? Statistical Self-Similarity and Fractional Dimension. He included some computer-generated illustrations with his research results. These images—a remarkable blend of math and art—captured the popular imagination and led to the development of computer programs designed to create fractal art. Popular fractal programs include XenoDream, Apophysis, ChaosPro, and Ultra Fractal.

Fractal artist Keith Mackay created Rainbow Garden with the Ultra Fractal program. He also uses the Apophysis program and Adobe Photoshop to enhance his pictures. “Ultra Fractal is the strongest fractal artist's tool. It does Mandelbrot-based fractals and Iteration Function System (IFS) fractals,” he explains. “Rainbow Garden was produced in 2007 specifically for the Fractal Universe 2009 calendar. It's a spiral design—spirals are the most common shapes in fractal art.” The compelling abstract image was chosen for the calendar's cover as well as the month of February. Rainbow Garden is aptly named; it seems to contain every color of the rainbow. This fractal is fascinating to behold—the large spiral seems to be swirling into infinity, taking with it numerous identical spirals in a variety of sizes. In addition to Rainbow Garden, Mackay contributed his Strong and Beautiful fractal to the Fractal Universe calendar. He and Panny Brawley served as co-editors of the publication.

Mackay was born and raised in Taylorsville, Utah, near Salt Lake City. Growing up, the closest he came to an art class was a course in drafting that he took in high school. Mackay did enroll in a sketching class during one summer while attending Brigham Young University in Provo, Utah. In 1985, he received a bachelor of science degree in design engineering technology from BYU. Since graduating from college, Mackay has been employed at an aerospace company in Seattle, Washington. He is a process engineer, responsible for numerical control programming.

Although Mackay has worked with CAD systems for more than 25 years, the first time he heard about fractal art was in the mid-1990s. “Someone at work told me about a fractal program called Fractint. I experimented with the software, and I thought it could produce pretty patterns and colors. But to me, it wasn’t art,” he recalls. “In the late ’90s, I started using Ultra Fractal, which enabled me to manipulate the composition, color, and texture of my images. It was then that I realized fractals could be art.”

Mackay quickly became an expert at creating beautiful fractals, and his work started to get noticed. A few years ago, he launched his fractal-related Web sites, keithmackay.com and idreamincolor.com. And in May 2008, the Renderosity Art Community Web site (renderosity.com) chose Mackay as their “Artist of the Month.” He was recognized for his outstanding collection of works in Renderosity's online fractal art gallery. In his interview on the Renderosity site, Mackay mentions that he also enjoys the art of photography. He has taken some striking nature photographs and astrophotographs, and imports some of these photos into his fractal images.

Mackay says that his knowledge of art has increased through correspondence with other fractal artists and by studying traditional art. “Van Gogh’s Starry Night painting stirs something within me,” he says. “It reminds me of looking at the Milky Way on a dark night.” His favorite fractal artists are Rick Spix (rykkart.com) and Janet Parke (parkenet.org/jp). Mackay believes that both of them sincerely try to create “real art,” not just “cool fractals.”

When asked about his upcoming projects, Mackay says, “My main project right now is home improvement. That might seem like an obstacle to working on my fractal art, but it’s not the case. I’d actually like to make some large-scale fractal artwork that would look good on my newly painted walls.

Sheila Macho
Cover Editor

COVER CREDIT

SOURCE
Interview with the artist.
Editorial Content and Peer Review

All articles, editorials, and commentary in JMCP undergo peer review; articles undergo blinded peer review. Letters may be peer reviewed to ensure accuracy. The fundamental departments for manuscript submission are:

- Research
- Subject Reviews
- Formulary Management
- Contemporary Subjects
- Brief Communications
- Commentary/Editorials
- Letters

All submissions other than Editorials, Commentary, and Letters should include an abstract and inform the reader at the end of the manuscript of what is already known about the subject and what the article adds to our knowledge of the subject.

For manuscript preparation requirements, see “JMCP Author Guidelines” in this Journal or at www.amcp.org.

Research

These are well-referenced articles based on original research that has not been published elsewhere and reflect use of the scientific method. The research is guided by explicit hypotheses that are stated clearly by the authors.

Subject Reviews

These are well-referenced, comprehensive reviews of subjects relevant to managed care pharmacy. The Methods section in the abstract and in the body of the manuscript should make clear to the reader the source of the material used in the review, including the criteria used for inclusion and exclusion of information.

Formulary Management

These are well-referenced, comprehensive reviews of subjects relevant to formulary management methods or procedures in the conduct of pharmacy and therapeutics (P&T) committees and may include description and interpretation of clinical evidence.

Contemporary Subjects

These are well-referenced submissions that are particularly timely or describe research conducted in pilot projects. Contemporary Subjects, like all articles in JMCP, must describe the hypothesis or hypotheses that guided the research, the principal methods, and results.

Brief Communications

The results of a small study or a descriptive analysis that does not fit in other JMCP departments may be submitted as a Brief Communication.

Editorials/Commentary

These submissions should be relevant to managed care pharmacy and address a topic of contemporary interest: they do not require an abstract but should include references to support statements.

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If the letter addresses a previously published article, an author response may be appropriate. (See “Letter to the Editor” instructions at www.amcp.org.)

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Editorial Office

Academy of Managed Care Pharmacy
100 North Pitt St., Suite 400
Alexandria, VA 22314
Tel.: 703.683.8416
Fax: 703.683.8417
E-mail: jmcppreview@amcp.org

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Manuscripts should include, in this order: title page, abstract, text, references, tables, and figures (see Manuscript Submission Checklist for details).

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For descriptions of editorial content, see “JMCP Editorial Policy” in this Journal or at www.amcp.org.

### Please note:

- The **JMCP Peer Review Checklist** is the best guide for authors to improve the likelihood of success in the **JMCP** peer-review process. It is available at: www.amcp.org (JMCP Peer Review Checklist and Guidelines at www.amcp.org).
- A subsection in the Discussion labeled “Limitations” is generally appropriate for all articles except Editorials, Commentaries, and Letters.
- Most articles, particularly Subject Reviews, should incorporate or at least acknowledge the relevant work of others published previously in **JMCP** (see “Article Index by Subject Category” at www.amcp.org).
- Product trade names may be used only once for the purpose of providing clarity for readers, generally at the first citation of the generic name in the article but not in the abstract.
- Many articles involve research that may pose a threat to either patient safety or privacy. It is the responsibility of the principal author to ensure that the manuscript is submitted with either the result of review by the appropriate institutional review board (IRB) or a statement of why the research is exempt from IRB review (see Policy for Protecting Patient Safety and Privacy at www.amcp.org).

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References should be prepared following modified AMA style. All reference numbers in the manuscript should be superscript (e.g., 1). Each unique reference should have only one reference number. If that reference is cited more than once in the manuscript, the same number should be used. Do not use ibid or op cit for **JMCP** references. Please provide Web addresses for references whenever possible. An access date should be included for every URL except links to **JMCP** articles. See examples 2 and 3 in the second column. See the following examples of common types of references:


5. **Book or monograph by editor, compiler, or chairperson as author**—Chernow B, ed. Critical Care Pharmacotherapy. Baltimore, MD: Williams & Wilkins; 1995.


11. **Paper (or Poster) presented at a meeting**—Reagan ME. Workers’ compensation, managed care, and reform. Poster presented at 1995 AMCRA Midyear Managed Care Summit, March 13, 1995; San Diego, CA.


### Supplement

A complete list of documents needed for submission to **JMCP** appears on the Manuscript/Supplement Submission page at LINK. All manuscripts are reviewed prior to peer review. See “Author Guidelines for description of pre-review process.” Peer review generally requires 4-6 weeks but may extend as long as 12 weeks in unusual cases. Solicited manuscripts are subject to the same peer-review standards and editorial policy as unsolicited manuscripts.

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Manuscript submissions should include a statement that identifies the nature and extent of any financial interest or affiliation that any author has with any company, product, or service discussed in the manuscript and clearly indicates the source(s) of funding and financial support and be accompanied by completed and signed author attestation forms for the principal author and each coauthor.

### Submission Checklist

Here are the key components for your manuscript submission to the **Journal of Managed Care Pharmacy**:

1. **COVER LETTER**: briefly describing the importance and scope of the manuscript, certifying that the paper has not been published previously and is not under consideration by any other publication, and identifying financial support and conflicts of interest.

2. **MANUSCRIPT**: with these specifications:
   - All text should be submitted in Microsoft Word, prepared in 12-point type, 1.5 line spacing.
   - Tables must be prepared in Microsoft Word, and may use a smaller font (e.g., 10-point).
   - Figures should be embedded in the Word document and submitted separately in their original native format, preferably in Adobe Illustrator, Microsoft Word, Excel, or PowerPoint (e.g., with the data points included in PowerPoint) to permit editing by the **JMCP** graphic designer. The **JMCP** graphic designer has permission to re-create any figures. Please identify each file submitted with the following information: software application and file name.
   - If the values are > 0.001 should be expressed as P = 0.001, to 3 decimal places, P values less than 0.001 should be shown as P < 0.001.
   - Include succinct, quantitative bullet points for (a) what is already known about this subject, and (b) what this study adds.
   - Electronic submission of cover letter, manuscript, and native files for figures at: http://jmcpmsubmit.net.

3. **DISCLOSURES AND CONFLICT OF INTEREST**: completed and signed author attestation forms for the principal author and each coauthor, including source(s) of funding and financial support.

### Reference

Direct All-Cause Health Care Costs Associated With Chronic Kidney Disease in Patients With Diabetes and Hypertension: A Managed Care Perspective

François Laliberté, MA; Brahim K. Bookhart, MBA, MPH; Francis Vekeman, MA; Mitra Corral, MS, MPH; Mei Sheng Duh, MPH, ScD; Robert A. Bailey, MD; Catherine Tak Piech, MBA; and Patrick Lefebvre, MA

ABSTRACT

BACKGROUND: Diabetes and hypertension are the 2 major causes of end-stage renal disease. The rate of chronic kidney disease (CKD) secondary to diabetes and/or hypertension is on the rise, and the related health care costs represent a significant economic burden.

OBJECTIVE: To quantify from a health system perspective the incremental direct all-cause health care costs associated with a diagnosis of CKD in patients with diabetes and/or hypertension.

METHODS: An analysis was conducted of medical claims and laboratory data with dates of service between January 1, 2000, and February 28, 2006, from a managed care database for approximately 30 million members enrolled in 35 health plans. Each patient’s observation period began on the date of the first diabetes or hypertension diagnosis (index date) and ended on the earlier of the health plan disenrollment date or February 28, 2006. Inclusion criteria were continuous insurance coverage in the 6 months prior to the index date and during the observation period, age at least 18 years, and at least 2 claims less than 90 days apart with a primary or secondary diagnosis for diabetes or hypertension. Exclusion criteria were cancer, lupus, or organ transplantation or chemotherapy at any time during the observation period. CKD was defined as at least 1 claim with a primary or secondary diagnosis for CKD and at least 2 glomerular filtration rate values of below 60 milliliters per minute per 1.73 square meters of body surface area (60 mL/min/1.73 m²) at any time during the observation period. Bivariate and Tobit regression analyses were conducted to compare patients who developed CKD versus those who did not for annualized (per patient per month) direct, all-cause, health care costs, defined as standardized net provider payments after subtraction of member cost-share. These costs consisted of outpatient services, inpatient services, and pharmacy claims. A subset analysis of the post-versus pre-CKD medical costs was also conducted for cohorts of patients with at least 60 days of observation before and after the development of CKD; that analysis measured both all-cause costs and costs for services directly related to CKD treatment (i.e., claims with a primary or secondary diagnosis of CKD or claims for dialysis services).

RESULTS: 11,531 patients with diabetes, 74,759 patients with hypertension, and 4,779 patients with both conditions were identified, of whom 123 (1.1%), 1,137 (1.5%), and 712 (14.9%), respectively, developed CKD during the observation period. The CKD group was older than the no-CKD group (61.8 years, 63.6 vs. 53.6 years, P < 0.001; diabetes: 60.7 vs. 49.9 years, P < 0.001; hypertension only cohort: 60.7 vs. 49.9 years, P < 0.001; diabetes and hypertension cohort: 63.4 vs. 61.8 years, P < 0.001). CKD was associated with significantly higher total all-cause health care costs in managed care patients with diabetes and/or hypertension. A subset analysis of the post-versus pre-CKD medical costs was also conducted for cohorts of patients with at least 60 days of observation before and after the development of CKD; that analysis measured both all-cause costs and costs for services directly related to CKD treatment (i.e., claims with a primary or secondary diagnosis of CKD or claims for dialysis services).

CONCLUSION: CKD was associated with significantly higher all-cause health care costs in managed care patients with diabetes and/or hypertension.


What is already known about this subject

• Diabetes and hypertension are the 2 major causes of chronic kidney disease (CKD) and end-stage renal disease, according to the 2007 Annual Data Report from the United States Renal Data System.
• According to the American Diabetes Association, people with diabetes incur average expenditures of $11,744 per year ($979 per month), of which $6,649 ($554 per month) is attributed to diabetes.
• Although the rate of CKD secondary to diabetes or hypertension is on the rise, the cost burden of CKD in diabetic and/or hypertensive populations has not been quantified from a managed care perspective.

What this study adds

• For cohorts of patients with diabetes only, hypertension only, and diabetes and hypertension, CKD was associated with significantly higher total all-cause direct health care costs, with unadjusted annualized mean per patient costs differences of $11,814, $8,412, and $10,625, respectively (P < 0.001 for all comparisons).
• After controlling for covariates, the adjusted annualized incremental all-cause health care costs associated with CKD were still pronounced and remained statistically significant (diabetes cohort: $7,190, P < 0.001; hypertension cohort: $5,450, P < 0.001; diabetes and hypertension cohort: $9,177, P < 0.001).
• Among those patients who developed CKD during the study, the post-CKD phase was associated with a significant increase in direct all-cause health care costs: incremental annualized mean per patient costs of $8,829 (P < 0.026), $4,175 (P = 0.004), and $9,397 (P < 0.001) relative to pre-CKD, for patients with diabetes only, hypertension only, and diabetes and hypertension, respectively.
Diabetes and hypertension are the 2 major causes of end-stage renal disease (ESRD—chronic kidney disease [CKD] stage 5 requiring dialysis). In most Western countries, diabetes accounts for 40%-50% of incident ESRD cases. Diabetes or hypertension are found to be present in more than 70% of patients who begin therapy for ESRD, according to the 2007 Annual Data Report from the United States Renal Data System (USRDS). Due to the increasing prevalence of both diabetes and hypertension, driven primarily by the aging population and increase in obesity, rates of CKD secondary to diabetes and/or hypertension are on the rise. During the period from 1992 to 2006, the incidence of reported diabetic ESRD in the United States has doubled while the prevalence of CKD (stages 1 to 4) among non-ESRD Medicare beneficiaries diagnosed with diabetes tripled from 4.4% to 13.6%.1

CKD is a significant driver of health-related expenditures. The total health care spending for the treatment of ESRD patients in 2005 was approximately $32 billion. Medicare ESRD program expenditures grew from $5.8 billion in 1991 to $21 billion by 2005, accounting for 6.4% of the total 2005 Medicare budget. Based on the Medicare population, the annual cost per dialysis patient was $68,585 in 2005.

According to the American Diabetes Association, people with diabetes incurred average health care expenditures of $11,744 per year ($979 per month) in 2007, of which $6,649 ($554 per month) was attributed to diabetes. Moreover, patients with both diabetes and hypertension incurred much higher annual health care costs than did patients with diabetes or hypertension alone ($13,446, $8,493, and $8,424, respectively).6

The rate of CKD secondary to diabetes and/or hypertension is on the rise, and the related health care costs represent a significant economic burden. Consequently, this topic has gained increased attention. However, to the best of our knowledge, the cost burden of CKD in patients with diabetes and/or hypertension has not been documented from a managed care perspective. The purpose of the current analysis was to quantify the incremental health care costs associated with CKD in managed care cohorts with diabetes only, hypertension only, and both diabetes and hypertension.

Methods

Data Source

De-identified health care claims and laboratory data from the Integrated HealthCare Information Services (IHCIS) National Managed Care Benchmark Database with dates of service between January 1, 2000, and February 28, 2006, were used to conduct the analysis. The IHCIS database included complete medical and pharmacy claims for more than 30 million managed care members from over 35 health care plans, covering all census regions of the United States. Data elements used in the present analysis included enrollment records, patient demographics, inpatient and outpatient medical claims, pharmacy dispensing claims, and laboratory results. Laboratory results from the IHCIS database are available for the subset of patients tested within a given carrier’s laboratory network, representing approximately 10% of the IHCIS population. In order to develop a database that accounts for differences in provider contracting and other pricing variations, IHCIS developed several approaches (e.g., proprietary algorithms and multivariate models) for standardizing pricing for different service categories (inpatient facility, outpatient facility, professional services, ancillary services, and pharmacy claims) across health plans. The resulting cost figures are therefore comparable across health plans and reflect net provider payments after subtraction of member cost-share.

Study Design

A retrospective, parallel-group design was employed to compare patients who developed CKD versus those who did not in 3 distinct cohorts: patients with diabetes only, patients with hypertension only, and patients with both diabetes and hypertension (Figure 1). Each patient’s observation period spanned from the date of the index date (index date) until the end of health plan enrollment or the defined study end date of February 28, 2006, whichever occurred earlier. For those patients who developed CKD during the observation period, the pre- and post-CKD periods were defined based on the first CKD claim.

To be included in the study sample, patients were required to meet all of the following criteria: (a) continuous health plan coverage in the 6 months prior to the index date and during the observation period, (b) at least 2 claims less than 90 days apart with a primary or secondary diagnosis for diabetes (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] codes: 250.xx; diabetes cohort) and/or hypertension (ICD-9-CM codes: 401.xx-405.xx; hypertension cohort), and (c) at least 18 years of age on the index date. To be included in the CKD cohort, patients were required to have at least 1 claim with a primary or secondary diagnosis commonly associated with CKD (ICD-9-CM codes: 250.4x [diabetes with renal manifestations], 403.xx [hypertensive kidney disease], 404.xx [hypertensive heart and kidney disease], 585.xx [chronic kidney disease], 586.xx [renal failure, unspecified], or 588.xx [disorders resulting from impaired renal function]) and have at least 2 estimated glomerular filtration rate (eGFR) values of below 60 milliliters per minute per 1.73 square meters of body surface area (60 mL/min/1.73m²) during the observation period. Patients were excluded from the study if they had received an organ transplant or had lupus, cancer, or received chemotherapy at any time during the observation period. The rationale behind these exclusion criteria is that these conditions generally result in substantial medical allowed charges, which are independent of CKD per se and would, therefore, potentially bias the estimation of the costs associated with CKD. We measured all-cause health care costs instead of costs specific to CKD for 2 main reasons: (a) we
conducted the current study from the managed care perspective; therefore, our objective was to quantify the overall cost change associated with a diagnosis of CKD, since health plans are paying for all charges, not the CKD-related charges only; and (b) we wanted to contrast our results with recent findings from the USRDS report, which reported all-cause medical costs.

We imposed a minimum of 6 months of insurance coverage prior to the index date to assess the baseline characteristics of the study population in order to appropriately control for confounding factors in the multivariate analysis. No further minimum follow-up time was imposed during the observation period to avoid introducing potential bias such as survival or observation bias.
bias. However, for the analysis that compared pre-CKD costs with post-CKD costs in the subgroup of patients who developed CKD during the study period, we required at least 60 days of observation in each of the 2 time periods to mitigate the effects of very short observation periods on study results.

**Definition of CKD based on eGFR**

Estimated GFR values were calculated using the Modification of Diet in Renal Disease (MDRD) study abbreviated formula,\(^7\) based on serum creatinine value, age, gender, and ethnicity:

\[
eGFR = 186(S_c)^{-1.154}(\text{Age})^{-0.203}(0.742 \text{if female})
\]

\[
\times (1.210 \text{ if African-American})
\]

where \(S_c\) = serum creatinine value. Because the patient ethnicity variable was not available in the database, non-African American race was assumed in the eGFR calculation. CKD was defined as an eGFR value below 60 mL/min/1.73m\(^2\) (i.e., stages 3 to 5).

**Outcome Measures**

The outcome measures for the analyses were annualized (per patient per month [PPPM] multiplied by 12) direct all-cause standardized health care costs, which consisted of 3 mutually exclusive components: (a) outpatient services, (b) inpatient services, and (c) pharmacy costs. Outpatient services were identified from the IHCIS Medical Claims table, containing medical claims for professional and outpatient services, such as outpatient surgery, laboratory, and radiology. This table contains claim line information specific to professional claims (coded with Current Procedural Terminology, Fourth Edition [CPT-4] or Healthcare Common Procedure Coding System [HCPCS] procedure codes) and outpatient facility claims. Included within this table are revenue codes, procedure codes, ICD-9-CM diagnosis codes, type of provider, place of service, and type of service.

Inpatient services were obtained from the IHCIS Inpatient Confinement table, which provides a summarized record for each inpatient episode with a length of stay of at least 1 day from an acute care hospitalization or skilled nursing facility setting. The database includes a single record for every hospitalization observed during the data period. Included in the record are the admitting and discharge dates; length of inpatient stay; ICD-9-CM codes for admitting diagnosis, up to 5 “other” diagnoses, and discharge diagnosis; and total standardized cost amount for the inpatient stay, including the costs of drugs used during the stay. The IHCIS inpatient record excludes professional services that have been rendered and billed separately during the confinement period; these are reported in the Medical Claims (professional and noninpatient) table. Finally, the IHCIS Pharmacy Claims table summarizing claims submitted by pharmacies for outpatient drugs was used to measure pharmacy costs.

**Statistical Analysis**

Both descriptive and multivariate analyses were conducted to determine the incremental all-cause costs associated with CKD relative to no-CKD in cohorts of patients with diabetes only, hypertension only, and both diabetes and hypertension. For each cohort, descriptive bivariate statistics were used to compare groups of CKD and no-CKD for medical costs, and cost differences were assessed as both incremental costs and cost ratios. Incremental cost was defined as the weighted average annualized per patient cost of the CKD group minus the weighted average annualized per patient cost of the no-CKD group. Because the observation period of each patient was used as the weight, the annualized per patient cost represents the mathematical equivalent of a standard PPPM value (aggregated costs divided by aggregated months, with both values summed across all patients) multiplied by 12 but produces a value for each patient, allowing for statistical testing. Costs for CKD patients were divided by costs for patients without CKD to obtain the cost ratio.

Cost differences were also used to compare annualized direct health care costs between the pre-CKD and post-CKD periods among patients who developed CKD, weighted by the lengths of the pre-CKD and post-CKD observation periods. A minimum of 60 days of observation pre- and post-CKD was imposed for the analysis evaluating the change in all-cause health care costs following a diagnosis of CKD. We also reported the cost of treating CKD, that is, costs for claims with a primary or secondary CKD diagnosis and claims for dialysis services for the post-CKD period. In addition, PPPM costs for each of the 12 months before and after the first CKD diagnosis were calculated and plotted over time to illustrate the cost impact of CKD development.

Multivariate analyses were also conducted to adjust for potential confounding factors (that may otherwise contribute to increased costs) in estimating the incremental cost burden of CKD. Because of the non-normality of the health cost outcome variables, which are truncated at zero and positively skewed, a Tobit regression model was used to estimate the adjusted annualized incremental costs associated with CKD, as measured by the marginal effect for the CKD group after controlling for other covariates. Covariates used for adjustment in the regression models were age, gender, and diagnoses representing additional baseline comorbidities. These diagnoses included acute myocardial infarction, other acute and subacute forms of ischemic heart disease, and old myocardial infarction (ICD-9-CM: 410.xx, 411.xx, and 412.xx, respectively); angina pectoris (ICD-9-CM: 413.xx); cardiac dysrhythmias, tachycardia unspecified, and palpitations (ICD-9-CM: 427.xx, 785.0, and 785.1, respectively); heart failure (ICD-9-CM: 428.xx); other forms of chronic ischemic heart disease (ICD-9-CM: 414.xx); unspecified hypertensive heart disease (ICD-9-CM: 402.9x); cardiomyopathy (ICD-9-CM: 429.3); and cerebrovascular disease (ICD-9-CM: 430.xx-437.xx).
Direct All-Cause Health Care Costs Associated With Chronic Kidney Disease in Patients With Diabetes and Hypertension: A Managed Care Perspective

**Table 1** Baseline Characteristics of the Study Populations

<table>
<thead>
<tr>
<th>Number (n) of patients</th>
<th>Diabetes Only Cohort</th>
<th>Hypertension Only Cohort</th>
<th>Diabetes and HTN Cohort</th>
</tr>
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<tr>
<td></td>
<td>No-CKD</td>
<td>CKD</td>
<td>All</td>
</tr>
<tr>
<td>Women, n (%)</td>
<td>11,408</td>
<td>123</td>
<td>11,531</td>
</tr>
<tr>
<td>Mean [SD] age in years</td>
<td>50.0</td>
<td>12.7</td>
<td>63.6</td>
</tr>
<tr>
<td>Observation period in days</td>
<td>Mean [SD]</td>
<td>Median</td>
<td></td>
</tr>
<tr>
<td>6 months</td>
<td>920</td>
<td>(8.1)</td>
<td>25 (0.6)</td>
</tr>
<tr>
<td>6-11 months</td>
<td>1,466</td>
<td>(12.9)</td>
<td>102 (2.5)</td>
</tr>
<tr>
<td>12 months or more</td>
<td>9,022</td>
<td>(79.1)</td>
<td>113 (9.1)</td>
</tr>
</tbody>
</table>

**Cardiovascular disease, n (%)**

- Acute myocardial infarction*: 145 (1.3) vs. 3 (3.3) vs. 149 (1.3)
- Angina*: 137 (1.2) vs. 3 (2.4) vs. 140 (1.2)
- Cardiac arrhythmia*: 565 (5.0) vs. 16 (13.0) vs. 581 (5.0)
- Heart failure*: 108 (0.9) vs. 8 (6.5) vs. 116 (1.0)
- Coronary artery disease*: 570 (5.0) vs. 21 (17.1) vs. 591 (5.1)
- Left ventricular hypertrophy*: 56 (0.5) vs. 1 (0.8) vs. 57 (0.5)
- Cerebrovascular disease*: 149 (1.3) vs. 6 (4.9) vs. 155 (1.3)

**Previous hospitalization related to CVD, n (%)**

- 104 (0.9) vs. 4 (3.3) vs. 108 (0.9)
- 978 (1.3) vs. 34 (3.0) vs. 102 (1.4)
- 69 (1.7) vs. 23 (3.2) vs. 92 (1.9)

*Denotes statistically significant comparison (P < 0.05) of No-CKD versus CKD using a Pearson chi-square test for comparisons of categorical variables and a Student’s t-test for the comparison of age and observation period.

All comorbidities were identified through claims with a primary or secondary diagnosis in the 6 months prior to the index date. The models also included a covariate for hospitalization with an admitting diagnosis of cardiovascular disease (CVD) in the 6-month baseline period.

Statistical comparisons between cohorts of patients were conducted using the Pearson chi-square test for categorical variables and the 2-sided Student’s t-test for continuous variables. In both cases, a 2-sided alpha error of 0.05 was used to declare statistical significance. All statistical analyses were performed using SAS version 9.1 (SAS Institute, Inc., Cary, NC).

**Results**

**Baseline Characteristics of the Study Populations**

A total of 11,531 patients with diabetes (123 CKD and 11,408 no-CKD), 74,759 patients with hypertension (1,137 CKD and 73,622 no-CKD), and 4,779 patients with both conditions (712 CKD and 4,067 no-CKD) met the entry criteria and formed the study populations (Table 1). The CKD group was older than the no-CKD group in each cohort (mean [SD] age—diabetes only cohort: 60.7 [12.9] vs. 49.9 [12.7] years, P < 0.001; hypertension only cohort: 63.6 [12.4] vs. 53.6 [12.6] years, P < 0.001; diabetes and hypertension cohort: 63.4 [10.5] vs. 61.8 [10.7] years, P < 0.001). The proportion of women was lower in the CKD group than in the no-CKD group in the hypertension only cohort (46.5% vs. 53.4%, P < 0.001) and the diabetes and hypertension cohort (40.3% vs. 53.3%, P < 0.001).

Overall, the CKD group had a higher rate of CVD during the 180 days prior to the index date than did the no-CKD group, with predominance of coronary artery disease (diabetes: 17.1% vs. 5.0%, P < 0.001; hypertension: 11.4% vs. 5.5%, P < 0.001; diabetes and hypertension: 11.5% vs. 8.1%, P < 0.001) and cardiac arrhythmia (diabetes: 13.0% vs. 5.0%, P < 0.001; hypertension: 8.5% vs. 6.7%, P = 0.012; diabetes and hypertension: 7.3% vs. 6.3%, P = 0.338).
### TABLE 2
Annualized Per Patient All-Cause Health Care Costs and Observation Period for Patients With and Without CKD

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<tbody>
<tr>
<td>Observation period in days, mean [SD] median</td>
<td>906 [583]</td>
<td>801</td>
<td>1,232 [588]</td>
<td>1,288</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Costs: All patients, mean [SD] median</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outpatient services</td>
<td>$3,362 [8,021]</td>
<td>2,158</td>
<td>$7,672 [15,405]</td>
<td>5,121</td>
<td>$4,310 [8,136]</td>
</tr>
<tr>
<td>Inpatient services</td>
<td>$1,425 [9,925]</td>
<td>0</td>
<td>$7,835 [24,513]</td>
<td>1,110</td>
<td>$6,410 [10,192]</td>
</tr>
<tr>
<td>Pharmacy claims</td>
<td>$1,843 [5,082]</td>
<td>1,153</td>
<td>$2,937 [7,113]</td>
<td>1,879</td>
<td>$1,094 [5,108]</td>
</tr>
<tr>
<td>Total costs</td>
<td>$6,631 [16,455]</td>
<td>4,131</td>
<td>$18,444 [38,124]</td>
<td>11,025</td>
<td>$11,814 [16,833]</td>
</tr>
<tr>
<td>Total costs for patients with &lt;12 months of observation (n = 2,386 no-CKD; n = 10 CKD)</td>
<td>$11,035 [18,507]</td>
<td>4,866</td>
<td>$30,874 [25,299]</td>
<td>13,410</td>
<td>$19,839 [18,548]</td>
</tr>
<tr>
<td>Total costs for patients with ≥12 months of observation (n = 9,022 no-CKD; n = 113 CKD)</td>
<td>$6,405 [15,769]</td>
<td>4,100</td>
<td>$18,239 [38,936]</td>
<td>11,025</td>
<td>$11,835 [16,281]</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hypertension Only Cohort (n = 73,622 no-CKD; n = 1,137 CKD)</th>
<th>Observation period in days, mean [SD] median</th>
<th>1,068 [600]</th>
<th>1,099</th>
<th>1,466 [536]</th>
<th>1,516</th>
<th>&lt;0.001</th>
</tr>
</thead>
<tbody>
<tr>
<td>Costs: All patients, mean [SD] median</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Outpatient services</td>
<td>$3,263 [6,534]</td>
<td>2,270</td>
<td>$5,961 [17,730]</td>
<td>3,880</td>
<td>$2,699 [6,843]</td>
<td>1,610</td>
</tr>
<tr>
<td>Inpatient services</td>
<td>$1,655 [10,491]</td>
<td>0</td>
<td>$7,153 [32,639]</td>
<td>1,110</td>
<td>$5,498 [11,162]</td>
<td>1,538</td>
</tr>
<tr>
<td>Pharmacy claims</td>
<td>$1,309 [3,518]</td>
<td>782</td>
<td>$1,523 [3,800]</td>
<td>1,002</td>
<td>$214 [3,523]</td>
<td>220</td>
</tr>
<tr>
<td>Total costs</td>
<td>$6,226 [15,713]</td>
<td>3,703</td>
<td>$14,638 [44,039]</td>
<td>7,817</td>
<td>$8,412 [16,512]</td>
<td>4,115</td>
</tr>
<tr>
<td>Total costs for patients with &lt;12 months of observation (n = 10,119 no-CKD; n = 30 CKD)</td>
<td>$11,139 [19,127]</td>
<td>4,498</td>
<td>$42,563 [41,294]</td>
<td>20,654</td>
<td>$31,424 [19,233]</td>
<td>16,156</td>
</tr>
<tr>
<td>Total costs for patients with ≥12 months of observation (n = 63,503 no-CKD; n = 113 CKD)</td>
<td>$6,086 [15,021]</td>
<td>3,687</td>
<td>$14,504 [43,937]</td>
<td>7,803</td>
<td>$8,418 [15,964]</td>
<td>4,116</td>
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</table>

<table>
<thead>
<tr>
<th>Diabetes and Hypertension Cohort (n = 4,067 no-CKD; n = 712 CKD)</th>
<th>Observation period in days, mean [SD] median</th>
<th>1,429 [550]</th>
<th>1,471</th>
<th>1,490 [535]</th>
<th>1,556</th>
<th>0.007</th>
</tr>
</thead>
<tbody>
<tr>
<td>Costs: All patients, mean [SD] median</td>
<td></td>
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</tr>
<tr>
<td>Outpatient services</td>
<td>$4,492 [9,076]</td>
<td>3,325</td>
<td>$8,140 [23,423]</td>
<td>5,262</td>
<td>$3,648 [12,325]</td>
<td>3,938</td>
</tr>
<tr>
<td>Inpatient services</td>
<td>$4,343 [20,215]</td>
<td>0</td>
<td>$10,810 [36,867]</td>
<td>4,075</td>
<td>$6,467 [23,462]</td>
<td>4,075</td>
</tr>
<tr>
<td>Pharmacy claims</td>
<td>$1,992 [4,393]</td>
<td>1,430</td>
<td>$2,501 [11,316]</td>
<td>1,706</td>
<td>$509 [4,512]</td>
<td>276</td>
</tr>
<tr>
<td>Total costs</td>
<td>$10,827 [27,203]</td>
<td>6,637</td>
<td>$21,452 [52,691]</td>
<td>13,840</td>
<td>$10,625 [32,308]</td>
<td>7,203</td>
</tr>
<tr>
<td>Total costs for patients with &lt;12 months of observation (n = 127 no-CKD; n = 13 CKD)</td>
<td>$25,636 [34,309]</td>
<td>11,855</td>
<td>$98,630 [89,911]</td>
<td>61,143</td>
<td>$72,995 [42,951]</td>
<td>49,288</td>
</tr>
<tr>
<td>Total costs for patients with ≥12 months of observation (n = 3,940 no-CKD; n = 699 CKD)</td>
<td>$10,743 [26,849]</td>
<td>6,623</td>
<td>$21,191 [50,932]</td>
<td>13,817</td>
<td>$10,448 [31,679]</td>
<td>7,194</td>
</tr>
</tbody>
</table>

*Cost per patient per month for each month of insurance eligibility following the index date, multiplied by 12.

CKD = chronic kidney disease.

Unadjusted All-Cause Health Care Cost Difference: CKD Versus No-CKD

In all 3 cohorts, CKD was associated with significantly higher total direct all-cause health care costs (Table 2), with unadjusted annualized per patient mean [median] cost differences of $11,814 [$6,895], $8,412 [$4,115], and $10,625 [$7,203], respectively (diabetes only cohort: $18,444 [$11,025] vs. $6,631 [$4,131], P < 0.001; hypertension only cohort: $14,638 [$7,817] vs. $6,226 [$3,703], P < 0.001; diabetes and hypertension cohort: $21,452 [$13,840] vs. $10,827 [$6,637], P < 0.001). The corresponding cost ratios for the CKD diabetes, hypertension, and diabetes and hypertension cohorts relative to no-CKD groups were 2.8:1, 2.4:1, and 2.0:1, respectively. The largest driver of the all-cause mean cost difference associated with CKD for each cohort was hospitalization cost (diabetes: $6,410, P < 0.001; hypertension: $5,498, P < 0.001; diabetes and hypertension: $6,467, P < 0.001). Stratified analyses by duration of observation period (subsets of patients with <12 months of observation and ≥12 months of observation) produced similar findings; however, both total annualized costs and the incremental annualized cost differences were much higher for patients with shorter observation periods.

Adjusted Cost Burden of CKD Relative to No-CKD

After controlling for covariates, the adjusted annualized incremental all-cause health care costs associated with CKD were

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among other statistically significant variables for most cost components were age, gender, and baseline history of coronary artery disease. As in the unadjusted results, regression analysis by cost category revealed that the largest driver of the adjusted incremental cost associated with CKD was cost of hospitalizations (diabetes cohort: $4,331, P < 0.001; hypertension cohort: $3,605, P < 0.001; diabetes and hypertension cohort: $6,225, P < 0.001; data not shown).

Change in All-Cause Health Care Costs Following a Diagnosis of CKD

Among patients who developed CKD during the observation period and who had at least 60 days of observation both pre-CKD and post-CKD, the post-CKD phase was associated with a significant increase in total direct all-cause health care costs (Table 4), with mean incremental annualized per patient costs of $8,829, $4,175, and $9,397 relative to pre-CKD, respectively (diabetes cohort: $22,062 vs. $13,233, P = 0.002; hypertension cohort: $15,540 vs. $11,365, P = 0.004; diabetes and hypertension cohort: $24,171 vs. $14,774, P < 0.001). The corresponding cost ratios for the post-CKD diabetes, hypertension, and diabetes and
CKD onset, respectively, while they were $736 and $1,295 for the hypertension cohort, and $1,089 and $1,573 for the diabetes and $1,386 during the 9-month periods preceding and following coupled with laboratory results. From January 2000 to February with hypertension, and 4,779 patients with both conditions.

We conducted this retrospective parallel-group study to assess the cost burden of CKD in cohorts of patients with diabetes only, hypertension only, and diabetes and hypertension. The analysis was based on administrative medical and pharmacy claims data coupled with laboratory results. From January 2000 to February 2006, a total of 11,531 patients with diabetes, 74,759 patients with hypertension, and 4,779 patients with both conditions were studied. Both unadjusted and adjusted results consistently indicated that CKD was associated with significantly higher all-cause health care costs in patients with diabetes, hypertension, and both conditions (mean annualized unadjusted differences of $11,814, $8,412, and $10,625, respectively). The largest driver of health care cost differences between the CKD and no-CKD groups was cost of hospitalizations. Among patients who developed CKD, the post-CKD phase was also associated with significantly higher health care costs, with cost increases of approximately 67%, 37%, and 64% compared with the pre-CKD period for the diabetes, hypertension, and diabetes and hypertension cohorts, respectively. For patients who developed CKD, approximately 9%-19% of all-cause health care costs were directly attributable to treatment of CKD.

Since a large percentage of people with kidney disease have diabetes and/or hypertension (the major causes of kidney failure), it is possible that early profiling and active management of patients with CKD might prevent or delay progression to more advanced costly stages of CKD including ESRD and the associated complications. Patients with a decline in renal function will generally notice no symptoms until their kidney function is reduced by 50%-75%. By screening at-risk patients regularly, referring those with early abnormal kidney test results to nephrologists, and having an organized system for recall and

### TABLE 4

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</thead>
<tbody>
<tr>
<td>All-cause medical services cost</td>
<td>$10,252 [20,754] 3,568</td>
<td>$19,038 [46,200] 6,477</td>
<td>$8,787 [35,994] 2,910</td>
<td>1.9</td>
<td>0.024</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>All-cause pharmacy claims cost</td>
<td>$2,981 [5,674] 1,460</td>
<td>$3,023 [5,626] 1,857</td>
<td>$42 [5,678] 379</td>
<td>1.0</td>
<td>0.945</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>Total costs</td>
<td>$13,233 [21,856] 5,738</td>
<td>$22,062 [46,580] 10,637</td>
<td>$8,829 [36,566] 4,899</td>
<td>1.7</td>
<td>0.026</td>
<td>&lt; 0.001</td>
<td></td>
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<tr>
<td>CKD-related medical services costd</td>
<td>–</td>
<td>$1,746 [10,695] 141</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Observation period in days, mean [SD] median</td>
<td>520 [341] 456</td>
<td>837 [450] 806</td>
<td>–</td>
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</tr>
</thead>
<tbody>
<tr>
<td>All-cause medical services cost</td>
<td>$10,185 [42,005] 3,114</td>
<td>$13,880 [42,122] 5,784</td>
<td>$3,695 [42,087] 2,671</td>
<td>1.4</td>
<td>0.012</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>All-cause pharmacy claims cost</td>
<td>$1,180 [1,791] 752</td>
<td>$1,660 [3,681] 1,102</td>
<td>$480 [2,896] 350</td>
<td>1.4</td>
<td>0.004</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>Total costs</td>
<td>$11,365 [42,081] 4,672</td>
<td>$15,540 [42,422] 7,413</td>
<td>$4,175 [42,276] 2,741</td>
<td>1.4</td>
<td>0.004</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>CKD-related medical services costd</td>
<td>–</td>
<td>$1,616 [12,070] 97</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Observation period in days, mean [SD] median</td>
<td>503 [355] 397</td>
<td>1,078 [477] 1,062</td>
<td>–</td>
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</thead>
<tbody>
<tr>
<td>All-cause medical services cost</td>
<td>$12,819 [32,347] 4,464</td>
<td>$21,547 [54,380] 10,616</td>
<td>$8,729 [44,779] 6,152</td>
<td>1.7</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>All-cause pharmacy claims cost</td>
<td>$1,955 [2,518] 1,324</td>
<td>$2,624 [4,806] 1,846</td>
<td>$669 [3,840] 522</td>
<td>1.3</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>Total costs</td>
<td>$14,774 [32,618] 6,540</td>
<td>$24,171 [54,940] 13,780</td>
<td>$9,397 [45,218] 7,240</td>
<td>1.6</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>CKD-related medical services costd</td>
<td>–</td>
<td>4,057 [29,946] 186</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Observation period in days, mean [SD] median</td>
<td>515 [355] 427</td>
<td>1,080 [472] 1,070</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
</tbody>
</table>

*Costs per patient per month for each month of insurance eligibility before (pre-CKD) and after (post-CKD) the CKD diagnosis, multiplied by 12.
*A minimum of 60 days of observation pre- and post-CKD was imposed.
*Paired t-tests were used to evaluate the statistical significance of the differences between the 2 repeated measures (i.e., post-CKD vs. pre-CKD period)
*Costs for claims with primary or secondary CKD diagnoses or claims for dialysis services

**CKD** chronic kidney disease.

Discussion

We conducted this retrospective parallel-group study to assess the cost burden of CKD in cohorts of patients with diabetes only, hypertension only, and diabetes and hypertension. The analysis was based on administrative medical and pharmacy claims data coupled with laboratory results. From January 2000 to February 2006, a total of 11,531 patients with diabetes, 74,759 patients with hypertension, and 4,779 patients with both conditions...
monitoring, primary care providers could make a significant difference to their patients long before they experience the first symptoms.8

The present study was the first to investigate the costs associated with the development of CKD in patients with diabetes and/or hypertension in a managed care population. The USRDS reported that PPPM all-cause combined inpatient and outpatient costs for CKD patients reached $1,294 in 2005.1 This figure is an average of the monthly cost of $2,113 for those CKD patients with diabetes and congestive heart failure (CHF), $831 for CKD patients with diabetes alone, and $780 for CKD patients with neither diabetes nor CHF. The estimated post-CKD monthly costs of $1,386 for the diabetic group, $1,295 for the hypertensive group, and $1,573 for the diabetic and hypertensive group reported in the current study are fairly comparable with the USRDS estimates, considering that we imposed no exclusion criteria for patients who developed CHF, which typically involves higher medical costs, and that our estimates also include pharmacy costs.

The present study had the advantages of a large sample size and the availability of laboratory results data, which enabled us to ascertain CKD status based on the eGFR measurement. CKD patients had higher morbidity at baseline, as reflected by more comorbidities and a greater proportion of patients with previous hospitalization related to CVDs. In addition, patients with CKD were more likely to use medical services in general due to their older age. Multivariate analyses, which controlled for these confounding factors, revealed that CKD was independently associated with increased medical costs.

**Limitations**

First, claims databases may contain inaccuracies or omissions in coded procedures or diagnoses, costs, or laboratory results.
Second, because patient ethnicity data were not available in our database, eGFR values for African-American patients were underestimated by a small increment because of the omission of this factor for the calculation. The measurement errors of the eGFR values affected the estimated subset of African-Americans, about 10% of the total employed population. The consequence of this omission is that some African-Americans may have been included in the CKD group, although they should not have been considered CKD patients. Considering that CKD patients incur higher medical costs, this subset of patients would have lowered the average costs of the CKD group. Therefore, from this perspective, we can qualify our estimate of the cost burden due to CKD as conservative.

Third, the study evaluated only direct medical costs. Information to determine the indirect costs of CKD, such as work productivity loss and reduced quality of life, was not available. Despite our attempt to control for measured covariates through multivariate analyses, we do not know the extent to which unmeasured confounding factors influenced the total all-cause cost differences observed in the current study.

Fourth, the observational design was susceptible to various biases. We recognize that a randomized trial would be the ideal way of addressing this question; however, it is impossible to randomize patients to develop CKD. It would be possible, on the other hand, to randomize patients to a program of early and intensive intervention versus standard care to evaluate the effects of early profiling and active management on the progression of CKD. Future research studies that address this issue are warranted. In the absence of such randomized trials, well-designed observational studies with appropriate statistical techniques adjusting for confounding factors provide valuable information with real-life scenarios and high generalizability. In the current analysis, we tried to identify the cost increase associated with CKD by comparing the costs in the CKD group with the costs in a reference no-CKD group. A subset analysis was conducted to compare the pre- versus post-CKD all-cause costs for patients developing CKD.

Fifth, the current study may also suffer from detection bias. Indeed, because laboratory results and diagnoses were not collected at pre-specified intervals as in randomized clinical trials, false negatives of CKD could have occurred in patients who did not seek care (especially those who did not have symptomatic manifestations). Furthermore, since laboratory results are available only for a subset of beneficiaries tested within a given carrier’s laboratory network, representing approximately 10% of the IHCIS population, it is possible that we are under-estimating the prevalence of CKD development. Finally, our database excluded information about long-term nursing home care.

Previous studies have demonstrated the detrimental health effects and associated costs of CKD-related complications such as anemia. The current study reported an adverse economic association between CKD and all-cause health care costs in patients with diabetes and/or hypertension. Early identification and assessment of CKD among diabetic and/or hypertensive patients may have the potential to reduce the utilization of health care resources and may also improve patient and clinical outcomes by delaying progression to more advanced costly stages of CKD.

Conclusion

Despite limitations associated with a retrospective observational design, this large study demonstrated that CKD was associated with a significant increase in all-cause health care costs in patients with diabetes and/or hypertension. The cost difference associated with CKD remained significant after adjusting for important comorbidities that may otherwise contribute to the increased costs. Among patients who developed CKD, costs directly attributable to CKD treatment represented 9%-19% of total all-cause medical service costs. Further studies are warranted to evaluate whether earlier identification of CKD could prevent cost escalations in patients with diabetes and/or hypertension.

Authors

FRANÇOIS LALIBERTÉ, MA, is Economist; FRANCIS VEKEMAN, MA, is Senior Economist; and PATRICK LEFEBVRE, MA, is Vice President, Groupe d’analyse Lté, Montréal, Québec. MEI SHENG DUH, MPH, ScD, is Vice President, Analysis Group, Boston, Massachusetts. At the time of the study, BRAHIM K. BOOKHART, MBA, MPH, was Director; and MITRA CORRAL, MS, MPH, was Manager, Centocor Ortho Biotech Services, LLC, Horsham, Pennsylvania. Currently, Bookhart is Director, Ortho-McNeil Janssen Scientific Affairs, Raritan, New Jersey; and Corral is Assistant Director, Novartis Pharmaceuticals Corporation, East Hanover, New Jersey. ROBERT A. BAILEY, MD, is Associate Director, and CATHERINE TAK PIECH, MBA, is Vice President, Centocor Ortho Biotech Services, LLC, Horsham, Pennsylvania.

AUTHOR CORRESPONDENCE: Patrick Lefebvre, MA, Groupe d’analyse, Lté, 1080 Beaver Hall Hill, Suite 1810, Montréal, QC H2Z 1S8, Canada. Tel.: 514-394-4471; E-mail: plefebvre@analysisgroup.com.

DISCLOSURES

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Study concept and design and data interpretation were primarily the work of Bookhart and Lefebvre, with assistance from the other authors. Laliberté performed the data collection with the assistance of Vekeman and Lefebvre. Writing of the manuscript was shared by Laliberté, Vekeman, Duh, and Lefebvre. Revision of the manuscript was shared by Bookhart, Corral, Bailey, and Piech.

REFERENCES

ABSTRACT

BACKGROUND: The Veterans Health Administration (VHA) develops guidelines for VHA providers that delineate specific criteria for use of certain complex, costly medications indicated for specialized populations. These criteria are disseminated to all VHA facilities.

OBJECTIVE: To (a) assess the concordance with VHA guidelines for use of 4 antiretroviral agents (atazanavir, darunavir, enfuvirtide, and tipranavir), and (b) to describe prescribing of these agents before and after implementation of the guideline criteria.

METHODS: In this retrospective cohort study, we evaluated all veterans in VHA care who received their first outpatient prescription for a target antiretroviral between its FDA approval date and December 31, 2007, using outpatient prescription records obtained from the VHA Human Immunodeficiency Virus (HIV) Clinical Case Registry (CCR:HIV), an observational registry database created through extraction of specific clinical data from the VHA's electronic medical record. Adherence to the VHA guideline criteria was assessed using CCR:HIV data overall and during 3 time periods: (a) pre-criteria: from FDA approval date to criteria implementation date (range 38 days to 192 days), (b) early-criteria: the first 6 months after criteria implementation, and (c) late-criteria: from 180 days after criteria implementation until December 31, 2007 (range 184 days to 1,525 days).

RESULTS: VHA providers prescribed target antiretroviral medications in accordance with the VHA guidelines for use more than 70% of the time. Comparing the pre-criteria with the post-criteria period (i.e., early-criteria and late-criteria combined), no significant differences in the percentages of veterans satisfying all VHA criteria were observed for any drug except atazanavir (P=0.010). For atazanavir in the post-criteria period compared with the pre-criteria period, significantly more antiretroviral-naive veterans met criteria for cardiovascular disease or risk (72.8% post-criteria vs. 45.5% pre-criteria, P=0.045), and significantly more antiretroviral-experienced veterans met criteria for resistance to other protease inhibitors requiring the need for ritonavir-boosted atazanavir (61.7% vs. 50.5%, respectively, P<0.001); however, fewer antiretroviral-experienced veterans met criteria for having documented intolerance to other protease inhibitors (78.9% vs. 89.9%, respectively, P=0.001). Fewer darunavir-treated patients in the post-criteria period than in the pre-criteria period met the criteria for treatment experience including failure of at least 1 prior protease inhibitor regimen (40.8% vs. 96.6%, respectively, P=0.002). Adherence to all darunavir criteria significantly waned over time (early-criteria 78.8% vs. late-criteria 62.5%, P<0.001). Overall, adherence to atazanavir criteria increased over time (66.3% early-criteria vs. 72.9% late-criteria, P<0.001).

CONCLUSIONS: After implementation of antiretroviral specific guideline criteria, the proportion of veterans prescribed a target antiretroviral medication in accordance with VHA guideline criteria varied by agent and improved only for atazanavir. Although adherence to criteria for atazanavir, enfuvirtide, and tipranavir persisted or improved during the post-criteria period, darunavir adherence to criteria waned over time, perhaps indicating that later prescribing patterns reflected changing practice patterns and the need for updated criteria. Revisiting and updating criteria may be especially important for HIV due to the speed with which new information becomes available.

What is already known about this subject

• Provider adherence to institutional medication criteria guidance generally ranges from 50% to 95%. Generally accepted rates for adherence to guidelines range from 80% to 90%.
• Institutional guidelines based on currently available evidence can improve the clinical appropriateness of therapy as suggested by Owen et al. in an evaluation describing the utilization of recombinant human coagulation factor VIIa pre- versus post-implementation of an evidence-based guideline at a university hospital. Gora-Harper et al. also demonstrated significantly more instances of appropriate use of neuromuscular blocking agents post-guideline implementation compared with pre-implementation.
• Not all guideline criteria are effective in influencing provider prescribing patterns. In a study of patients in Veterans Affairs medical centers, Burk et al. found no meaningful differences in prescribing patterns before versus after posting of national formulary guidelines for use of tamsulosin.
• The Department of Health and Human Services Panel on Antiretroviral Guidelines for Adults and Adolescents has developed national guidelines for initiation and selection of antiretroviral regimens in individuals infected with human immunodeficiency virus (HIV-1).

What this study adds

• In this retrospective cohort study of patients in Veterans Health Administration (VHA) care, who received their first outpatient prescription for a target antiretroviral between its FDA approval date and December 31, 2007, VHA providers prescribed target antiretroviral medications in accordance with criteria more than 70% of the time.
• After implementation of antiretroviral-specific guideline criteria, the proportion of veterans prescribed a target antiretroviral medication (atazanavir, darunavir, enfuvirtide, or tipranavir) in accordance with guideline criteria varied by drug. Comparing the pre-criteria with post-criteria periods, no significant differences in the percentages of veterans satisfying all VHA criteria were observed for any drug except atazanavir.
• Although adherence to criteria generally persisted, adherence to all darunavir criteria waned over time. Later prescribing patterns may reflect changing practice patterns and the need for updated criteria.
• Revisiting and updating criteria may be especially important for HIV due to the speed with which new information becomes available.
Four new antiretroviral agents received U.S. Food and Drug Administration (FDA) approval for the treatment of human immunodeficiency virus (HIV) infection between June 2003 and June 2006: atazanavir (June 2003), darunavir (June 2006), enfuvirtide (March 2003), and tipranavir (June 2005). Each of these agents offered antiretroviral-experienced HIV-infected patients options when previously few existed. These agents were FDA approved based on data from 24-week analyses that included very specific patient inclusion criteria.1-7

With the introduction of several new classes and agents, antiretroviral treatment has become increasingly complex because of resistance, long-term toxicities, regimen complexities, adherence, and drug-interactions.8 The Department of Health and Human Services (DHHS) Panel on Antiretroviral Guidelines for Adults and Adolescents published national antiretroviral treatment guidelines for initiation and selection of antiretroviral regimens in HIV-1 infected individuals.8 An evaluation of HIV-infected veterans in 2004 found that 60% were receiving a preferred or alternative regimen in accordance with these published guidelines.9

Although these nationally published guidelines provide recommendations on the criteria for selecting preferred components in an antiretroviral regimen and provide details on selecting appropriate agents for special populations of patients, they do not provide agent-specific criteria to follow. The influence of local criteria to help guide providers as to which HIV-infected patients may be most appropriate to receive selected antiretroviral agents has not been extensively evaluated. Although some data exist on antiretroviral prescribing patterns and utilization, provider adherence to local institutionally established antiretroviral criteria for use is understudied.9-11

The Veterans Health Administration (VHA) develops guidelines for VHA providers that delineate criteria for use of certain complex, costly medications indicated for specialized populations. These guideline criteria are disseminated for use by all VHA facilities. Enforcement at individual facilities varies to some extent, but criteria are available to all providers on the VHA Intranet. Once an electronic order for these medications is entered in the system, clinical pharmacists review electronic medical records (EMRs) to verify that patients prescribed these medications have met the guideline criteria.

Concerns regarding potentially inappropriate use, safety, and cost of the antiretroviral agents atazanavir, darunavir, enfuvirtide, and tipranavir led to efforts to standardize their use. VHA criteria were modeled after inclusion criteria used in the key licensing trials for each agent; current medical evidence available at the time the criteria were developed; and input from VHA HIV experts (Table 1). The guideline criteria are dynamic and are revised as new data become available.

Though such criteria are often implemented within health care delivery systems, little information has been published about adherence to such criteria or about changes in adherence over time, particularly for antiretroviral prescribing. This analysis sought to assess the concordance with VHA guidelines of 4 antiretroviral agents and to describe the prescribing of these agents before and after implementation of these criteria.

### Methods

#### Patient Selection

Target medications were atazanavir, darunavir, enfuvirtide, and tipranavir. Veterans were identified using outpatient prescription records obtained from the VHA HIV Clinical Case Registry (CCR:HIV), an observational registry database created through extraction of specific clinical data from the VHA’s EMR. We included all veterans in VHA care who received their first outpatient prescription for a target medication between its FDA approval date and December 31, 2007. We required that at least 1 VHA prescription for any medication be filled within 90 or more days before the first prescription for the target medication to indicate that the patient was currently receiving care from the VHA. Other than this, no specific length of time enrolled in VHA care was required. Veterans transferring into VHA care already on a target antiretroviral from another outside source were excluded, as were veterans receiving a target medication as part of a pre-approval clinical trial and continuing it after FDA approval. The present analysis includes only veterans who received the target medication, whether or not those individuals met criteria and were in concordance with VHA guidelines; we did not include veterans who may have met criteria but did not receive a target medication. Because the study data were extracted from the EMR, the data reflect only prescriptions for the target medications rather than claims indicating that the prescriptions were actually filled.

#### VHA Guideline Criteria

The dates of implementation of VHA criteria for the target medications ranged between 38 days (tipranavir) and 192 days (darunavir) after FDA approval (Table 2). After guideline criteria are developed by a clinical pharmacist with expertise in the therapeutic field, they are reviewed by 2 VHA committees consisting of formulary leaders (mostly pharmacists) and a medical advisory panel (mostly physicians). The guidelines are then sent to field providers in the practice area for review and comments before final approval by the committees and posting on the VHA Intranet. Generally guidelines are posted within 90 days after FDA approval. Implementation of atazanavir criteria was delayed because this was the first antiretroviral for which VHA guidelines had been established. Darunavir guideline development was delayed because of staffing shortages and postponement of committee review. Different atazanavir criteria were established for antiretroviral-naive and antiretroviral-experienced veterans and these were evaluated separately (Table 1).

The numbers of veterans satisfying each separate criterion and satisfying all criteria for a target medication were automatically extracted from the EMR in January 2008 using the CCR:HIV
### TABLE 1 Criteria of Target Medications in the Veterans Health Administration

<table>
<thead>
<tr>
<th>Target Medication</th>
<th>Criteria in Use at Time of Study</th>
<th>Criteria Currently in Use</th>
<th>Source and Rationale</th>
</tr>
</thead>
</table>
| Atazanavir        | **Antiretroviral naïve:**  
1. Cardiovascular disease or multiple (3 or more) risk factors for cardiovascular disease or  
2. Not a candidate for other once daily medications (specifically efavirenz)  
**Antiretroviral experienced:**  
1. Documented intolerance to other PIs  
2. Documented resistance to other PIs where atazanavir plus ritonavir would be expected to have activity  
3. Stable on antiretroviral regimen (VL < 1,000 copies per mL) but with uncontrolled LDL-C (> 100 mg per dL) and/or triglycerides (> 300 mg per dL)  
Criteria no longer in use in VHA (archived October 2006); medication is available without restriction to HIV-infected individuals in VHA care in accordance with DHHS guidelines.  
**Antiretroviral naïve:**  
1. Data from clinical trial AI424-0346 demonstrating that lipids, including cholesterol and triglycerides, did not increase with short-term exposure to the drug. Atazanavir would be the preferred PI in patients for whom the potential worsening of LDL-C may place them at a high risk of a clinical event.  
2. Patients who would likely fail any regimen administered more than once daily would be appropriate for atazanavir. Since efavirenz was also approved as a daily agent, consideration should be given as to whether the patient would benefit from an efavirenz-containing regimen in place of atazanavir.  
**Antiretroviral experienced:**  
1. At the time of the criteria, atazanavir was not a preferred PI according to DHHS guidelines; VHA experts agreed that other preferred PIs should be initiated first if tolerated.  
2. In clinical trial AI424045, the virologic response to ritonavir-boosted atazanavir was similar to that seen with lopinavir/ritonavir; hence, in patients sensitive to atazanavir but resistant to preferred PIs, boosted atazanavir would be appropriate.  
3. Data from clinical trial AI424-0346 demonstrating that lipids, including cholesterol and triglycerides, did not increase with short-term exposure to the drug. Atazanavir would be the preferred PI in patients for whom the potential worsening of LDL-C may place them at a high risk of a clinical event. Definition of uncontrolled dyslipidemia includes patients who do not reach VHA-recommended target goals with lifestyle changes and/or pharmacologic intervention. |  |
| Darunavir         | 1. Highly treatment-experienced patients (defined in criteria as including at least 1 prior failed PI regimen) and  
2. Evidence of virologic failure documented by a VL > 1,000 copies per mL and  
3. Able to tolerate low-dose ritonavir  
Criteria no longer in use in VHA (archived January 2009); medication is available without restriction to HIV-infected individuals in VHA care in accordance with DHHS guidelines.  
1. FDA-approved indication is for the treatment of HIV-1 infection, with concomitant ritonavir and other antiretroviral drugs, in treatment-experienced patients, such as those with HIV-1 strains resistant to more than 1 PI. Similar to inclusion criteria from POWER 1 and 2 studies.  
2. In POWER 1 and 2, patients’ plasma HIV-1 RNA had to be > 1,000 copies per mL for inclusion.  
3. Darunavir must be administered with low-dose ritonavir to achieve its desired efficacy. |  |
| Enfuvirtide       | 1. Exposure to at least 2 antiretroviral classes and  
2. Documented VL > 5,000 copies per mL or  
3. Intolerance to at least 2 antiretroviral regimens  
Existing criteria still in use  
1. TORO-1 and 2 inclusion criteria: HIV-infected patients exposed to all 3 antiretroviral drug classes.  
2. TORO-1 and 2 inclusion criteria: HIV viral load > 5,000 copies per mL.  
3. VHA expert recommendation to provide the option to use enfuvirtide if patient has intolerance to other regimens. |  |
### TABLE 1  Criteria of Target Medications in the Veterans Health Administration

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Tipranavir</th>
<th>Darunavir</th>
<th>Ritonavir</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Treatment-experienced patient (defined as 3-class experience including PI regimen)</td>
<td>1. Highly treatment-experienced patients (including at least 2 prior failed PI regimens) and 2. Evidence of virologic failure documented by a VL &gt; 1,000 copies per mL and 3. Able to tolerate low-dose ritonavir</td>
<td>1. Treatment-experienced patient (defined as 3-class experience including PI regimen) and 2. Evidence of virologic failure documented by a VL &gt; 1,000 copies per mL</td>
<td>1. Highly treatment-experienced patient (defined as 3-class experience including PI regimen) and 3. Able to tolerate low-dose ritonavir</td>
</tr>
<tr>
<td>2. FDA approved for patients with evidence of viral replication.</td>
<td>4. Under the care of an experienced HIV practitioner</td>
<td>4. Under the care of an experienced HIV practitioner</td>
<td></td>
</tr>
</tbody>
</table>

Duration prior to starting atazanavir in the RESIST-1 and RESIST-2 studies included heavily pre-treated patients with triple antiretroviral class (NRTI, NNRTI, and PI) experience. 2. FDA approved for patients with evidence of viral replication. 3. Tipranavir must be administered with low-dose ritonavir to achieve its desired efficacy. 4. The DHHS currently recommends darunavir as first-line treatment for both treatment-naive and treatment-experienced patients.

Cardiovascular disease risk factors documented in the medical record at any time prior to starting atazanavir: (1) age in years (male ≥ 45, female ≥ 55), (2) male sex, (3) tobacco use, (4) hypertension, (5) diabetes, (6) HDL-C < 40 mg per dL, and (7) LDL-C ≥ 130 mg per dL (adapted from VA/DoD Clinical Practice Guidelines for Management of Dyslipidemia Update 2006). Availabe at: http://www.guideline.gov/summary/summary.aspx?doc_id=9907.

### Virologic Cutoffs Defined in the Criteria

Virologic cutoffs defined in the criteria were determined using laboratory results for the HIV viral load closest (but within 1 year prior) to the first target medication prescription. Per the VHA criteria and as defined in the key licensing trials for these agents, virologic failure was defined as a viral load more than 1,000 copies per milliliter (mL) for darunavir and tipranavir and a viral load more than 5,000 copies per mL for enfuvirtide.

At the time the atazanavir guidelines were developed in the VHA, atazanavir was substantially more costly than other DHHS preferred agents (efavirenz and lopinavir/ritonavir) but offered potential benefits to patients in whom worsening lipid abnormalities may place them at a higher risk of a clinical event. Hence, VHA guidelines recommended atazanavir use in experienced patients with uncontrolled dyslipidemias and naive patients with a history of cardiovascular disease or multiple risk factors for cardiovascular disease. For the atazanavir criteria, inpatient and outpatient International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) primary and secondary diagnoses codes were used to identify veterans with cardiovascular disease, cardiovascular risk factors, and serious mental illness documented on or anytime before the first atazanavir prescription (Table 3). Cardiovascular risk factors based on ICD-9-CM codes included tobacco use, hypertension, and diabetes. Patients were also classified as having diabetes if they had 2 or more random glucose results of 200 milligrams per deciliter (mg per dL) or more on or before (but within 1 year prior to) the first atazanavir prescription. Serious mental illness was defined as bipolar disorder, depression, post-traumatic stress disorder or schizophrenia. Low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglyceride values were determined using the laboratory results closest (but within 1 year prior) to the first atazanavir prescription. "Uncontrolled" LDL-C values were defined as greater than 100 mg per dL in accordance with National Cholesterol Education Program Adult Treatment...
Provider Prescribing of 4 Antiretroviral Agents After Implementation of Drug Use Guidelines in the Department of Veterans Affairs

**FIGURE 1** Patient Selection

HIV-infected veterans confirmed in the VHA CCR:HIV as of 12/31/2007 (n=22,956)

Veterans in VHA care (defined as having at least 1 VHA prescription for any medication filled ≥90 days before the first prescription for the target medication) who received their first outpatient prescription for atazanavir, darunavir, enfuvirtide, or tipranavir between FDA approval date and 12/31/2007 (n=7,220)

**TABLE 2** FDA Approval Dates and VHA Criteria Implementation Dates for Target Medications

<table>
<thead>
<tr>
<th>Drug</th>
<th>FDA Approval Date</th>
<th>Criteria Implementation Date</th>
<th>Length of Pre-Criteria Period (Days)a</th>
<th>Length of Late-Criteria Period (Days)b</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atazanavir</td>
<td>June 20, 2003</td>
<td>November 1, 2003</td>
<td>133</td>
<td>1,340</td>
</tr>
<tr>
<td>Darunavir</td>
<td>June 23, 2006</td>
<td>January 1, 2007</td>
<td>192</td>
<td>184</td>
</tr>
<tr>
<td>Enfuvirtide</td>
<td>March 13, 2003</td>
<td>April 30, 2003</td>
<td>48</td>
<td>1,525</td>
</tr>
<tr>
<td>Tipranavir</td>
<td>June 22, 2005</td>
<td>July 30, 2005</td>
<td>38</td>
<td>703</td>
</tr>
</tbody>
</table>

aNumber of days from FDA approval until criteria implementation.
bNumber of days from end of early-criteria period (180 days after implementation) until study end date (December 31, 2007).

FDA = U.S. Food and Drug Administration; VHA = Veterans Health Administration.
To determine adherence to criteria, we assessed the proportions of veterans satisfying criteria pre- and post-implementation of criteria. In an effort to assess continued adherence to criteria over time after implementation, 3 time periods were assessed based on the date of the first prescription for the target medication: immediately after FDA approval and before criteria implementation (pre-criteria); the first 180 days after criteria implementation (early-criteria); and more than 180 days after criteria implementation (late-criteria).

### Statistical Analysis

Pearson chi-square tests (a priori statistical significance level, 0.05) were used to test for differences in the proportions of veterans satisfying criteria, comparing (a) pre- versus post-criteria and (b) the 3 time periods pre-criteria, early-criteria and late-criteria. Data were analyzed using SAS version 8.2 (SAS Institute, Cary NC).

This protocol was approved by the Department of Veterans Affairs Palo Alto Health Care System Office of Research Administration, the Stanford University Institutional Review Board, and the VHA Clinical Case Registry Research Committee.
Results

After implementation of inclusion and exclusion criteria, the sample included 7,220 initial veterans who received a new outpatient prescription for the 4 target agents: atazanavir (n = 5,667), darunavir (n = 559), enfuvirtide (n = 669), and tipranavir (n = 325; Figure 1). In veterans receiving the 3 target medications indicated solely for antiretroviral-experienced patients (darunavir, enfuvirtide, and tipranavir), 99.0% were antiretroviral-experienced, while 90.9% of veterans initiating atazanavir were antiretroviral-experienced.

Daranavir

From the FDA approval date of darunavir in June 2006 through December 2007, 559 veterans received an initial outpatient prescription for darunavir: 175 pre-criteria, 184 early-criteria, and 200 late-criteria (Table 4). Overall, 71.0% of veterans satisfied all darunavir criteria. Although the percentages of veterans satisfying all darunavir criteria in the pre-criteria and post-criteria periods did not significantly differ (P = 0.585), significant differences in some individual criteria and in adherence to the criteria over time were observed. Significantly fewer veterans were treatment experienced and had failed a prior protease inhibitor regimen in the post-criteria period compared with the pre-criteria period and adherence to this criteria waned over time (96.0% pre-criteria, 93.5% early-criteria, and 82.5% late-criteria [pre-criteria vs. post-criteria, P = 0.002, early-criteria vs. late-criteria, P < 0.001]). In fact, adherence to all darunavir criteria decreased significantly between the early- and late-criteria periods (early-criteria 78.8% vs. late-criteria 62.5%, P < 0.001) Although immediately after criteria implementation there was an initial increase in the percentage of veterans who had evidence of virologic failure (viral load more than 1,000 copies per mL) before tipranavir initiation. Evidence of virologic failure prior to tipranavir initiation remained consistent in the post-criteria time periods (78.1% pre-criteria, 87.2% early-criteria, and 86.9% late-criteria, P = 0.941 for comparison of early vs. late). Ninety-six percent of veterans demonstrated ability to tolerate ritonavir.

Atazanavir

Atazanavir was prescribed to 5,667 veterans over the evaluation period: 484 pre-criteria, 833 early-criteria, and 4,350 late-criteria. Overall, 71.4% of all veterans prescribed atazanavir satisfied the criteria. Significantly more veterans met criteria in the post-criteria period compared with the pre-criteria period (71.9% vs. 66.3%, P = 0.010). Prior to implementation of the criteria, only 2.3% (n = 11) of patients prescribed atazanavir were antiretroviral-naïve. By late-criteria, a significantly higher percentage of those initiating atazanavir were antiretroviral-naïve (10.9%, P < 0.001).

Enfuvirtide

During the evaluation period, 669 veterans were prescribed enfuvirtide: 9 pre-criteria, 140 early-criteria, and 520 late-criteria. Because so few patients were prescribed enfuvirtide in the 1-month interval between FDA approval and criteria implementation, statistical comparisons of the pre- and post-implementation periods could not be reasonably made.

Slightly less than 95% of veterans prescribed enfuvirtide satisfied all criteria. The proportions of veterans fulfilling each criterion and fulfilling all criteria were similar between the 3 evaluation periods with no significant differences. In accordance with VHA criteria, 98.2% of veterans had prior exposure to at least 2 antiretroviral classes, and 88.6% had evidence of intolerance to 2 previously VHA-prescribed antiretroviral regimens. Post-criteria, 81.7% of veterans had a documented viral load of more than 5,000 copies per mL just prior to initiating enfuvirtide compared with 77.8% pre-criteria.

Tipranavir

In all, 325 veterans were prescribed tipranavir: 32 pre-criteria, 125 early-criteria, and 168 late-criteria (Table 4). Overall, 75.1% of veterans satisfied all tipranavir prescribing criteria with no significant differences between the pre- and post-criteria periods (P = 0.675). Consistent with VHA criteria, 84.6% of veterans prescribed tipranavir had received at least 2 prior protease inhibitor regimens (90.6% pre-criteria, 88.0% early-criteria, and 81.0% late-criteria, P = 0.156). Eighty-six percent of veterans had evidence of virologic failure (viral load of more than 1,000 copies per mL) before tipranavir initiation. Evidence of virologic failure prior to tipranavir initiation remained consistent in the post-criteria time periods (78.1% pre-criteria, 87.2% early-criteria, and 86.9% late-criteria, P = 0.941 for comparison of early vs. late). Ninety-six percent of veterans demonstrated ability to tolerate ritonavir.

Atazanavir-Antiretroviral Naïve: Among antiretroviral-naïve veterans receiving atazanavir (n = 513), 11 received it pre-criteria, 29 early-criteria, and 475 late-criteria. In all, 86.2% of antiretroviral-naive veterans met all criteria for atazanavir use with no significant differences among time periods. Cardiovascular disease or multiple risk factors for cardiovascular disease were present in 72.2% of antiretroviral-naive veterans prescribed atazanavir with significantly more veterans having cardiovascular disease or risk factors in the post-criteria period (45.5% pre-criteria, 58.6% early-criteria, and 73.7% late-criteria; pre-criteria vs. post-criteria, P = 0.045). Fifty-six percent of veterans were unlikely to tolerate efavirenz because of a documented history of serious mental illness. No significant difference in adherence to this criteria was observed pre-criteria versus post-criteria (P = 0.497).

Atazanavir-Antiretroviral Experienced: Ninety-one percent of veterans prescribed atazanavir were antiretroviral experienced (n = 5,152): 473 pre-criteria, 804 early-criteria, and 3,875 late-criteria. Of antiretroviral-experienced veterans receiving atazanavir, 69.9% satisfied all criteria. Although the proportions of veterans satisfying criteria in the pre- versus post-criteria periods did not
TABLE 4  Veterans Satisfying VHA Criteria for Target Medications

<table>
<thead>
<tr>
<th>Target Medication</th>
<th>Veterans Evaluated Total N (Pre/Early/Late)</th>
<th>Veterans Satisfying Criteria % (n)</th>
<th>Pre-Criteria % (n)</th>
<th>Early-Criteria % (n)</th>
<th>Late-Criteria % (n)</th>
<th>P Valuea (3-way)</th>
<th>P Valuea (Early vs. Late)</th>
<th>P Valuea (Pre vs. Post)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atazanavir antiretroviral naïve (all criteria)</td>
<td>515 (11/29/475)</td>
<td>86.2 (444)</td>
<td>81.8 (9)</td>
<td>75.9 (22)</td>
<td>86.9 (413)</td>
<td>0.222</td>
<td>0.092</td>
<td>0.669</td>
</tr>
<tr>
<td>1. Cardiovascular disease or multiple (≥3) risk factors for cardiovascular disease</td>
<td>72.2 (372)</td>
<td>45.5 (3)</td>
<td>58.6 (17)</td>
<td>73.7 (350)</td>
<td>0.029</td>
<td>0.077</td>
<td>0.045</td>
<td></td>
</tr>
<tr>
<td>2. Not a candidate for other once daily medications (specifically elaviren2)</td>
<td>55.5 (286)</td>
<td>45.5 (5)</td>
<td>58.6 (17)</td>
<td>55.6 (264)</td>
<td>0.754</td>
<td>0.749</td>
<td>0.497</td>
<td></td>
</tr>
<tr>
<td>Atazanavir antiretroviral experienced (all criteria)</td>
<td>5,152 (473/804/3,875)</td>
<td>69.9 (3,601)</td>
<td>66.0 (312)</td>
<td>65.9 (530)</td>
<td>71.2 (2,759)</td>
<td>0.002</td>
<td>0.003</td>
<td>0.050</td>
</tr>
<tr>
<td>1. Documented intolerance to other PIs</td>
<td>79.9 (4,115)</td>
<td>89.9 (425)</td>
<td>82.6 (664)</td>
<td>78.1 (3,026)</td>
<td>&lt;0.001</td>
<td>0.004</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>2. Documented resistance to other PIs where atazanavir plus ritonavir would be expected to have activity</td>
<td>60.8 (3,130)</td>
<td>50.5 (239)</td>
<td>55.8 (449)</td>
<td>63.0 (2,442)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>3. Stable on antiretroviral regimen (VL &lt; 1,000 copies per mL) but with uncontrolled LDL-C (&gt; 100 mg per dL) and/or triglycerides (&gt; 300 mg per dL)</td>
<td>64.8 (1,287)</td>
<td>66.7 (116)</td>
<td>68.8 (181)</td>
<td>64.0 (990)</td>
<td>0.270</td>
<td>0.127</td>
<td>0.597</td>
<td></td>
</tr>
<tr>
<td>Atazanavir all (naive and experienced)</td>
<td>5,667 (48/833/3,350)</td>
<td>71.4 (4,045)</td>
<td>66.3 (321)</td>
<td>66.3 (532)</td>
<td>72.9 (3,172)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.010</td>
</tr>
<tr>
<td>Darunavir (all criteria)</td>
<td>559 (175/184/200)</td>
<td>71.0 (397)</td>
<td>72.6 (127)</td>
<td>78.8 (145)</td>
<td>62.5 (125)</td>
<td>0.002</td>
<td>&lt;0.001</td>
<td>0.585</td>
</tr>
<tr>
<td>1. Highly treatment-experienced patients (defined in criteria as including at least 1 prior failed PI regimen)</td>
<td>90.3 (505)</td>
<td>96.0 (168)</td>
<td>93.5 (172)</td>
<td>82.5 (165)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.002</td>
<td></td>
</tr>
<tr>
<td>2. Evidence of virologic failure documented by a VL &gt; 1,000 copies per mL.</td>
<td>76.4 (427)</td>
<td>75.4 (132)</td>
<td>81.5 (150)</td>
<td>72.5 (145)</td>
<td>0.108</td>
<td>0.036</td>
<td>0.719</td>
<td></td>
</tr>
<tr>
<td>3. Able to tolerate low-dose ritonavir</td>
<td>95.2 (532)</td>
<td>97.7 (171)</td>
<td>97.3 (179)</td>
<td>91.0 (182)</td>
<td>0.003</td>
<td>0.010</td>
<td>0.060</td>
<td></td>
</tr>
<tr>
<td>Enfuvirtide (all criteria)</td>
<td>669 (9/140/520)</td>
<td>94.5 (632)</td>
<td>100.0 (9)</td>
<td>92.9 (130)</td>
<td>94.8 (493)</td>
<td>NA</td>
<td>0.373</td>
<td>NA</td>
</tr>
<tr>
<td>1. Exposure to at least 2 antiretroviral classes</td>
<td>98.2 (657)</td>
<td>100.0 (9)</td>
<td>99.2 (139)</td>
<td>97.9 (509)</td>
<td>0.002</td>
<td>&lt;0.271</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>2. Documented VL &gt; 5,000 copies per mL</td>
<td>81.6 (546)</td>
<td>77.8 (7)</td>
<td>81.4 (114)</td>
<td>81.7 (425)</td>
<td>NA</td>
<td>0.935</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>3. Intolerance to at least 2 antiretroviral regimens</td>
<td>88.6 (593)</td>
<td>100.0 (9)</td>
<td>89.3 (125)</td>
<td>88.3 (459)</td>
<td>NA</td>
<td>0.738</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Tipranavir (all criteria)</td>
<td>325 (32/125/168)</td>
<td>73.1 (244)</td>
<td>78.1 (25)</td>
<td>78.4 (98)</td>
<td>72.0 (121)</td>
<td>0.420</td>
<td>0.214</td>
<td>0.675</td>
</tr>
<tr>
<td>1. Highly treatment-experienced patients (including at least 2 prior failed PI regimens)</td>
<td>84.6 (275)</td>
<td>90.6 (29)</td>
<td>88.0 (110)</td>
<td>81.0 (136)</td>
<td>0.156</td>
<td>0.104</td>
<td>0.321</td>
<td></td>
</tr>
<tr>
<td>2. Evidence of virologic failure documented by a VL &gt; 1,000 copies per mL.</td>
<td>86.2 (280)</td>
<td>78.1 (25)</td>
<td>87.2 (109)</td>
<td>86.9 (146)</td>
<td>0.382</td>
<td>0.941</td>
<td>0.166</td>
<td></td>
</tr>
<tr>
<td>3. Able to tolerate low-dose ritonavir</td>
<td>96.0 (312)</td>
<td>100.0 (32)</td>
<td>97.6 (122)</td>
<td>94.0 (158)</td>
<td>0.147</td>
<td>0.144</td>
<td>0.224</td>
<td></td>
</tr>
</tbody>
</table>

aP value determined by Pearson chi-square test.

bDenominator is limited to patients with VL < 1,000 copies per mL (n = 1,985: 174 pre, 263 early, and 1,548 late).

dL = deciliter; LDL-C = low-density lipoprotein cholesterol; mL = milliliter; NA = not applicable (no comparison made because of small n pre-criteria); PI = protease inhibitor; VHA = Veterans Health Administration; VL = viral load.
significantly differ ($P=0.050$), significantly more veterans in the late-criteria period met criteria compared with the early-criteria period (65.9% vs. 71.2%, $P=0.003$).

Overall, 79.9% had received prior protease inhibitor therapy; however, the proportion of veterans with prior protease inhibitor therapy decreased with each time period: 89.9% pre-criteria, 82.6% early-criteria, and 78.1% late-criteria ($P<0.001$). Although we could not assess documented resistance to other protease inhibitors from available data elements in the CCR:HIV, in veterans with resistance to other protease inhibitors where atazanavir plus ritonavir would be expected to have activity, ritonavir-boosted atazanavir was prescribed in 60.8% of patients who had previously received protease inhibitor treatment, 50.5% pre-criteria, 55.8% early-criteria, and 63.0% late-criteria (pre- vs. post- criteria $P=0.001$, early- vs. late-criteria, $P=0.001$).

Of veterans stable on another regimen prior to initiating atazanavir ($n=1,985$), 64.8% had uncontrolled LDL-C or triglycerides. This percentage was similar across the 3 evaluation periods. The mean LDL-C and triglyceride concentrations in patients initiating atazanavir were 101 mg per dL and 228 mg per dL, respectively. Among those with lipids above the cutoffs, 22.1% were receiving lipid lowering medication.

### Discussion

One of the primary purposes of implementing institutional guidelines is to ensure appropriate medication use. Hence, after dissemination of such guidelines, it seems appropriate to assess adherence to criteria. Such critical evaluation is necessary to determine if guidelines are having the intended effect. This process can be particularly challenging in rapidly changing fields such as HIV treatment, where pharmacotherapy is extremely dynamic.

In the present study, we described different aspects of adherence to VHA criteria: (a) overall adherence, (b) adherence to the same criteria before and after implementation of the VHA guidelines (pre- vs. post-criteria), and (c) adherence to criteria in the early post-implementation phase versus later, after the criteria had been in place for at least 6 months. Overall adherence indicates whether providers are prescribing the target medications as intended by the guidelines. Adherence pre- versus post-criteria implementation provides insight on any changes in provider prescribing once criteria are instituted. Early- versus late-criteria assessments provide information on whether adherence to criteria diminishes over time.

Some data are available regarding the impact of institutional medication criteria on provider prescribing in the United States. $^{13-16}$ Reported provider adherence to such local guidance generally ranges between 50% to 95%. $^{13,14,16-20}$ Generally accepted rates for adherence to guidelines range from 80% to 90%. $^{17,18}$ These adherence rates were cited by studies whose scope ranges from very specific target populations (i.e., recombinant human coagulation factor VIIa prescribing at a single university teaching facility)$^{13}$ to a review of over 17,000 prescriptions written by general practitioners spanning 236 medications included on a regional formulary.$^{14}$ Previous studies also include a review of tamsulosin prescribing at 6 VHA facilities$^{20}$ and a study reviewing appropriateness, effectiveness, safety, and cost pre- and post-implementation of voluntary guidelines for neuromuscular blocking agents administered at a university hospital.$^{19}$ As suggested by these studies, implementation of guidelines based on currently available evidence may improve the clinical appropriateness of therapy. Owen et al. described improvements in the clinical appropriateness of recombinant factor VIIa upon implementation of an evidence-based guideline at a university hospital.$^{13}$ Gora-Harper et al. also demonstrated significantly more instances of appropriate neuromuscular blocking agent use post-guideline implementation compared with a pre-implementation period.$^{19}$ However, all studies were pre- versus post-implementation comparisons that lacked a control group. Not all guideline criteria have been shown to be effective in influencing provider prescribing patterns. This is evidenced by the work of Burk et al., whose data showed “no meaningful differences” in prescribing after posting of guidelines for tamsulosin use.$^{16}$

As do many other health care institutions, the VHA routinely develops guidance for providers on the use of specific medications or classes of medications that may require special monitoring or are indicated for a highly specialized patient population. Specific evidence-based criteria are developed as part of these guidelines by clinical pharmacists with expertise in the particular disease state and are then reviewed by other VHA clinical experts. Because these criteria are generally developed soon after an agent is FDA approved, most of the currently available evidence comes from licensing trials. Often VHA criteria are modeled after inclusion criteria used in these studies with additional input from VHA experts in the field. Guideline criteria must then be presented and approved by the VHA’s Medical Advisory Panel (consisting of physician volunteers and pharmacy benefit management pharmacists) and regional formulary leaders. Once approved, these guideline criteria are posted on the VHA website and disseminated through the regional pharmacy managers. Guideline criteria are reviewed and revised at periodic intervals if and when important new information becomes available. Because VHA has a national formulary, it is against VHA policy for local facilities to modify the criteria, although enforcement by the various facilities may differ. Individual facilities are responsible for implementing the guidelines; thus, the VHA lacks a standardized method to ensure guideline implementation. Generally it is the responsibility of the local clinical pharmacist assigned to that therapeutic area to enforce adherence to the guideline criteria.

Although the VHA criteria are evidence-based, many factors other than available evidence influence clinical decision making, such as the providers’ clinical experience in prescribing the medication and patient-related factors such as tolerability, comorbidities, and drug interactions.$^{20}$ How much these factors contributed
to decisions regarding target drug selection in the present study is difficult to ascertain without a comprehensive chart review. Even with chart review, providers frequently do not document their decision-making process. Nevertheless, using available information from an observational database (CCR:HIV), we found that VHA providers prescribed target medications in accordance with criteria more than 70% (and as high as 95%) of the time. As expected, adherence to individual criteria for a target medication varied: atazanavir (antiretroviral naive) 56% to 72%, atazanavir (antiretroviral experienced) 60% to 80%, darunavir 77% to 95%, enfuvirtide 82% to 97%, and tipranavir 85% to 96%.

Except for atazanavir, rates of conformity to the criteria in the pre-criteria and post-criteria periods were similar. This finding suggests that for the most part providers tended to follow current medical evidence when prescribing these agents. Since the VHA criteria were developed from the same published information available to providers, it is likely that in the pre-criteria time period, providers used similar criteria to those that would eventually be incorporated into VHA criteria to assess whether a patient was a good candidate for a therapy.

We also chose to evaluate adherence to criteria over time after implementation of the VHA guidelines (early-criteria vs. late-criteria) to see if waning adherence was an issue of concern. Waning adherence to criteria did occur for darunavir; compliance with the criteria decreased significantly by the late-criteria period. This decrease in adherence to criteria over time may have been attributable to reports describing the efficacy of darunavir in antiretroviral-naïve patients for whom it had not yet been FDA approved and to its favorable tolerability profile.21-23 Furthermore, since many veterans receive non-nucleoside reverse transcriptase inhibitor-based regimens as first line treatment, providers may have been moving to darunavir-based regimens as a second line regimen rather than other protease-inhibitor-based regimens. According to VHA criteria in place during the time of the evaluation period, veterans must have first failed a protease-inhibitor-based regimen before initiating darunavir. Several months after the evaluation period ended, darunavir received FDA approval for use in antiretroviral naive-patients and is now recommended as a preferred first-line agent for both naïve and experienced patients in the most recent DHHS recommendations.8 VHA darunavir criteria have since been archived, and this agent is currently available for both antiretroviral naive and experienced veterans as a first line protease inhibitor in accordance with DHHS recommendations.

Because of the rapid release of the criteria after FDA approval and the inherently limited number of patients for whom these agents are indicated, few veterans received enfuvirtide and tipranavir prior to the dissemination of criteria. Thus, reliable comparisons of adherence to VHA guidelines pre- versus post-criteria implementation could not be made. However, we felt it was important to include these drugs to see if adherence to the criteria changed over time, finding that it did not. Unlike the other agents evaluated, the standard of care and DHHS guideline recommendations for use of enfuvirtide and tipranavir did not change over the evaluation period, nor did VHA criteria. This consistency in guidelines may explain why no significant changes in adherence to the VHA criteria occurred over the course of the evaluation period.

The majority of veterans included in this study received atazanavir, and the atazanavir evaluation period was one of the longest evaluated. The availability of prescribing data on atazanavir over a long period of time offers a unique perspective on provider adherence to VHA guidelines of a highly prescribed agent whose place in therapy evolved over the evaluation period. Few antiretroviral-naïve patients received atazanavir either pre-criteria or early-criteria; 92% of the antiretroviral-naïve veterans who received atazanavir received it in the late-criteria period.

Touted for its lack of effect on lipids,4,5,7 atazanavir offered potential benefits to patients who had hyperlipidemia or significant cardiovascular disease. Although atazanavir was available to antiretroviral-naive veterans, few received atazanavir in the pre-criteria period, and of those that did, less than one-half met VHA criteria for cardiovascular disease or risk factors. This pattern changed in the post-criteria period, when more antiretroviral-naïve patients received atazanavir (particularly in the late-criteria period), and more patients being prescribed atazanavir met VHA cardiovascular risk criteria, although the difference was not statistically significant. This therapeutic niche for atazanavir, in addition to its favorable once-daily administration, made atazanavir a more attractive agent to patients and providers. In 2006, DHHS guidelines changed atazanavir to a preferred agent.8 VHA atazanavir criteria were revised to reflect the change in the DHHS guidelines; atazanavir could be used in any HIV-infected veteran but was preferred in veterans with cardiovascular disease or risks for cardiovascular disease. Currently, atazanavir criteria are no longer in use in VHA—atazanavir is available as a preferred protease inhibitor in accordance with current DHHS guidelines.

The change in atazanavir status in the DHHS guidelines is reflected in the adherence to VHA criteria for atazanavir use in antiretroviral-experienced patients. Over time, significantly fewer veterans met criteria for intolerance (measured as exposure) to other protease inhibitors; this change was likely a result of atazanavir being used increasingly as a first-line protease inhibitor in VHA in accordance with the DHHS guideline recommendation. Moreover, significantly more veterans who had received prior protease inhibitor therapy were being prescribed ritonavir-boosted atazanavir in accordance with both VHA and DHHS guidelines.

Since this evaluation, the VHA has developed and implemented guideline criteria for newer agents, including maraviroc, raltegravir, and etravirine. Thus far, all available antiretrovirals have been added to and remain on the VHA national formulary.
As more and more HIV medications become available, there may come a time when VHA formulary status of these agents is revisited and comes under greater scrutiny. The existence of guideline criteria and periodic assessment of provider adherence to such criteria have been helpful in lending support to arguments for keeping all antiretroviral agents available to providers and patients.

Limitations
First, this study employed an observational design and lacked a control group. The absence of a control group prevented us from examining the potential effect of other factors that may have influenced provider prescribing, such as published changes in other national guidelines or data presented at national conferences, although we realize that this information influences prescribing. This is particularly true in the rapidly changing field of HIV, in which information about antiretroviral resistance, sequencing of antiretrovirals, complex drug interactions, and adverse events is constantly evolving and influences prescribing decisions. Furthermore, as we assessed concordance only to VHA guidelines, our results do not address whether veterans that were appropriate for these medications actually received them. This is an area where future study may be warranted.

Second, the lack of a standardized method to ensure guideline criteria enforcement at the local facility level creates an obstacle in the ability to assess provider adherence because some facilities may be more lenient in allowing providers to prescribe outside criteria. The small sample sizes in the target medication groups, particularly enfuvirtide and tipranavir in the pre-criteria and early-criteria periods, limited our ability to perform statistical analyses comparing the pre-criteria and post-criteria periods.

Third, we did not assess outcomes (virologic or immunologic) in veterans who did or did not meet criteria, nor did we assess physician or patient characteristics as predictors of adherence with the guidelines. This assessment might have provided further information about the implementation of criteria and potential benefits of identifying veterans who would be most likely to have successful outcomes on the target antiretroviral. Because we focused only on prescribing of specific antiretrovirals, we cannot comment on prescribing of other agents in accordance with guidelines or criteria.

Fourth, although this study sample represents national VHA data, provider prescribing observed in this evaluation may not be generalizable outside of VHA. Other institutions may have different guidelines and criteria or policies relating to prescribing of antiretrovirals. HIV-infected veterans are typically male, 50 to 60 years of age, and often have other chronic diseases requiring pharmacologic treatment that might affect the selection of antiretrovirals; thus, prescribing patterns for veterans may differ from those for younger HIV-infected individuals or those seen by other health care systems.

Conclusions
After implementation of antiretroviral specific guideline criteria, the proportion of veterans prescribed a target antiretroviral medication in accordance with the guidelines varied by agent and improved only for atazanavir. For agents for which provider adherence to evidence-based criteria is high, implementation of guidelines may not significantly change prescribing patterns. Although adherence to criteria for atazanavir, enfuvirtide, and tipranavir generally improved or persisted after guideline implementation, adherence to criteria for darunavir waned over time; these later prescribing patterns may have reflected changing practice patterns and the need for updated criteria. It is important that institutional guidelines be reassessed periodically to address changes in available evidence, including additional information and availability of newer, better tolerated agents so that providers continue to use highly specialized medications appropriately yet in accordance with the current standard of care. An ongoing process of revisiting and updating criteria is especially important for HIV due to the speed with which new information becomes available.

Authors

PAMELA S. BELPERIO, PharmD, is National Public Health Clinical Pharmacist; LARRY A. MOLE, PharmD, is Director; DEREK B. BOOTHROYD, PhD, is Senior Statistician; and LISA I. BACKUS, MD, PhD, is Clinical Manager, HIV and HCV Clinical Case Registry, Center for Quality Management in Public Health, Department of Veterans Affairs, Palo Alto, California.

AUTHOR CORRESPONDENCE: Pamela S. Belperio, PharmD, Center for Quality Management in Public Health, Department of Veterans Affairs, 3801 Miranda Ave. M/C 132, Palo Alto, CA 94304. Tel.: 310.441.0251; E-mail: pamela.belperio@va.gov

DISCLOSURES
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Study concept and design were contributed primarily by Belperio and Mole. The authors shared responsibility for data collection and data interpretation. Belperio wrote the manuscript with assistance from Backus. The revision was made primarily by Belperio. The authors would like to acknowledge Gale Yip, Health Science Specialist at the Center for Quality Management in Public Health, Department of Veterans Affairs, for her assistance in preparation of this manuscript.

REFERENCES


Critical Review of Prasugrel for Formulary Decision Makers

Jeremy A. Schafer, PharmD; Nicole K. Kjesbo, PharmD, BCPS; and Patrick P. Gleason, PharmD, BCPS, FCCP

ABSTRACT

BACKGROUND: Cardiovascular disease, including acute coronary syndromes (ACS) comprising ST-elevation and non-ST-elevation myocardial infarction (STEMI/NSTEMI) and unstable angina (UA), remains the leading cause of death in the United States. The direct and indirect costs of cardiovascular disease are estimated to surpass $165 billion in 2009. Antiplatelet pharmacotherapy has been shown to reduce ACS-related death and is part of the American College of Chest Physicians (ACCP) and the American College of Cardiology/American Heart Association (ACC/AHA) treatment guideline recommendations.

OBJECTIVE: To provide formulary decision makers with information on the pharmacokinetics and pharmacodynamics of the thienopyridine antiplatelet agent prasugrel as well as an analysis of available efficacy and safety data and its risk-benefit profile in comparison with clopidogrel.

METHODS: Literature search for information on prasugrel with a focus on (a) the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction (TRITON-TIMI) 38 trial, (b) briefing documents from the FDA available as of March 1, 2009, and (c) ongoing phase III studies of prasugrel.

RESULTS: TRITON-TIMI 38 was a double-blind, randomized superiority study involving 13,608 patients with moderate- to high-risk acute coronary syndromes with scheduled percutaneous coronary intervention (PCI). TRITON-TIMI 38 data were available in a published manuscript and in an FDA review. Study patients were randomized to either prasugrel or clopidogrel once daily. The primary end point (composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke) occurred in 643 patients (9.9%) in the prasugrel group and 781 patients (12.1%) in the clopidogrel group (HR = 0.82, 95% CI = 0.73-0.93, P = 0.002). Non-coronary artery bypass graft (non-CABG) TIMI major hemorrhage occurred in 146 patients (2.4%) in the prasugrel group compared with 111 patients (1.8%) in the clopidogrel group (HR = 1.32, 95% CI = 1.03-1.68, P = 0.03). A subanalysis of the TRITON-TIMI 38 trial data revealed a net harm for patients with a prior history of stroke or transient ischemic attack (TIA) when treated with prasugrel (HR = 1.54, 95% CI = 1.02-2.32, P = 0.04). Combination prasugrel and aspirin is currently being studied in comparison with clopidogrel and aspirin for the treatment of UA/NSTEMI patients that are medically managed.

CONCLUSIONS: For every 1,000 patients treated with prasugrel instead of clopidogrel, a total of 24 end points would be prevented at the cost of 10 additional bleeding events. On February 3, 2009, the FDA Cardiovascular and Renal Drugs Advisory Committee deemed this to be an acceptable risk-benefit profile. The committee recommended a label contraindication for patients with prior history of stroke or transient ischemic attack or stroke. Treatment versus time analyses demonstrated both early and sustained benefit for prasugrel compared with clopidogrel. However, prasugrel was associated with fewer cardiovascular events prevented per bleeding case the longer the duration of therapy. The study population of TRITON-TIMI 38 was limited to patients undergoing PCI. Managed care decision makers should consider specific criteria limiting prasugrel use to health plan members with characteristics similar to the study population in TRITON-TIMI 38 that benefited from treatment and avoiding use in patients with prior history of stroke or TIA. More data are needed before prasugrel can be recommended in patient groups not addressed by TRITON-TIMI 38.

What is already known about this subject

• Cardiovascular disease is the leading cause of death in the United States. The estimated direct and indirect cost of cardiovascular disease is $165.4 billion in 2009.
• American College of Chest Physicians (ACCP) and the American College of Cardiology/American Heart Association (ACC/AHA) treatment guidelines recommend the use of antiplatelet medications (aspirin, clopidogrel) for patients presenting with unstable angina (UA), non-ST-elevation myocardial infarction (NSTEMI) and ST-elevation myocardial infarction (STEMI). Aspirin (75 mg-325 mg) is recommended indefinitely, and clopidogrel (300 mg loading dose and 75 mg once daily maintenance) is recommended for use up to 12 months. A 600 mg loading dose of clopidogrel is recommended in select populations (i.e., NSTEMI patients undergoing percutaneous coronary intervention [PCI]).
• Prasugrel is a thienopyridine being studied for the treatment of acute coronary syndromes (ACS).

What this review adds

• Prasugrel demonstrated significantly enhanced reductions in the composite end point of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke compared with clopidogrel in the TRITON-TIMI 38 trial. Prasugrel was also associated with a significantly higher risk of bleeding, including fatal bleeding compared with clopidogrel.
• For each 1,000 patients treated with prasugrel instead of clopidogrel, a total of 24 cardiovascular end points would be prevented at the expense of 10 bleeding events. The FDA Cardiovascular and Renal Drugs Advisory Committee considered this to be a favorable risk benefit profile and unanimously voted (9-0) for approval of prasugrel.
• Patients with a prior history of stroke or transient ischemic attack (TIA) had worse outcomes on prasugrel compared with the rest of the study group. The FDA Cardiovascular and Renal Drugs Advisory Committee recommended that prasugrel be contraindicated in patients with history of stroke or TIA.
• The benefit of prasugrel post-PCI may vary with time. For patients with STEMI, the difference in primary cardiovascular end points prevented between prasugrel and clopidogrel was greatest at 18 days. The difference was sustained but did not increase through 450 days in STEMI patients. Patients with NSTEMI experienced sustained increases in benefit through 450 days. Fewer cardiovascular end points may be prevented per bleeding event with extended therapy.
• Prasugrel has been studied in a limited ACS population undergoing PCI. Managed care decision makers should consider limiting use of prasugrel to patients who are representative of the TRITON-TIMI 38 population that showed benefit until more data are available in other patient groups. Patients likely to benefit include those younger than 75 with no history of stroke and undergoing PCI (not coronary artery bypass graft [CABG]).
A critical review of prasugrel for formulary decision makers

Acut e coronary syndromes (ACS) comprise non-ST elevation myocardial infarction (NSTEMI), unstable angina (UA), and ST-elevation myocardial infarction (STEMI).1 Percutaneous coronary intervention (PCI), a therapeutic procedure to treat stenotic coronary arteries, is recommended for both STEMI and UA/NSTEMI by the American College of Cardiology/American Heart Association (ACC/AHA) and the American College of Chest Physicians (ACCP).2-6

Cardiovascular disease (CVD) is the leading cause of death in the United States with 1 of every 2.8 deaths attributed to CVD.1,7,8 In 2006, ACS was the discharge diagnosis for more than 1.3 million hospitalizations. Of these, 810,000 were diagnosed with myocardial infarction (MI) and 537,000 were diagnosed with UA.7 Additionally, an estimated 1,313,000 inpatient PCI procedures, 448,000 inpatient bypass procedures, 1,115,000 inpatient diagnostic cardiac catheterizations, 114,000 inpatient implantable defibrillators, and 418,000 pacemaker procedures were performed for inpatients in the United States during 2006.9 The estimated direct and indirect cost of CVD for 2009 is $165.4 billion.1

According to the ACC/AHA, PCI is recommended for most patients presenting with UA/NSTEMI.2 A more conservative approach such as medical therapy may be recommended for UA/NSTEMI patients with a low-risk score or based upon patient or physician preference in absence of high-risk features.10 Patients that present with STEMI are also candidates for PCI.10 Data from the CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the ACC/AHA Guidelines) Quality Improvement Initiative (March 2000-September 2002) revealed that only 26.4% of high-risk NSTEMI ACS patients underwent PCI within 48 hours following presentation.11 Current ACCP and ACC/AHA treatment guidelines recommend the use of antiplatelet medications for patients presenting with UA, NSTEMI, and STEMI. In addition to indefinite aspirin (75 mg-325 mg daily) therapy, clopidogrel (300 mg loading followed by 75 mg daily maintenance) is recommended for up to 12 months for the majority of patients for the secondary prevention of ischemic events following an ACS.3-6 A 600 mg loading dose of clopidogrel is recommended in certain populations (i.e., NSTEMI patients undergoing PCI; Table 1).3

Like clopidogrel, prasugrel is a thienopyridine adenosine diphosphate (ADP) receptor antagonist that irreversibly inhibits platelet activation and aggregation.10 Prasugrel is approximately 10-fold more potent than clopidogrel and 100-fold more potent than ticlopidine in inhibiting platelet aggregation, inhibiting thrombus formation, and prolonging bleeding times.10 The active metabolites of prasugrel and clopidogrel appear to have antiplatelet effects that are approximately equipotent in vitro.10 Clinical studies have provided significant information regarding the pharmacokinetics, pharmacodynamics, safety, and efficacy of prasugrel. The objective of this article is to provide a critical review of these aspects and provide managed care decision makers with insights regarding the risks and benefits of prasugrel.

Pharmacokinetics and Pharmacology

The bioavailability of prasugrel exceeds 79%.10 The peak plasma concentration of the active metabolite occurs 30 minutes after dosing.10,12 The parent compound is not detectable in the plasma. Protein binding is estimated to be 98% with an apparent volume of distribution ranging from 30 L to 84 L.10 Prasugrel is cleared via the liver and kidney with an estimated clearance between 73 L per hour and 266 L per hour.10 Approximately 68% of the dose is excreted in the urine and 27% in the feces as inactive metabolites.10,12 The half life of the active metabolite of prasugrel is 7.4 hours (range 2-15 hours) compared with 8 hours for the active metabolite of clopidogrel.10,12 Repeated dosing of prasugrel 10 mg daily did not result in accumulation.10

Following oral administration, prasugrel is metabolized by esterases in the blood and intestines to an inactive thiolactone.14 Cytochrome P (CYP) enzymes, principally 3A4 and 2B6, convert the thiolactone to the active metabolite R-138727.10,14-16 The parent molecule is not active in vitro.13 Similarly, clopidogrel is converted from the inactive parent compound to the active metabolite via the CYP system in a 2-step process compared with one for prasugrel.14 R-138727, like the active metabolite of clopidogrel, binds irreversibly to the P2Y12 ADP receptor site, causing inhibition of platelet aggregation for the life of the platelet.14,16

The PRINCIPLE-TIMI 44 trial randomized patients undergoing planned PCI to treatment with prasugrel or clopidogrel within 1 hour of PCI. The treatment regimens were prasugrel 60 mg loading dose and 10 mg daily maintenance dose (n = 102) or clopidogrel 600 mg loading dose and 150 mg daily maintenance dose (n = 99) for 14 days.17 Clopidogrel 600 mg has demonstrated more rapid platelet inhibition, faster onset, and fewer nonresponders compared with the standard 300 mg dose.17 PRINCIPLE-44 was not powered to be a clinical end point study. The primary end point was the difference in inhibition of platelet aggregation (IPA) between prasugrel and clopidogrel at 6 hours and 14 days.17 IPA at 6 hours is clinically relevant as ACC/AHA guidelines recommend that clopidogrel be administered at least 6 hours prior to planned catheterization or PCI.2 The IPA at 6 hours was significantly greater with prasugrel 60 mg (74.8±13.0%) compared with clopidogrel 600 mg (31.8±21.1%) (P<.001).17 This difference was apparent at 30 minutes (30.8±29.0% prasugrel vs. 4.9±13.2%; P<0.001).17 At day 14±2, the IPA was significantly greater with prasugrel 10 mg (61.3±17.8%) compared with clopidogrel 150 mg (46.1±21.3%) (P<.001).17

Drug Interactions

A retrospective cohort study (n=8,205) found concomitant use of clopidogrel and proton-pump inhibitor (PPI) after hospital discharge for ACS was associated with a significant increased risk of adverse outcomes, including increased risk of death or rehospitalization for ACS, higher risk of hospitalizations for recurrent ACS, and more revascularization procedures than use of clopidogrel without PPI.18 An open-label, 4-period crossover
The Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction (TRITON-TIMI) 38 compared prasugrel with clopidogrel in patients with ACS and scheduled PCI. Data from TRITON-TIMI 38 were available as a published manuscript and as an FDA review. Inclusion criteria for patients with UA or NSTEMI were ischemic symptoms lasting 10 minutes or more and occurring within 72 hours before randomization, a TIMI risk score of 3 or more, and either ST segment deviation of 1 mm or more or elevated levels of a cardiac biomarker of necrosis. Patients with STEMI could be enrolled within 12 hours after onset of symptoms if PCI was planned within 14 days. Exclusion criteria included increased risk of bleeding, anemia, thrombocytopenia, history of pathologic intracranial findings, or use of a thienopyridine within 5 days before enrollment. A total of 13,608 patients were enrolled including 10,074 with moderate- to high-risk unstable angina or non-ST-elevation myocardial infarction (NSTEMI/UA) and 3,534 with ST-elevation myocardial infarction (STEMI). Patients were randomized to prasugrel 60 mg as a loading dose and 10 mg once daily maintenance or clopidogrel 300 mg loading dose and 75 mg once maintenance or clopidogrel 300 mg loading dose and 75 mg once

### TABLE 1 Clopidogrel and Aspirin Dosing per AHA/ACC Guidelines for ACS

<table>
<thead>
<tr>
<th>Patient Group</th>
<th>Dose and Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients presenting with NSTEMI ACS without aspirin allergy</td>
<td>Immediate aspirin 162 to 325 mg orally and then daily oral aspirin 75 to 100 mg</td>
</tr>
<tr>
<td>Patients presenting with NSTEMI ACS with aspirin allergy</td>
<td>Clopidogrel 300 mg oral bolus, followed by 75 mg daily indefinitely</td>
</tr>
<tr>
<td>For NSTEMI ACS patients who are at moderate or greater risk for an ischemic event and who will undergo an early invasive management strategy</td>
<td>“Upstream” treatment either with clopidogrel (300 mg oral bolus, followed by 75 mg per day) or a small-molecule IV GP IIb/IIIa inhibitor (eptifibatide or tirofiban)</td>
</tr>
<tr>
<td>For NSTEMI ACS patients who are at moderate or greater risk for an ischemic event and for whom an early conservative or delayed invasive strategy of management is to be used</td>
<td>Upstream treatment with clopidogrel (300 mg oral bolus, followed by 75 mg daily)</td>
</tr>
<tr>
<td>For NSTEMI ACS patients who undergo PCI</td>
<td>Loading dose of 600 mg of clopidogrel given at least 2 hours prior to planned PCI followed by 75 mg daily</td>
</tr>
<tr>
<td>If patients cannot tolerate aspirin, loading dose of clopidogrel 600 mg be given at least 24 hours prior to planned PCI</td>
<td></td>
</tr>
<tr>
<td>Acute STEMI with or without fibrinolytic therapy</td>
<td>Aspirin 160-325 mg orally at initial evaluation, then 75 to 162 mg daily indefinitely</td>
</tr>
<tr>
<td>Acute STEMI</td>
<td>Dosing if patients receive fibrinolytic agents or no reperfusion therapy: 75 years or younger: 300 mg Older than 75 years: 75 mg Followed by: 75 mg daily for 28 days</td>
</tr>
<tr>
<td>Acute STEMI with no coronary stent</td>
<td>Clopidogrel 75 mg daily up to 1 year</td>
</tr>
<tr>
<td>Acute STEMI undergoing primary PCI</td>
<td>Aspirin + clopidogrel with recommended initial dosing of at least 300 mg, followed by 75 mg daily</td>
</tr>
</tbody>
</table>


The 600 mg loading dose of clopidogrel more rapidly inhibits platelet aggregation, but the additive clinical efficacy and the safety of higher oral loading doses have not been rigorously established.

ACS = acute coronary syndromes; AHA/ACC = American Heart Association/American College of Cardiology; GP = glycoprotein; NSTEMI = non-ST-elevation myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST-elevation myocardial infarction.

Critical Review of Prasugrel for Formulary Decision Makers
The primary efficacy end point was the composite of death from cardiovascular causes, nonfatal MI, or nonfatal stroke. The key secondary end point was the composite of death from cardiovascular causes, nonfatal MI, and need for urgent target revascularization. The primary end point was similar to those studied for clopidogrel. The CURE study compared clopidogrel plus aspirin with aspirin alone for the composite end point of cardiovascular death, nonfatal MI, and stroke in patients with UA/NSTEMI. The PCI-CLARITY study analyzed the same end point between PCI and 30 days post for clopidogrel in patients with STEMI.

The primary end point occurred in 643 patients (9.9%) in the prasugrel group and 781 patients (12.1%) in the clopidogrel group (HR=0.81, 95% CI=0.73-0.90, P<0.001). The number needed to treat (NNT) with prasugrel versus clopidogrel to avoid 1 primary end point was 46. Superiority of prasugrel was evident as early as 3 days with 4.7% of patients having the primary end point compared with 5.6% in the clopidogrel group (HR=0.82, 95% CI=0.71-0.96, P=0.01). This difference persisted to the end of the study (5.6% prasugrel group vs. 6.9% clopidogrel group; HR=0.8, 95% CI=0.7-0.93, P=0.003). Prasugrel achieved significantly improved outcomes compared with clopidogrel for several secondary end points (Table 2).

A subanalysis of TRITON-TIMI 38 involving the STEMI trial population was performed by Montalescot et al. (2009). The analysis included 3,534 patients stratified by those receiving PCI within 12 hours of symptom onset (primary PCI) and those receiving PCI 12 hours to 14 days after symptom onset (secondary PCI). The primary end point at 15 months occurred in 174 patients (10.0%) in the prasugrel group compared with 216 patients (12.4%) in the clopidogrel group (HR=0.79, 95% CI=0.65-0.97, P=0.022; Table 2). Prasugrel was significantly better than clopidogrel for the primary end point in patients with secondary PCI (P=0.015) but not primary PCI (P=0.266). At 15 months, there was no difference between prasugrel and clopidogrel in cardiovascular death (2.4% vs. 3.4%, P=0.129) or all-cause death (3.3% vs. 4.3%, P=0.113). The authors of the TRITON-TIMI 38 trial emphasized that the study was not prospectively designed or powered to show superiority of prasugrel over clopidogrel in the STEMI cohort alone.

The TRITON-TIMI 38 results were driven by the difference in nonfatal MI between prasugrel (475 events, 7.3%) and clopidogrel (620 events, 9.5%) (P<0.001). The NNT was 48.
Cardiovascular death and nonfatal stroke outcomes were not significantly different between the prasugrel and clopidogrel groups (Table 2). These data led the FDA reviewer to recommend that prasugrel’s indication be limited to prevention of MI post PCI.10

Safety
Safety end points in the TRITON-TIMI 38 trial included TIMI major bleeding not related to coronary artery bypass grafting (CABG), non-CABG related TIMI life-threatening bleeding, and TIMI major and minor bleeding. Non-CABG TIMI major hemorrhage occurred in 146 patients (2.4%) in the prasugrel group compared with 111 patients (1.8%) in the clopidogrel group (HR = 1.32, 95% CI = 1.03-1.68, P = 0.03).13 Prasugrel was associated with a significantly higher rate of life-threatening bleeds (85 patients, 1.4%) compared with clopidogrel (56 patients, 0.9%) (HR = 1.52, 95% CI = 1.08-2.13, P = 0.01).13 Fatal TIMI major hemorrhage occurred in 21 patients (0.4%) in the prasugrel group compared with 5 patients (0.1%) in the clopidogrel group (HR = 4.19, 95% CI = 1.58-11.11, P = 0.002).13 All 5 fatal bleeds in the clopidogrel group were intracranial hemorrhage. Fatal bleeding sites in the prasugrel group included intracranial hemorrhage (9 patients), gastrointestinal (5 patients), puncture and surgical sites (2 patients each), retroperitoneal locations (2 patients), and intra-abdominal location (1 patient).13

CABG-related TIMI major bleeding occurred in 24 patients (13.4%) in the prasugrel group compared with 6 patients (3.2%) in the clopidogrel group (HR = 4.73, 95% CI = 1.9-11.82, P < 0.001).13 Fatal CABG-related bleeding occurred in 2 patients in the prasugrel group and none (0) in the clopidogrel group.13 An FDA review concluded that CABG-related TIMI major bleeding associated with prasugrel was a cause for concern in the setting of urgent CABG. On February 3, 2009, the FDA Cardiovascular and

### Table 3: Incidence of Bleeding Events in TRITON-TIMI 38

<table>
<thead>
<tr>
<th>Bleeding End Point</th>
<th>Prasugrel (n = 6,741)</th>
<th>Clopidogrel (n = 6,716)</th>
<th>HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIMI fatal</td>
<td>0.3% (21)</td>
<td>0.1% (5)</td>
<td>4.19 (1.58-11.1)</td>
<td>0.002</td>
</tr>
<tr>
<td>TIMI life threateni</td>
<td>1.3% (n = 85)</td>
<td>0.8% (56)</td>
<td>1.52 (1.08-2.13)</td>
<td>0.015</td>
</tr>
<tr>
<td>TIMI major</td>
<td>2.2% (146)</td>
<td>1.7% (111)</td>
<td>1.32 (1.03-1.68)</td>
<td>0.029</td>
</tr>
<tr>
<td>TIMI minor</td>
<td>2.4% (164)</td>
<td>1.9% (125)</td>
<td>1.31 (1.04-1.66)</td>
<td>0.022</td>
</tr>
<tr>
<td>TIMI minimal</td>
<td>6.8% (460)</td>
<td>4.7% (314)</td>
<td>1.47 (1.28-1.70)</td>
<td>0.022</td>
</tr>
</tbody>
</table>

### Table 4: Incidence of Bleeding Events in TRITON-TIMI 38 Subanalysis of STEMI Patients

<table>
<thead>
<tr>
<th>Bleeding End Point</th>
<th>Prasugrel (n = 1,769)</th>
<th>Clopidogrel (n = 1,765)</th>
<th>HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIMI fatal</td>
<td>0.45% (7)</td>
<td>0.13% (2)</td>
<td>3.48 (0.72-16.75)</td>
<td>0.097</td>
</tr>
<tr>
<td>TIMI life threatening</td>
<td>1.3% (20)</td>
<td>1.1% (18)</td>
<td>1.11 (0.59-2.10)</td>
<td>0.750</td>
</tr>
<tr>
<td>TIMI major</td>
<td>2.4% (38)</td>
<td>2.1% (34)</td>
<td>1.11 (0.70-1.77)</td>
<td>0.645</td>
</tr>
</tbody>
</table>

Source: U.S. Food and Drug Administration. February 3, 2009. 10

*aTIMI life-threatening bleeding = a subset of TIMI major bleeding in which “life-threatening” is fatal, or causes hypotension that requires intravenous inotropic agents, or surgical intervention, or 4 or more units of blood or packed red blood cells within 48 hours, or symptomatic ICH.
*bTIMI major bleeding = any ICH or overt bleeding associated with an Hb decrease from baseline of 5 gm or more per dL.
*cTIMI minor bleeding = clinically overt bleeding associated with an Hb decrease from baseline equal to or greater than 3 gm per dL but less than 5 gm per dL.
*dTIMI minimal bleeding = an Hb decrease from baseline less than 3 gm per dL.

CABG = coronary artery bypass graft; Hb = hemoglobin; HR = hazard ratio; ICH = intracranial hemorrhage; TIMI = thrombolysis in myocardial infarction; TRITON = Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel.
Renal Drugs Advisory Committee recommended that prasugrel be avoided around CABG or surgical procedures. The committee also recommended that preference to prasugrel be given only when coronary anatomy was known. Bleeding results from TRITON-TIMI 38 can be found in Tables 3 and 4.

According to the FDA review, prasugrel may not be appropriate for patients with a prior history of transient ischemic attack (TIA) or stroke. A subanalysis of the TRITON-TIMI 38 trial data revealed a net harm for this patient group when treated with prasugrel (HR=1.54, 95% CI=1.02-2.32, P=0.04). A total of 518 patients with prior history of TIA or stroke were enrolled in TRITON-TIMI 38 and randomized to prasugrel (n=262) or clopidogrel (n=256). In contrast to the overall study results that found prasugrel superior to clopidogrel for the primary end point, 47 patients (17.9%) with history of stroke or TIA in the prasugrel group and 35 patients (13.7%) in the clopidogrel group experienced a primary end point event (HR=1.38, 95% CI=0.89-2.13, P=0.15). Stroke occurred in 17 (6.9%) and 3 patients (1.2%) in this cohort treated with prasugrel and clopidogrel, respectively (HR=5.64, 95% CI=1.65-19.3, P=0.002). In patients without a prior history of stroke or TIA, a stroke occurred in 58 (0.9%) and 68 subjects (1.0%) treated with prasugrel and clopidogrel, respectively (HR=0.85, 95% CI=0.6-1.21, P=0.36). Additionally, patients with a recent history of hemorrhagic stroke or ischemic stroke (up to 3 months prior to screening) were excluded from TRITON-TIMI 38. The safety concerns regarding use of prasugrel in this patient group led the Cardiovascular and Renal Drugs Advisory Committee to recommend that prasugrel be contraindicated in patients with prior history of stroke or TIA.

Two other patient subgroups were identified for additional analysis in TRITON-TIMI 38: patients weighing ≤60 kg or 75 years of age and older. Patients with body weight of 60 kg or less experienced no net clinical benefit with prasugrel compared with clopidogrel (HR=1.03, 95% CI=0.69-1.53, P=0.89). The FDA review stated that while the relative risk for bleeding with prasugrel was higher in this subgroup (HR=1.72, 95% CI=1.07-2.79, P<0.05), the body weight cutoff was arbitrary and the subgroup was small (n=856). Patients 75 years of age and older (n=1,809) had no net benefit from prasugrel (HR=0.99, 95% CI=0.81-1.21, P=0.92). Non-CABG TIMI major or minor bleeding occurred in 80 (9.0%) and 62 patients (6.9%) 75 years of age and older in the prasugrel and clopidogrel groups, respectively (HR=1.35, 95% CI=0.97-1.88, P=0.078). Of these patients, 9 (1.0%) in the prasugrel group and 1 (0.1%) in the clopidogrel group died of hemorrhage.

**Managed Care Considerations**

Selected efficacy and safety end points including death from any cause, nonfatal MI, nonfatal stroke, and TIMI major bleed were used in an analysis to determine net clinical benefit. The analysis favored patients in the prasugrel group (12.2%) compared with those treated with clopidogrel (13.9%) (HR=0.87, 95% CI=0.79-0.95, P=0.004). Death from cardiovascular causes or fatal hemorrhage occurred in 142 (2.2%) and 151 patients (2.4%) in the prasugrel and clopidogrel groups, respectively (HR=0.94, 95% CI=0.75-1.18, P=0.59). Wiviott et al. stated that the number needed to treat with prasugrel compared with clopidogrel to avoid 1 primary efficacy end point was 46. The number needed to harm for 1 excess non-CABG related TIMI major hemorrhage was 167, and 10 for 1 excess CABG-related TIMI major hemorrhage.

The FDA review displayed the risk-benefit profile in quantitative terms. For each 1,000 patients treated with prasugrel instead of clopidogrel, there were the following:

- 24 cardiovascular end points prevented:
  - 21 nonfatal myocardial infarctions
  - 3 cardiovascular deaths
  - 0 strokes

10 excess TIMI major or minor bleeding events would occur, comprising the following:

- 2 fatal bleeding events
- 3 nonfatal TIMI major bleeding events (intracranial hemorrhage or a hemoglobin (Hb) decrease greater than 5 gm per dL)
- 5 TIMI minor bleeds (Hb decrease between 3 gm and 5 gm per dL)

The FDA review division stated that this was a worthwhile risk-benefit profile. On February 3, 2009, the Cardiovascular and Renal Drugs Advisory Committee voted unanimously (9-0) for approval of prasugrel to treat patients with ACS.

Hospital and managed care formulary decision makers may view prasugrel differently based on the efficacy and safety in relation to time. The FDA conducted an analysis of the TRITON-TIMI 38 data to determine how prasugrel affects clinical end points over time. A plot of the treatment difference between prasugrel and clopidogrel was generated for the STEMI and NSTEMI/UA patient groups over 450 days (Figure 1). The data showed that for patients with STEMI, the maximum benefit was achieved at 18 days and remained constant thereafter. In contrast, the benefit for patients experiencing NSTEMI/UA continued to grow throughout the study.

An analysis of end points prevented per bleeding event was also conducted. The FDA review stated that the benefit between efficacy and bleeding was greatest at day 12 and gradually declined to day 80. Between days 80 and 180, the relationship was constant. These data show that the risk-benefit appears to be greatest early in therapy with prasugrel, with fewer end points prevented per bleed as therapy is continued (Figure 2). Managed care decision makers should consider careful patient selection and duration of use to maximize the benefit-risk profile of prasugrel.
Prasugrel demonstrated superiority for multiple cardiovascular end points compared with standard-dose clopidogrel in a randomized, double blind superiority trial but was also associated with an increased bleeding risk, including fatal bleeds. Patients with a prior history of stroke or TIA are at risk of bleeding with prasugrel, and a contraindication in this population has been recommended. ACS continues to be 1 of the leading causes of morbidity and mortality in the United States; its prevalence underscores the need to provide safe, effective therapies.

The formulary decision maker has several issues to consider regarding addition of prasugrel. Patents on clopidogrel are anticipated to expire in 2011 and be followed by the release of low cost generics. However, history has shown that generic launches may be delayed when multiple patents are present. Prasugrel has only 1 phase III clinical outcomes trial and will likely not be addressed immediately in cardiovascular guidelines. Questions remain regarding optimal dosing and proper patient selection. Clopidogrel is indicated for patients with recent MI, stroke, or established peripheral artery disease and for patients with ACS who are medically managed or following PCI/CABG. Additionally, clopidogrel is recommended in combination with aspirin for secondary prevention of cardiovascular events following ACS. The added bleeding risks and negative findings in patients with prior history of stroke indicate that prasugrel cannot completely replace clopidogrel.

Prasugrel requires a risk-benefit approach when considering placement on the formulary. The benefit of cardiovascular end points prevented compared with bleeding events was largest in the first weeks. Hospital formulary decision makers should consider the benefit since patients will be initiated on therapy in this setting. Data on the use of prasugrel in ACS patients outside the inclusion criteria of TRITON-TIMI 38 are scarce. A phase III clinical trial (TRILOGY ACS, NCT00699998) is currently underway in which prasugrel plus aspirin is compared with clopidogrel plus aspirin in patients with UA/NSTEMI who are medically managed (do not undergo acute coronary revascularization) with estimated completion in 2011-2012. An analysis of clopidogrel prescriptions found that only 47% of patients met “literature based” criteria, and 39% met the FDA-approved indication; a similar challenge is likely to occur with prasugrel in which the drug could be hazardous in select patient populations (e.g., CABG, prior TIA/stroke).

Until more data are available in other patient groups,
managed care decision makers may consider implementing strategies ensuring that prasugrel is used in the patient population represented in TRITON-TIMI 38, with judicious monitoring of member safety. Patients likely to benefit include those younger than 75 with no history of stroke, undergoing PCI (not CAGB). Hospital decision makers may consider developing order sets supporting proper patient selection for initiation of therapy.

Authors

JEREMY A. SCHAFER, PharmD, is Manager of Formulary Development; NICOLE K. KJESBO, PharmD, BCPS, is Senior Clinical Pharmacist; and PATRICK P. GLEASON, PharmD, BCPS, FCCP, is Director of Outcomes Assessment, Prime Therapeutics LLC, Eagan, Minnesota. Patrick Gleason is also Associate Professor, College of Pharmacy, University of Minnesota, Minneapolis, Minnesota.

AUTHOR CORRESPONDENCE: Jeremy A. Schafer, PharmD, Prime Therapeutics, 1305 Corporate Center Drive, Eagan, MN 55121. Tel.: 612.777.5097; Fax: 612.777.5143; E-mail: jschafer@primetherapeutics.com

DISCLOSURES

The authors report no financial or other conflicts of interest related to the subject of this article. Prime Therapeutics, LLC, is a pharmacy benefits management company for stand-alone pharmacy plans and for health plans.

Schafer and Kjesbo conducted the literature search with assistance from Gleason. Concept, design, and data interpretation were the work of all 3 authors. Schafer was the primary writer of the manuscript with assistance from Kjesbo. The revision of the manuscript was the work of all 3 authors.

REFERENCES


BRIEF REPORT

Results of an Intervention in an Academic Internal Medicine Clinic to Continue, Step-Down, or Discontinue Proton Pump Inhibitor Therapy Related to a Tennessee Medicaid Formulary Change

Kristie L. Ramser, PharmD; Laura R. Sprabery, MD; Gale L. Hamann, PharmD; Christa M. George, PharmD; and Aaron Will, PharmD

ABSTRACT

BACKGROUND: In July 2005, the State of Tennessee Medicaid Program (TennCare) announced formulary changes for proton pump inhibitors (PPIs) to be implemented in August 2005. Prior to these changes, pantoprazole was the only preferred PPI, and there were no restrictions to its use. The revised formulary included 3 preferred PPIs (esomeprazole, lansoprazole, and omeprazole OTC), all of which required prior authorization (PA). In order to obtain an approved PA for a PPI, the patient was required to have either (a) a diagnosis of erosive esophagitis, Barrett’s esophagus, Schatzki’s ring, a pathological hypersecretory condition (e.g., Zollinger-Ellison syndrome, multiple endocrine adenoma), grade III-IV gastroesophageal reflux disease (GERD), non-steroidal anti-inflammatory drug gastropathy, significant gastrointestinal bleed; or (b) another indication for acid suppression therapy (e.g., GERD, hyperacidity in cystic fibrosis, gastric or duodenal ulcer, gastroparesis) with a history of failure of prior therapy with a histamine-2 receptor antagonist (H2-blocker). The internal medicine clinic of a regional medical center implemented an intervention to address these changes in formulary status of PPIs.

OBJECTIVE: To (a) describe the process used by an internal medicine clinic to ensure that patients requiring acid suppression therapy received appropriate treatment according to revised TennCare formulary criteria without unnecessary interruption of therapy, and (b) assess self-reported symptom control 8 months after intervention in the patients who either discontinued therapy or stepped-down to H2-blocker therapy.

METHODS: This study involved TennCare patients in an internal medicine clinic who received a new or refill prescription for pantoprazole between April 20 and June 20, 2005, from the medical center’s outpatient pharmacy. A clinical pharmacist and an internal medicine physician collaborated to develop a protocol for adjusting acid suppression therapy. A clinical pharmacist reviewed medical records for all patients identified to verify indications for acid suppression therapy and review medication history. Patient telephone interviews were also conducted for patients whose indication or medication history could not be determined by chart review. Patients who met TennCare criteria for PPI therapy were continued on PPI therapy after a PA was obtained (PA group). Patients who had a documented indication for acid suppression therapy but did not meet the PA criteria for PPI therapy were changed to H2-blocker therapy (step-down group). Patients without a documented indication for acid suppression therapy were discontinued from acid suppression therapy (discontinuation therapy group). A follow-up chart review and patient telephone interview were conducted 8 months after the intervention for patients in the step-down and discontinue therapy groups. The purpose of this follow-up review was to determine (a) the proportion of patients who were taking acid suppression therapy, (b) the type of acid suppression therapy (PPI or H2-blocker), and (c) self-report of adequate control of symptoms (defined as symptoms once weekly or less).

RESULTS: Of 135 TennCare beneficiaries who were active patients of the internal medicine clinic and received a prescription from the outpatient pharmacy for PPI therapy (pantoprazole) between April 20 and June 20, 2005, 6 patients were excluded because they reported stopping PPI therapy on their own. Of the remaining 129 patients, 18 (14.0%) did not have an indication for PPI therapy and acid suppression therapy was discontinued (discontinuation therapy group). 40 (31.0%) met the TennCare PA criteria for continuation of PPI therapy (PA group), and 71 (55.0%) did not meet the TennCare PA criteria and were stepped down to a H2-blocker (step-down group). At the 8-month follow-up, acid suppression therapy was assessed in 68 patients (21 patients were lost to follow-up): 13 patients (19.1%) had resumed PPI therapy; 38 (55.9%) were using an H2-blocker; and 17 (25.0%) were not using acid suppression therapy. Telephone interviews were completed for 45 of the 75 patients in the step-down and discontinue therapy groups who did not receive an escalation in acid suppression therapy after the initial intervention (i.e., who did not make a change from H2-blocker therapy to PPI therapy or from no acid suppression therapy to H2-blocker or PPI therapy). Twenty-eight patients (62.2%) reported symptoms once per week or less; 14 patients (31.1%) reported symptoms more often than once weekly. Symptom control was unable to be determined in 3 patients (6.7%) because of incomplete information obtained from the patient during the interview.

CONCLUSIONS: After a proactive collaboration between physicians and clinical pharmacists in response to changes in TennCare formulary criteria for PPIs, more than one-half of patients were stepped down to H2-blocker therapy, and 14% were discontinued from acid suppression therapy. Among the step-down or therapy discontinuation patients for whom data were available at the 8-month follow-up, 81% were still using either an H2-blocker or no acid suppressing therapy at all, and 19% had resumed PPI use.

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What is already known about this subject

- Between 1999 and 2004, proton pump inhibitor (PPI) use in the United States steadily increased, while the use of histamine-2 receptor antagonists (H2-blockers) steadily decreased. PPIs are frequently prescribed for inappropriate reasons and for longer than recommended treatment periods.
- PPIs are more effective at eliminating symptoms of gastroesophageal reflux disease and healing esophagitis than are H2-blockers; however, all PPIs except omeprazole OTC are more expensive than H2-blockers. Strategies for cost-effective use of PPIs include “step-up” or “step-down” PPI therapy using H2-blockers, “on demand” PPI therapy, and adding the less costly PPI omeprazole OTC to formularies.
- Reported results of step-down therapy have been conflicting. Piterman et al. (2004) reported that approximately 70% of patients whose PPI therapy is stepped-down will have relapse of symptoms within 6 months. In contrast, Inadomi et al. (2001) reported that 58% of patients whose therapy was stepped down remained asymptomatic without PPI therapy at one year.
Proton pump inhibitors (PPIs) are the most widely prescribed class of drugs used to suppress gastric acid secretion. They are used to treat numerous gastrointestinal disorders, including peptic ulcer disease (PUD), gastroesophageal reflux disease (GERD), erosive esophagitis, Zollinger-Ellison syndrome, Barrett’s esophagus, and upper gastrointestinal bleeding.

Between 1999 and 2004, PPI use in the United States steadily increased, while the use of histamine-2 receptor antagonists (H2-blockers: cimetidine, famotidine, nizatidine, ranitidine) steadily decreased. PPIs continue to be prescribed more often than H2-blockers. In 2007, esomeprazole, lansoprazole, and pantoprazole were the fourth, eighth, and thirteenth leading brand name prescription drugs dispensed in the United States, with 26.4, 20.4, and 16.1 million prescriptions, respectively. Comparatively, ranitidine and famotidine were ranked 47th and 120th for generic drugs with 13 and 3 million prescriptions dispensed, respectively, in 2007. Neither cimetidine nor nizatidine ranked among the top 200 drugs dispensed in 2007.

Esomeprazole OTC was the third leading over-the-counter brand name product sold in the United States in 2007, with over $388 million in sales. Ranitidine and famotidine ranked 77th and 111th, respectively, in sales of nonprescription agents in 2007. Nonprescription cimetidine and nizatidine were not ranked among the top 200 in 2007.

PPIs are frequently prescribed for inappropriate reasons and for longer than the recommended treatment periods. They are more effective at eliminating symptoms of GERD and healing esophagitis than H2-blockers. However, PPIs are more expensive than H2-blockers (e.g., the generic H2-blockers ranitidine, cimetidine, and famotidine cost less than $20 per month of therapy compared with more than $120 per month for the PPIs, except omeprazole OTC (less than $30 per month)). A 2005 report from the Agency for Healthcare Research and Quality showed that all PPIs at standard doses are equally effective at relieving the symptoms of GERD. This equivalence has led to an increase in the inclusion of less costly PPIs on many third-party formularies. West et al. reported that adding omeprazole OTC to a prescription drug formulary resulted in a 38% net savings to a state employee health plan in Arkansas.

Strategies to improve the cost-effectiveness of GERD treatment such as step-down, step-up, and on-demand therapy have also been recommended. Step-down therapy consists of either decreasing the PPI dose or switching to an H2-blocker in patients who have achieved symptomatic relief with PPI treatment. Step-up therapy, which has been shown to be cost-effective, consists of starting with either nonprescription or standard dose H2-blockers and increasing to high-dose H2-blockers or PPIs if symptoms are not controlled. On-demand (intermittent) therapy is the periodic use of PPIs in response to symptom recurrence following an initial symptomatic response to PPIs.

Like many payers, the Tennessee Medicaid Program (TennCare) has implemented formulary changes in an effort to provide cost-effective care. In August 2005, the TennCare Program implemented formulary changes for PPIs. Prior to these changes, pantoprazole (Protonix) was the only preferred formulary PPI, and there were no PPI prescribing restrictions. To receive PPI therapy under the new formulary guidelines, all patients were required to fail a 2-week trial of H2-blocker unless 1 of several conditions was met (Table 1). These conditions included a diagnosis of erosive esophagitis, Barrett’s esophagus, Schatzki’s ring, a pathological hypersecretory condition (e.g., Zollinger-Ellison syndrome, multiple endocrine adenoma), grade III-IV GERD, nonsteroidal anti-inflammatory drug gastropathy, or significant gastrointestinal bleed. Additionally, the prescriber was required to submit a prior authorization (PA) form via facsimile to TennCare requesting PPI therapy. For the patient to meet the H2-blocker failure criterion, the prescriber was required to document failure on the PA form.

Generic ranitidine, famotidine, nizatidine, and cimetidine were the preferred H2-blockers on the new formulary. The preferred PPIs on the revised formulary were esomeprazole, lansoprazole, and omeprazole OTC. Any of these 3 could be selected for therapy if prescribing criteria were met. TennCare allowed 30 days for prescribers to ensure that patients met the new criteria and submit the PA request. At the end of 30 days, claims for PPI therapy were rejected by TennCare for patients who did not meet the new criteria. Nonprescription (OTC) H2-blockers were not included on the TennCare formulary.

The academic internal medicine clinic at the Memphis Regional Medical Center provides approximately 15,000 patient care visits annually for about 5,100 patients. An estimated one-third of this patient population receives TennCare benefits.
discontinued therapy or stepped down to H2-blocker therapy. Acid suppression therapy received appropriate treatment according to revised TennCare formulary criteria without unnecessary interruption of therapy, and (b) assess self-reported symptom control 8 months after intervention in the patients who either discontinued therapy or stepped down to H2-blocker therapy.

Approximately 30%-40% of the clinic population obtains their prescriptions from the medical center’s outpatient pharmacy. Between July 1, 2005, and December 31, 2005, the outpatient pharmacy filled 65,363 prescriptions for 5,857 patients. Patients treated at our facility rarely purchase OTC medications because of personal financial limitations.

The internal medicine clinic is staffed by attending and resident physicians who provide care to an indigent population. Clinical pharmacists manage anticoagulation, diabetes, hypertension, and hyperlipidemia. They also work collaboratively with physicians in the clinic to aid in drug selection in order to comply with numerous third-party formularies. In response to previous TennCare formulary changes, clinical pharmacists have collaborated with physicians to develop therapeutic substitution protocols for statins, angiotensin-converting enzyme inhibitors, angiotensin II receptor blocking agents, nasal corticosteroids, and inhaled corticosteroids. These protocols were used in the outpatient pharmacy to avoid interruptions in therapy.

The purpose of this article is to (a) describe the process used by an internal medicine clinic to ensure that patients requiring acid suppression therapy received appropriate treatment according to revised TennCare formulary criteria without unnecessary interruption of therapy, and (b) assess self-reported symptom control 8 months after intervention in the patients who either discontinued therapy or stepped down to H2-blocker therapy.

### Methods

This project was approved and granted an exempt status by the University of Tennessee Health Science Center Institutional Review Board. Because the internal medicine clinic utilizes a paper-based medical chart system, it was not possible to use medical charts to identify all TennCare patients treated by the internal medicine clinic who were receiving PPI therapy. Therefore, PPI therapy for TennCare patients was identified from prescription dispensing records in the medical center’s outpatient pharmacy. A list of TennCare patients receiving new or refill prescriptions for PPI therapy with pantoprazole between April 20 and June 20, 2005, was generated from the outpatient pharmacy database. This 2-month time frame was chosen to ensure the identification of all clinic patients on PPI therapy including those who may not have adhered to obtaining prescription refills at 30-day intervals. Because pantoprazole was the only preferred PPI on both the TennCare and medical center’s formularies prior to the changes implemented in 2005, it was the only agent used to identify patients on PPI therapy.

Clinical pharmacists and the director of the internal medicine clinic collaborated to develop a protocol for adjusting acid suppression therapy (Figure 1). The protocol was designed to meet TennCare criteria. A gastroenterologist reviewed the protocol and was available for any questions that arose. A clinical pharmacist evaluated each patient identified, excluding those who were not patients of the internal medicine clinic. A medical record review was conducted to verify medication history and indications for acid suppression therapy. If the medication history or indication for acid suppression therapy were not documented in the medical record, patient telephone interviews were conducted to obtain the indication and medication history.

Three groups of patients were defined. Patients with an indication for PPI therapy that met TennCare criteria were continued on PPI therapy after obtaining a PA (PA group). All patients in the PA group were converted from pantoprazole to esomeprazole because it was the only PPI available on both the medical center’s formulary and the revised TennCare formulary. A one-to-one dose conversion was used in the transition from pantoprazole to esomeprazole. Patients with a documented indication for acid suppression therapy that did not meet the TennCare criteria for PPI therapy were changed to H2-blocker therapy (step-down group). Because ranitidine was the only H2-blocker on both the institution’s and TennCare formularies, the step-down patients were converted to ranitidine 150 milligrams (mg) twice daily or 150 mg once daily for those patients with a creatinine clearance of less than 50 milliliters (mL) per minute. Patients without a documented indication for acid suppression therapy were discontinued from therapy (discontinue therapy group).

This process was completed by July 2005, and all changes were documented in the medical record. In March 2006, a follow-up review was conducted of patients who had discontinued acid suppression therapy or stepped down to H2-blocker therapy. The review was limited to these patient groups because it was assumed that patients who had continued on PPI therapy

### Tennessee Medicaid Clinical Criteria for Use of Proton Pump Inhibitors

- Erosive esophagitis-Grade II or higher diagnosed on endoscopy within 2 months
- Barrett’s esophagus, Schatzki’s ring – diagnosed on endoscopy within last 2 years
- Pathological hypersecretory condition – diagnosed by serum gastrin and serum secretin stimulation test
- GERD-Grade III-IV diagnosed on endoscopy within last 2 years OR upper GI series or barium swallow within 1 year
- Continuing, symptomatic GERD OR atypical GERD with symptoms of chronic laryngitis, hoarseness, or cough due to reflux – failed 2-week trial of H2-blocker. Diagnosed by endoscopy within 2 years or upper GI series or barium swallow within 1 year
- NSAID gastropathy – diagnosed by endoscopy within 2 years
- Significant gastrointestinal bleeding
- Hyperacidity associated with cystic fibrosis – recent failure of H2-blocker
- Gastric or duodenal ulcer or PUD – failed 2 week trial of H2-blocker. Diagnosed by upper GI procedure within 1 month
- Gastroparesis – failed trial of prokinetic agent AND failed trial of more than 1 anti-emetic agent

The 2005 prior authorization criteria for PPI therapy required attestation from the prescriber that the patient failed a trial of H2-blocker therapy. GERD = gastroesophageal reflux disease; GI = gastrointestinal; H2 = histamine-2; NSAID = nonsteroidal anti-inflammatory drug; PPI = proton pump inhibitor; PUD = peptic ulcer disease.
Results of an Intervention in an Academic Internal Medicine Clinic to Continue, Step-Down, or Discontinue Proton Pump Inhibitor Therapy Related to a Tennessee Medicaid Formulary Change

**FIGURE 1** Protocol for Evaluating Patients on PPI Therapy

- **Active clinic patients** (estimated 5,100)
  - TennCare beneficiaries with prescription for pantoprazole at outpatient pharmacy
    - n = 135
  - Patient terminated PPI therapy
    - n = 6
  - Patients included in evaluation
    - n = 129
  - Indication for PPI therapy

  - Yes
    - n = 111
    - TennCare criteria for PPI therapy met
      - n = 40
      - PA group (PA obtained for esomeprazole)
    - TennCare criteria for PPI therapy not met
      - n = 71
      - Step-down group (Changed to H2-blocker)
  - No
    - n = 18
    - Discontinue therapy group

  - Follow-up group
    - n = 89
    - Chart review
      - n = 68
    - Telephone interview
      - n = 45
      - Unable to determine level of symptom control
        - n = 3
      - Adequate symptom control
        - n = 28
      - Inadequate symptom control
        - n = 14

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*184 TennCare patients had a prescription filled for pantoprazole at the medical center's outpatient pharmacy between April 20 and June 20, 2005. After medical record review, 49 patients were eliminated because they were not active internal medicine clinic patients.

*To receive PPI therapy under the new TennCare guidelines, patients were required to meet 1 of the criteria in Table 1. The prescriber was also required to submit a written request for prior authorization of PPI therapy to the TennCare Program.

*The follow-up group included patients who received a step-down from PPI therapy to H2-blocker therapy or were discontinued from acid suppression therapy.

*Of 89 patients eligible for follow-up, 14 were excluded from telephone interviews because they received an escalation in acid suppression therapy after the initial intervention. Of the remaining 75 patients, 45 could be reached by telephone.

*Adequate control was defined as patient report of symptoms once per week or less.

*Inadequate control was defined as patient report of symptoms more than once weekly. These patients were referred to their resident physician for evaluation.

H2 = histamine-2; PPI = proton pump inhibitor.
remained controlled symptomatically. This interval of 8 months after intervention was chosen arbitrarily. The goals of this review were to determine the post-intervention acid suppression therapy and to evaluate whether patients who had received a change in acid suppression therapy maintained control of symptoms.

The follow-up included a review of the medical record and a telephone interview conducted by a member of the pharmacy staff. Patients whose medical chart review indicated escalation of therapy (either from H2-blocker therapy to PPI therapy, or from no therapy to H2-blocker or PPI therapy) were excluded from telephone interview attempts. Patients were determined to be lost to follow-up if they were no longer patients of the internal medicine clinic or did not have any clinic visits since the intervention. Telephone interviews were conducted to assess the patient’s level of symptom control. Patients were defined as unable to contact if there was no working telephone number or they were unable to be reached after 3 separate attempts. The following questions were asked during the telephone interview: (a) Are you taking a medication for your stomach? (b) Do you know the name of the medication? (c) Do you have trouble remembering to take your medication? (d) How often do you have symptoms of reflux (heartburn, indigestion, or stomach pain) within 1 week? (e) How do you treat your symptoms? Patients reporting symptoms more than once weekly were referred to their resident physician for evaluation. The next course of action was left to the physician’s discretion.

### Results

Between April 20 and June 20, 2005, 184 patients filled a prescription for pantoprazole therapy at the medical center's outpatient pharmacy. After medical record review, 49 patients were eliminated because they were not active internal medicine clinic patients, and 6 patients were eliminated because they reported stopping acid suppression therapy on their own. Thus, 129 patients receiving pantoprazole were identified and included in this evaluation (Figure 1). The indications for acid suppression therapy for each of the groups as well as all of the groups combined are listed in Table 2. The majority (75.2%) of patients were receiving PPI therapy for GERD.

Of the 129 patients evaluated, 119 (92.2%) were receiving pantoprazole 40 mg once daily. The remaining 10 patients (7.8%) were receiving pantoprazole 40 mg twice daily. Forty patients (31.0%) met criteria for PPI therapy. After PA was successfully obtained for these patients, their PPI therapy was changed to esomeprazole 40 mg daily or twice daily as indicated (PA group). Seventy-one patients (55.0%) did not meet TennCare criteria for PPI therapy and were changed to H2-blocker therapy (step-down group). Of these 71 patients, 53 (74.6%) were changed to ranitidine 150 mg twice daily; the remaining 18 patients (25.4%) were changed to ranitidine 150 mg daily because of a creatinine clearance of less than 50 mL per minute. Acid suppression therapy was discontinued in 18 patients (14.0%) because no indication was identified (discontinue therapy group).

At the March 2006 follow-up evaluation of the step-down and discontinue therapy groups, post-intervention acid suppression therapy was unable to be determined in 21 of the 89 patients because they had no clinic visits after the intervention (Table

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### Table 2: Indications for Acid Suppression Therapy and Distribution of Occurrence by Group

<table>
<thead>
<tr>
<th>Indication</th>
<th>PA</th>
<th>Step-Down</th>
<th>Discontinue</th>
<th>All Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>GERD</td>
<td>37 (92.5)</td>
<td>60 (84.5)</td>
<td>0 (0)</td>
<td>97 (75.2)</td>
</tr>
<tr>
<td>GUD/PUD</td>
<td>2 (5.0)</td>
<td>7 (9.9)</td>
<td>0 (0)</td>
<td>9 (7.0)</td>
</tr>
<tr>
<td>Acute necrotizing inflammation of esophageal mucosa</td>
<td>1 (2.5)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (0.8)</td>
</tr>
<tr>
<td>Colitis</td>
<td>0 (0)</td>
<td>1 (1.4)</td>
<td>0 (0)</td>
<td>1 (0.8)</td>
</tr>
<tr>
<td>Gastritis</td>
<td>0 (0)</td>
<td>1 (1.4)</td>
<td>0 (0)</td>
<td>1 (0.8)</td>
</tr>
<tr>
<td>Diverticulitis</td>
<td>0 (0)</td>
<td>1 (1.4)</td>
<td>0 (0)</td>
<td>1 (0.8)</td>
</tr>
<tr>
<td>Esophageal stricture</td>
<td>0 (0)</td>
<td>1 (1.4)</td>
<td>0 (0)</td>
<td>1 (0.8)</td>
</tr>
<tr>
<td>No indication</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>18 (100.0)</td>
<td>18 (14.0)</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>40 (100.0)</td>
<td>71 (100.0)</td>
<td>18 (100.0)</td>
</tr>
</tbody>
</table>

---

### Table 3: Follow-Up Results at 8 Months After PPI Intervention

<table>
<thead>
<tr>
<th>Follow-Up Results</th>
<th>Step-Down</th>
<th>Discontinue</th>
<th>All Evaluated</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>H2-blocker continued</td>
<td>37 (52.1)</td>
<td>0 (0)</td>
<td>37 (54.4)</td>
</tr>
<tr>
<td>H2-blocker initiated</td>
<td>0 (0)</td>
<td>1 (5.6)</td>
<td>1 (5.1)</td>
</tr>
<tr>
<td>No acid suppression therapy</td>
<td>12 (16.9)</td>
<td>5 (27.8)</td>
<td>17 (25.0)</td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>11 (15.5)</td>
<td>10 (55.6)</td>
<td>21 (31.0)</td>
</tr>
<tr>
<td>Re-initiated PPI</td>
<td>11 (15.5)</td>
<td>2 (11.1)</td>
<td>13 (19.1)</td>
</tr>
<tr>
<td>Total</td>
<td>71 (100.0)</td>
<td>18 (100.0)</td>
<td>89 (100.0)</td>
</tr>
</tbody>
</table>

---

PA group = Patients with an indication for a PPI, who were continued on PPI therapy by obtaining a prior approval for the therapy.

Step-down group = Patients with an indication for acid suppression therapy who did not meet the criteria for a PPI. These patients were changed to an H2-blocker.

Discontinue group = Patients without an indication for acid suppression therapy. These patients were discontinued from any form of acid suppression therapy.

Excludes patients lost to follow-up. Patients were classified as lost to follow-up if they did not return to the clinic for continued medical care after the change in acid suppression therapy.

H2 = histamine-2; PPI = proton pump inhibitor.
Results of an Intervention in an Academic Internal Medicine Clinic to Continue, Step-Down, or Discontinue Proton Pump Inhibitor Therapy Related to a Tennessee Medicaid Formulary Change

3. Post-intervention acid suppression therapy could be assessed in 68 (76.4%) of the 89 patients. Of the 68 patients, 13 (19.1%) had resumed PPI therapy, and 55 (80.9%) were either using an H2-blocker (n = 38) or no acid suppression therapy (n = 17).

Perceived symptom control in the step-down and discontinue therapy groups was assessed through telephone interviews. Patients who received an escalation in acid suppression therapy after the initial intervention (n = 14; from H2-blocker to PPI therapy [n = 11], from no acid suppression therapy to PPI therapy [n = 2], or from no acid suppression to H2-blocker therapy [n = 1]) were excluded from this assessment. Of the remaining 75 patients, 45 could be reached by telephone; of these, 28 (62.2%) reported symptoms less than or equal to once weekly (adequate control), and 14 (31.1%) were determined to have symptoms more than once weekly (inadequate control). Symptom control was unable to be determined in 3 patients (6.7%) because of difficult interviews or irregular use of acid suppression therapy. All patients reporting symptoms more than once weekly were referred to their resident physician for evaluation. They were provided assistance in making appointments with their physician if needed. The next course of action was then left to the physician's discretion.

Discussion

PPIs are more effective at eliminating symptoms of GERD and healing esophagitis than H2-blockers; however, they are also more expensive. Overuse of PPIs is evidenced by Naunton et al., who evaluated PPI use at the Royal Hobart Hospital in Australia, using chart review and patient interview. They found that only 37.1% of 200 inpatients taking PPIs met prescribing criteria according to the Schedule of Pharmaceutical Benefits and other standard therapeutic guidelines in Australia.

Clinical criteria for PPI therapy have been established by many health system institutions. Pohland et al. evaluated adherence to institutional guidelines for twice daily lansoprazole use at the Veterans Affairs Pittsburgh Healthcare System. The authors reviewed the pharmacy database, electronic medical records, and interviewed patients via telephone. They reported that only 34% of 248 patients taking twice daily lansoprazole met institutional prescribing criteria and recommended step-down therapy in 48%. Reports regarding the outcomes of step-down therapy have been conflicting. In a 2004 review, Piterman et al. reported that approximately 70% of patients whose PPI therapy is stepped down will have relapse of symptoms within 6 months. In contrast, Inadomi et al. reported that in a Veterans Affairs Health Care facility, 41 (58%) of 71 patients with GERD were asymptomatic 1 year after PPI therapy was discontinued; 34% required an H2-blocker, 7% required a prokinetic agent, 1% required both H2-blocker and prokinetic agents, and 11 (15%) of the 71 patients remained asymptomatic without any acid suppression therapy. Quality of life was not affected by these changes, and treatment costs were decreased by 37%.

This report describes how clinical pharmacists collaborated with physicians to proactively implement new formulary mandates established by TennCare to avoid unnecessary interruption in acid suppression therapy. Because of this intervention, approximately 31.1% were successfully switched to a preferred PPI to avoid interruption in therapy. While 68.9% of patients did not meet criteria for PPI therapy, 55.0% were switched to H2-blocker therapy and 14.0% did not require acid suppression therapy.

Limitations

The primary limitation of this study is the large number of patients who were lost to follow-up. Unfortunately, many Medicaid patients face financial difficulties and frequently relocate, making follow-up difficult. The “no show” rate in the clinic is approximately 30%, further decreasing the follow-up rate. Second, only patients receiving PPI therapy at the medical center’s outpatient pharmacy could be identified proactively. A larger number of patients received their medications in outside community pharmacies. Without an electronic medical record (EMR), all patients receiving PPI therapy could not be identified. An EMR would also allow one to easily identify indications as well as previous therapies. Other organizations with an EMR could identify all patients receiving PPI therapy and apply a similar methodology to transition patients in response to third-party formulary changes. Third, the TennCare formulary was limited to esomeprazole, lansoprazole, and omeprazole OTC. Omeprazole OTC is the least expensive PPI therapy option. However, TennCare had special contracts with the manufacturers and received rebates from them. TennCare does not release information about the amount of money saved via these rebates. Fourth, the survey used for the telephone interviews was not validated; however, it does reflect real-world practice. A strength of this report is that the results are based on real-time data, including chart review and patient interview, not a retrospective analysis of administrative data. Fifth, information that could have helped explain acid suppression use, such as diet, comorbidities, and concomitant medications was not obtained because those data were beyond the scope of this project. Finally, because the majority of patients were being treated for GERD, outcomes may not be transferable to other conditions.

Conclusions

This report describes a proactive collaboration between physicians and clinical pharmacists in response to changes in TennCare formulary criteria for PPIs. Patients with indications for acid suppression therapy were prescribed formulary acid suppressive medications to avoid interruption of therapy. Additionally, many patients had been prescribed PPI therapy for conditions not warranting PPI use. This finding reinforces the notion that a percentage of PPI prescriptions may be unnecessary given the availability of H2-blocker therapy.
Results of an Intervention in an Academic Internal Medicine Clinic to Continue, Step-Down, or Discontinue Proton Pump Inhibitor Therapy Related to a Tennessee Medicaid Formulary Change

Authors

KRISTIE L. RAMSER, PharmD, is Clinical Ambulatory Care Pharmacist and Assistant Professor, Regional Medical Center at Memphis and University of Tennessee, College of Pharmacy, Memphis, Tennessee. LAURA R. SPRABERY, MD, is Director, Internal Medicine Clinic and Associate Professor, Regional Medical Center at Memphis and University of Tennessee, College of Medicine, Memphis, Tennessee. GALE L. HAMANN, PharmD, is Clinical Ambulatory Care Pharmacist and Associate Professor, Regional Medical Center at Memphis and University of Tennessee College of Medicine and College of Pharmacy, Memphis, Tennessee. CHRISTA M. GEORGE, PharmD, is Clinical Ambulatory Care Pharmacist and Assistant Professor, Regional Medical Center at Memphis and University of Tennessee, College of Pharmacy, Memphis, Tennessee. AARON WILL, PharmD, is Pharmacy Clinical Coordinator Surgery, Duke University Hospital, Durham, North Carolina.

AUTHOR CORRESPONDENCE: Kristie L. Ramser, PharmD, Regional Medical Center at Memphis, Pharmacy Administration, 877 Jefferson Avenue, Memphis, TN 38103. Tel: 901.545.6252; Fax: 901.545.7184; E-mail: kramser@the-med.org

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REFERENCES
Fractal Mathematics in Managed Care? How a Simple and Revealing Analysis Could Improve the Forecasting and Management of Medical Costs and Events

Kathleen A. Fairman, MA; and Michael L. Rucker, MS, PE

In 1995, Christopher Barton, a research geologist who had worked for a decade with mathematician Benoit Mandelbrot, met with a group of U.S. research scientists interested in improving methods of forecasting hurricane wind speed at landfall and consequent damage. Noting that most hurricanes were small and of little consequence, while a few produced catastrophic damage, the group sought a more accurate way to forecast cataclysmic wind events. In response, Barton used U.S. historical data documenting maximum wind speeds for each hurricane at landfall dating from the year 1900 to create a cumulative frequency distribution (CFD) for wind speed, that is, the total number of hurricanes that had attained a given landfall wind speed for locations along the U.S. coast from Maine to Mexico. He then plotted the base 10 logarithms (log10) of CFD versus wind speed for each location. The resulting plot revealed a striking pattern of 2 separate mathematical functions. Noting that the wind speed where the 2 slopes intersected was approximately 40-50 meters per second (m/s), or about 90-110 miles per hour, Barton asked a group of research meteorologists at the National Oceanic and Atmospheric Administration’s National Hurricane Research Center if there was any meteorological significance to a 40 m/s wind speed. The startled meteorologists replied that approximately 40 m/s signals the formation of the hurricane’s eyewall and the transition from one physical process to another.1,2

In less than 15 years since that meeting, a growing number of forecasters and researchers—including meteorologists, geophysicists, and biologists—have applied similar mathematical approaches to the measurement and forecasting of a broad range of natural physical phenomena.3-7 When plotted on log-log scales, data representing the magnitude versus number of many natural phenomena often reveal much the same mathematical pattern as did the hurricane wind speeds plotted by Barton and his colleagues. Specifically, these data exhibit “power law” (fractal) scaling. In this editorial, we explain fractal scaling, highlight current health care trends that could make the use of fractal mathematical analysis increasingly important for the managed care industry, present a sample analysis from the physical sciences, and propose potential uses of the technique. We begin with 2 key concepts of fractal mathematics that apply across multiple venues and fields of study.

Key Concept 1: Self-Similarity Facilitates Event Forecasting. First, natural phenomena tend to form patterns in space and time that repeat over many orders of magnitude, a property that is described as “self-similarity.”7 An object in nature (space) displays self-similarity “if it can be decomposed into smaller copies of itself,”7 that is, if smaller components are essentially scaled-down versions of the larger object of which they are a part. Visible examples include some organs, such as lungs and the circulatory system, or cruciferous vegetables, such as broccoli or cauliflower. Events (time) display similar patterns of smaller and larger occurrences.

Mathematically, self-similarity is represented by a power law function rather than by the Gaussian statistics more familiar to many of us. Ordinary least squares linear regression assumes that for each 1 unit change in X (the independent variable), Y (the dependent variable) will increase or decrease by a fixed amount (the equation slope).8 In reality, though, most relationships between variables in nature are not identical across all values of a predictor variable; instead, they are similar, meaning that the direction of the relationship is the same, but the magnitude of the relationship differs at various values of the predictor, often by a great deal. Power law regression accounts for similarity by taking the multiplicative form Y = M×Xb; where M and b are constants.7 The mathematical relationship is “scale invariant” or “scale independent,” meaning that the function is the same across a wide range of values of X and Y. For example, in a family of similar animals, body mass is the product of a power law function: mass = M×surface areab, regardless of animal size.7 Fractal mathematics provides “a unified framework and explanation for many of these power laws.”7

The seminal character of self-similarity is profound and extends across multiple scientific disciplines. In his 1977 book introducing the concept of fractal mathematics, The Fractal Geometry of Nature, Mandelbrot observed that the science of geometry was often considered “cold” because of its “inability to describe” most objects that we observe in nature. “Clouds are not spheres, mountains are not cones, coastlines are not circles, and bark is not smooth, nor does lightning travel in a straight line,” he wrote. “Nature exhibits not simply a higher degree but an altogether different level of [geometric] complexity.”9 After considering the fractal patterns evident in numerous natural phenomena, including galaxies, coastlines, and air turbulence, Mandelbrot...
observed in retrospect that “exploring the consequences of self-similarity [proved] full of extraordinary surprises, helping me to understand the fabric of nature.”

The Gutenberg-Richter Law—Managed Care’s Dilemma

Although it is unlikely that managed care decision makers would routinely encounter the name of the Gutenberg-Richter Law, the power law for CFD versus magnitude of global earthquake events, most would quickly recognize its manifestation in health care—small events are numerous, whereas large events are both rare and typically difficult to forecast or manage. The question of how to manage both healthier and sicker enrollees in a cost-effective and clinically appropriate manner has become increasingly important because of 2 clinically distinct trends.

High Volume, Low Intensity Members. The first trend is the expansion of chronic medication indications to increasingly healthier populations. For example, an analysis of National Health and Nutrition Education Survey IV (NHANES) data, reported by Kahn et al. in 2008, found that an estimated 78% of U.S. adults aged 20 to 80 years are candidates for at least 1 cardiovascular disease (CVD) prevention strategy—for example, providing aspirin to individuals at high CVD risk, lowering blood pressure in patients with diabetes, and reducing levels of low-density lipoprotein cholesterol—under current treatment guidelines. Applying statistical modeling to the NHANES data, Kahn et al. estimated that full implementation of all preventive strategies would reduce rates of myocardial infarction and stroke by approximately 63% and 31%, respectively, increasing life expectancy by a mean of 1.3 years for all U.S. adults. Similarly, Fletcher et al. (2009), using Markov-type modeling to estimate the impact and cost-effectiveness of primary prevention with lipid-lowering therapy according to Adult Treatment Panel III (ATP-III) guidelines, found that full ATP-III compliance would require initiating new statin therapy in 9.7 million adults and intensifying treatment in another 1.4 million adults.

The trend toward expanded indications for chronic medications appears to be increasing in intensity and scope. A November 2008 study, conducted by Ridker et al. as part of the Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) trial, randomly assigned 17,802 “apparently healthy” subjects without hyperlipidemia but with elevated levels of C-reactive protein to rosuvastatin 20 mg daily or placebo. After a median of 1.9 years follow-up, rates of major cardiovascular events (measured per 100 person-years of follow-up; combined outcome of myocardial infarction, stroke, arterial revascularization, hospitalization for unstable angina, or death from cardiovascular causes), were 0.77 for rosuvastatin and 1.36 for placebo (hazard ratio for rosuvastatin=0.56, 95% CI=0.46-0.69). In an interview conducted shortly after release of the JUPITER findings, the director of the National Heart, Lung, and Blood Institute indicated that the study would become part of the effort to “generate an evidence-based, comprehensive set of clinical guidelines for primary-care practitioners to help adult patients reduce their risk for cardiovascular disease.”

Key Concept 2: “Fractal Transitions” Provide Critical Insights.

Transformations of recalcitrant (typically skewed or curvilinear) data are not new to researchers familiar with quantitative techniques. As early as the 1970s, the SPSS (SPSS, Inc., Chicago IL) manual included advice on what statistician Marija Norusis later described as “coaxing” skewed and curvilinear distributions into linearity, using various methods that included logarithmic transformation of the data and the addition of polynomial terms to equations. More recently, many health care researchers routinely use general linear modeling, often employing non-Gaussian distributions, to characterize the relationships between various predictor variables and health care outcomes.

Much less well understood among health care researchers is the second, crucial concept derived from the growing understanding of fractal mathematics among physical scientists—the value of identifying the “fractal transition,” that is, the point at which the mathematical relationship between event CFD and magnitude changes from one power law to another power law. Specifically, when the cumulative numbers of physical phenomena are plotted against their magnitudes in log-log space, the point at which the slope changes—like the 40 m/s wind speed that signaled the eye of a hurricane in Barton’s study—often provides a fundamental insight into the scale at which the underlying processes of a phenomenon change. A familiar example from chemistry is a phase change (e.g., from water to steam or ice). Scholz (1995) observed that “many [geological] objects may exhibit self-similarity over only a limited range of scales and different characteristics at widely separated scales.” The roughness of “natural geological surfaces,” Scholz observed, exhibits such transitions, which “occur at wavelengths corresponding to characteristic lengths in the system that generates the surface and these lengths may provide clues to the underlying physics.” Thus, however tempting it might be to assume that “one power law fits all” in characterizing the relationship between the frequency and magnitude of events, doing so may cause us to miss an opportunity to learn about the processes that generate events, whether minor or catastrophic, that affect us.

What might the application of this understanding look like in the managed care industry? What fundamental insight might we gain from applying fractal mathematics and an understanding of the pivotal nature of fractal transitions to analyses of health care events and costs?
It is widely recognized that this expansion of chronic medication indications for primary prevention comes at a high economic cost, primarily because of the large and growing numbers of relatively healthy people who would be treated. Pletcher et al. found that the annual net cost of bringing all U.S. adults into full compliance with ATP-III guidelines (after accounting for medical cost savings attributable to avoidance of cardiac events) would be $3.6 billion, an estimated $42,000 per quality-adjusted life year (QALY) if low-intensity statin treatment costs $2.11 per pill.23 Similarly, Ramsey et al. found that the cost of using atorvastatin for primary prevention of cardiovascular events in patients with type 2 diabetes was $137,276 per QALY over a 5-year time horizon, $3,640 per QALY over a 10-year time horizon, and cost saving only after 25 years.18 Kahn et al. found that over a 30-year time horizon, the only cost-effective CVD prevention strategy was smoking cessation.14 These estimated costs are enough to give decision makers pause in attempting to predict or manage the care required by these patients, especially considering that cost estimates typically do not account for the potential clinical risks associated with use of chronic medications for long-term primary prevention. For example, in commenting on the JUPITER trial, Hlatky (2008) pointed out that the lack of long-term safety data for rosvastatin “is clearly important in considering committing low-risk subjects without clinical disease to 20 years or more of drug treatment.”19

Low Volume, High Intensity Members. The second trend affects the other end of the cost/intensity spectrum—the increased development and use of very high-cost medications with marginal clinical benefits in the treatment of catastrophic illnesses with low prevalence. For example, Curtiss (2006) observed that the cost of adding lenalidomide to a dexamethasone regimen for treatment of multiple myeloma was more than $6,000 per month, at a higher risk of serious side effects that included febrile neutropenia and deep vein thrombosis, in exchange for a reduction in median time to progression of disease of only 17 weeks (19.9 weeks for lenalidomide and dexamethasone vs. 37.1 weeks for dexamethasone alone).20 Schrag (2004) observed that a near-doubling of the median survival rate for metastatic colorectal cancer (MCC), from approximately 12 months in the mid-1990s to approximately 21 months a decade later, had been accompanied by “a staggering 340-fold increase in drug costs”21 for a typical 8-week course of chemotherapy, the cost of fluorouracil and leucovorin (the “Mayo Clinic regimen”) was $63, whereas the cost of a 4-drug regimen consisting of fluorouracil, leucovorin, oxaliplatin, and bevacizumab was $21,033. Similarly, the cost of a combination of irinotecan and cetuximab for second- and third-line treatment of MCC, producing a 1.7-month increase in median survival, was $30,790 for an 8-week course. For all 56,000 patients with either new or recurrent MCC in the United States in 2004, Schrag estimated a total 8-week initial treatment cost of approximately $1.2 billion using therapies indicated in 2004.21 Prosser et al.’s (2004) estimates of the cost of treating newly diagnosed nonprimary progressive multiple sclerosis with interferon beta-1a, interferon beta-1b, or glatiramer acetate are even more striking; with a projected treatment duration of 10 years, interferon beta-1a was the most cost-effective treatment at $2.2 million per QALY for women and $1.8 million per QALY for men, compared with no treatment. Over a 5-year time horizon, a “no treatment” strategy yielded more estimated QALYs than did any of the drug treatment strategies.22

Hurricanes, Large Rocks, and Medical Cost Outliers—Management Clues Provided by Studying Fractal Transitions

The provocative question of whether to provide drug treatments of limited cost-effectiveness, although important and raised elsewhere,21 is beyond the scope of decisions made by most managed care organizations, which generally cover all drug treatments that are approved by the U.S. Food and Drug Administration. A more typical dilemma faced by a managed care decision maker is when and with which patients to intervene by providing services intended to enhance the clinical and economic benefits of treatment. Managed care organizations routinely make such decisions that affect their members—for example, whether to provide medication adherence programs to primary prevention patients, how often patients with various diseases should be contacted by a nurse telephone advice service, which patients and disease states are appropriate for step-therapy programs, or which drugs should be subject to prior authorization requirements. Fundamentally, the challenge is targeting the right program to the right patient.

The question of where to target interventions is certainly not unique to managed care. A surprisingly good analogy to managed care targeting is found at construction sites prior to ground-breaking for roads, bridges, and buildings. Civil engineers must determine how powerful a machine is required to dig foundations and whether the use of explosives is necessary. Gaussian statistical analyses cannot effectively answer these questions because an extraordinary volume of dirt and rock samples, and therefore extraordinary expense, would be required to include a sufficient number of large rocks in the sample. A few civil engineers are beginning to use fractal mathematics to address these questions.23-26

An example of the benefits of fractal analysis is shown in Figures 1 and 2. Figure 1 may initially seem familiar to managed care decision makers who routinely examine highly skewed distributions of medical cost or event data, with a classic pattern of high volume/low magnitude (left side) and low volume/high magnitude (right side) events. However, Figure 1 is actually a histogram of the sizes (in millimeters [mm]) of gravel, cobble, and boulder particles at the site of a proposed mass transit system at Sky Harbor Airport in Phoenix, Arizona, in 2003. To assess the feasibility of tunneling at the airport, it was necessary to estimate
the probability of encountering 2-foot boulders, which exceed
the capacity of tunneling equipment. However, the maximum
particle size that could be obtained with the available sampling
equipment was 150 mm, or approximately 6 inches. The civil
engineer’s dilemma in this situation is similar to that of the
managed care decision maker whose utilization experience
includes numerous low-cost medical events and few or no
catastrophic events—but who must determine how to forecast
and, if possible, prevent the future “large rocks,” that is, the
very high-cost medical incidents that Gaussian statistics do not
explain or predict well.

Like typical histograms of health care utilization and cost
experience in managed care, Figure 1 provides no information
about the probability of encountering a catastrophic event,
in this example a 2-foot boulder. The mean particle size of
approximately 7 mm (0.28 inches) is clearly not informative. In
contrast, in Figure 2 the CFS of particle sizes have been plotted
against their magnitudes in log-log space. When power laws are
log transformed, the result is a linear function; hence, Figure 2
reveals a distinct linear trend that abruptly changes at a fractal
transition point of approximately 30 mm (approximately 1.2 on
log10 scale). The fractal transition marks a critical point in the
physics of the system; this is the scale at which the soil’s “matrix,”
or underlying structure, changes for small versus large rocks.
This information was used by engineers both to understand bet-
ter the geophysical characteristics of the site and to forecast the
probability of encountering a 2-foot boulder. Using the fractal
transition as a guide to the logarithmic trend expected for large
rocks (i.e., extending the trend line for larger rocks from
the 2-foot marker), calculations indicated that tunneling equipment
would encounter a large boulder at each 100 cubic meters of
material, making tunneling infeasible. This information was
taken into account in making the decision not to tunnel at Sky
Harbor Airport. Subsequent excavation at the site of a new con-
trol tower confirmed boulder counts consistent with the predic-
tion based on fractal analysis.
Current Uses of Fractal Analyses in Health Care

Although the technique of plotting cumulative frequencies against magnitude in log-log space is both simple and powerful, we can find no evidence that it has been applied to analyses of medical costs or events in published work. PubMed searches on the terms power law costs logarithm, power law expenditures logarithm, Gutenberg-Richter costs logarithm, Gutenberg-Richter expenditures logarithm, fractal costs, and fractal expenditures identified only 10 studies, many of which involved the Fibrillation Registry Assessing Costs, Therapies, Adverse events and Lifestyle (FRACTAL) study, which is unrelated to fractal mathematics. Only a few managed care studies were identified, most published in the mid-1990s. Two, conducted by Davis and Lowell, used the Gutenberg-Richter power law to examine the adequacy of a behavioral health network and the relationship between fiscal structure and costs in mental health care systems. Several additional studies, conducted by business forecaster H. Richard Priesmeyer and colleagues, applied chaos theory (mathematically similar to fractal analysis) to business tasks such as evaluations of expert systems, prediction of the costs incurred by various business units within a health care system, and management of accounts receivable backlogs, and to clinical tasks such as knee arthroscopy. Although our PubMed search was not intended to be a comprehensive literature review, it reveals ample opportunity for contribution to the published managed care literature.

Fractal concepts are used much more frequently in the
Fractal Mathematics in Managed Care? How a Simple and Revealing Analysis Could Improve the Forecasting and Management of Medical Costs and Events

A Proposed Underlying Theory

Although the concept of applying fractal mathematics to medical events and costs in managed care appears to be new, use of this type of mathematical application in efforts to improve the understanding of human behavior is decades old. For example, Zipf posited in 1949 that the relationship between city population size and frequency follows a power law distribution. His theory spawned a huge body of research conducted by demographers and economists, almost all of it supporting his hypothesis. More recently, biologist Ethan Decker and his colleagues (2007) argued that the distribution of resources within and among cities should follow fractal branching patterns similar to those in natural systems such as river basins and biological organisms. For example, distributions of road networks arrayed in a fractal pattern “determine the rate of flow of people and goods in cities, in much the same way that the cardiovascular system determines the rate of oxygen delivery to cells.” Interestingly, Decker et al. identified (although they did not name) a fractal transition point, a point at which the log-log mathematical relationship between cumulative frequency and population size changed, signaling a change in “fundamental demographic (i.e., ecological) behaviors.”

As a starting point that is intended to be hypothesis-generating, we posit that it may be useful to conceptualize the array of health care costs paid by a managed care organization as a system of natural phenomena, in which frequent low-intensity events and rare high-intensity events contribute to the outcomes experienced by the whole system. As in any natural system, low- and high-intensity medical events will likely display fractal scaling behavior. We expect that low- and high-intensity events may be characterized well by a single power law, up to a point. At that point, the fractal transition point, the relationship may change. If the system of health care costs behaves as have other natural systems in previous scientific work, the fractal transition point may reveal something important about the physics of the system, that is, what “drives” it. Fundamental new insights into both the characteristics of the system and its appropriate management could be gained. However, as is always true of new technological approaches, the exact use of the method, and the specific insights that could be yielded from it, are impossible to determine before examining the data. An “outside-the-box” perspective is necessary to explore this possibility.

What Might a Fractal Analysis of Medical Costs and Events Show?

Although many different analyses of medical events and costs using fractal mathematics are possible, the basic approach would be the same in each: (a) construct a database of summed medical costs or events of interest, aggregated to the member level; (b) for each specific cost level, determine the cumulative frequency (number of members with costs of that level or more); (c) sort by cumulative frequency; (d) calculate log10 of both cumulative frequency and cost, and plot cost magnitude on the abscissa (x axis) and frequency on the ordinate (y axis); and (e) observe the fractal transition point(s), that is, the point(s) on the abscissa at which the slope appears to change.

If this analysis were performed on an entire population of members, we expect that at least 2 groups of members would be identified using fractal transition points. The group at the lowest cost and highest volume might consist primarily of members who use few or no medical services, perhaps also including those using chronic medications for primary prevention. The group at the highest cost and lowest volume might include patients with catastrophic illnesses and/or those using injectable biologic therapies. An intermediate cost/volume group might include patients with long-term stable chronic diseases, such as diabetes, coronary artery disease, or multiple cardiovascular disease risk factors. Decision makers could use this information in a variety of ways.

First, we posit that the fractal transition grouping method may improve the accuracy of currently available predictive indices. For example, the relationship between chronic disease score (CDS) in a baseline year and mortality and medical cost in a subsequent year is well established. Yet the CDS, like other currently used comorbidity indices that are based on administrative data, typically explains only about 15%-20% of total health care cost. Researchers who subdivide their samples into groups formed by fractal transition points may find that the mathematical relationship between CDS and outcomes is different for members in one group than in others. Mathematically accounting for that difference in statistical modeling could increase the overall predictive accuracy of the CDS and other similar comorbidity scales. Second, demographic and clinical profiles (e.g., CDS, Charlson Comorbidity Index, or Medical Outcomes Short Form scales such as the SF-36) of the various groups could help explore what, if anything, the fractal transition points show about the underlying “physics” of health care cost generation.

biological sciences. A PubMed search on the word fractal, without specification of additional search terms related to expenditures or costs, yields more than 5,000 studies, many (although not all) of which employed fractal mathematics in clinical studies. This greater frequency of use is not surprising, given that many biological structures—for example, lungs, kidneys, and the circulatory system—are formed of networks that are visibly self-similar and readily characterized by fractal mathematics. Recent work has posited ways in which fractal mathematics could be applied to the study of pharmacokinetics.
Also intriguing is the reverse of the first analysis—the possibility of grouping members into categories using already known risk scales, then profiling members in those categories using fractal mathematics. This approach is analogous to the current application of the hurricane forecasting model, in which the data used for a given fractal analysis are limited to a sample of hurricane landfalls from a specific area of longitude and latitude (e.g., a single metropolitan area or region), and fractal modeling of that sampled area is used to make forecasts specific to that geographic location.\(^2\)\(^5\)\(^6\) As an analogous example in health care, answers to the General Self-Rated Health (GSRH) item—“In general, would you say your health is: Excellent, Very Good, Good, Fair, Poor?”—are associated with risk of subsequent hospitalization and mortality.\(^4\)\(^10\)\(^41\) In a meta-analysis of 22 study cohorts reported by DeSalvo et al. in 2006, the relative risks for all-cause mortality were 1.23 (95% CI=1.09-1.39), 1.44 (95% CI=1.21-1.71), and 1.92 (95% CI=1.64-2.25) for those indicating good, fair, or poor health status, respectively, compared with those reporting that their health was excellent.\(^41\) However, room for improvement in prediction is clear. In DeSalvo’s (2005) analysis of data gathered from veterans, the GSRH produced a c-statistic (area under the receiver operator curve) of 0.74 for prediction of mortality and 0.63 for prediction of hospitalization, where a 0.50 indicates chance prediction and a 1.0 represents perfect prediction.\(^49\) These GSRH results were comparable to those of more complex scales currently in use by health care researchers.\(^60\)

Whatever the technique used, the general idea is to apply the understanding that the fractal transition point can provide important clues to the underlying causes of low- and high-intensity events.

**State of the Art—Fractal Mathematical Cost and Event Analysis in Managed Care**

Does the dearth of published information about fractal analysis in health care cost forecasting and management represent insight—a wise decision to eschew an exercise in data manipulation that is too simple to provide anything new? Or is it oversight—rejection of an analytic gem that has been “hiding in plain sight” from the managed care industry? We think that the answer is closer to the latter possibility than the former, but only time, rigorous data analysis, and the willingness of creative researchers to engage in trial and error will tell.

Seemingly disparate fields of study often have much to learn from each other. Decker et al. have observed that “common [mathematical] distributions may result from very general processes in natural, economic and engineered systems.”\(^36\) The similarity of findings in fractal-based research conducted in multiple fields of study may be showing us that the basic laws underlying diverse systems—biological, demographic, economic, and geological—are more similar than is generally understood.

Perhaps there is an opportunity for managed care to increase its use of an analytic approach that has been applied successfully by demographers, economists, and physical scientists to improve their understanding of the behavior of natural physical and human ecological systems. The mathematical tools that are commonly used in managed care to analyze health care costs, such as per member per month measures and even cost per QALY, may be inadequate to explain or manage care patterns that “drive” expenditures for clinical trends at dramatically different end points of the volume/intensity spectrum. Fractal mathematics may provide new and fascinating insights into care management. Our hope is that this editorial will encourage readers to explore that exciting possibility.

**Authors**

KATHLEEN A. FAIRMAN, MA, is Associate Editor and Senior Methodology Reviewer, Journal of Managed Care Pharmacy. MICHAEL L. RUCKER, MS, PE, is Senior Engineer, AMEC Earth and Environmental, Tempe, Arizona.

AUTHOR CORRESPONDENCE: Kathleen A. Fairman, MA, Kathleen Fairman LTD, P.O. Box 31278, Phoenix, AZ 85046. Tel.: 602.867.1343; E-mail: kfairman@amcp.org

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1. Personal communication with Christopher C. Barton, Professor, Wright State University, Dayton, OH. April 29, 2009.
Development of a Hospital Pharmacy Medication Safety Fellowship

To the Editor:
The increased awareness of medication safety initiatives is a result of additional requirements for maintaining health care organization accreditation that focus on prioritizing patient safety. The Joint Commission and the Centers for Medicare & Medicaid Services released the first set of core measures in 2002 and began requiring institutions to measure performance for the areas of acute myocardial infarction (e.g., aspirin and beta-blocker at hospital admission and discharge), heart failure (e.g., weight monitoring), pneumonia (e.g., pneumococcal and influenza immunization at discharge), and pregnancy (e.g., rate of vaginal births after a history of cesarean section delivery). In 2003, a surgical infection prevention core measure was added, and the Joint Commission initiated the annual publication of its National Patient Safety Goals (NPSGs) aimed at promoting quality care in health care settings. Consequently, accredited health care organizations are required to comply with the above core measures and the NPSGs in a nationwide effort to reduce the incidence of medical errors and patient harm.

It is not always feasible for acute care settings to dedicate resources exclusively to the area of medication safety due to economic and staffing restraints. However, it is imperative for every health care institution to prioritize medication safety and implement novel approaches in an effort to optimize patient outcomes. In January 2007, 3 pharmacy practice faculty, newly affiliated with an urban teaching hospital, met with hospital pharmacy administration to develop clinical practice safety goals. Various medication safety initiatives were discussed, such as improvement in meeting the Joint Commission core measures, pharmacist involvement with the Stroke Team, and creation of a medication safety subcommittee of the Pharmacy & Therapeutics (P&T) Committee. Acknowledging limited internal financial and personnel resources, the group’s discussion focused on innovative ideas for tackling these medication safety initiatives. The concept of a postgraduate education program in the form of a pharmacy fellowship in medication safety was proposed. The idea was well-received, and potential funding sources for such a program were identified. The next step was to apply for funding and justify the need for such a program.

One funding opportunity was the college of pharmacy’s seed funds and commit to continuing the fellowship beyond 1 year. At the same time, the director of pharmacy initiated discussions with senior administrators regarding the fellowship proposal and the required funding. Additionally, the director and the pharmacy practice faculty submitted a grant application to the hospital’s Education & Research Fund in an attempt to secure a portion of the funds for the remaining stipend. The discussions and grant application highlighted the many potential opportunities and benefits that the fellowship would create for the hospital in the areas of clinical practice, institutional service, education, and research. In May 2007, notification was received that the Education & Research Fund had awarded support that would cover some of the remaining stipend for 1 year. Shortly thereafter, hospital administration committed to covering the remaining amount including the cost of medical and dental benefits as well as vacation time for the first year.

Recruitment for potential candidates occurred over a 6-week time span and targeted the graduating classes at local colleges of pharmacy. Requirements of prospective candidates included completion of a doctor of pharmacy degree from an accredited college of pharmacy and an interest in medication safety; completion of a pharmacy practice residency was highly advantageous but not required. Following interviews with the pharmacy director, faculty, hospital administration, and physicians, a candidate was identified and began the 1-year fellowship on July 1, 2007.

Fellowship Description
The director of pharmacy and 3 pharmacy practice faculty serve as co-directors of the fellowship. The purpose of the fellowship program is 2-fold: (a) to improve patient outcomes through promoting the safe and effective use of medications, and (b) to provide the fellow with opportunities to become a clinical researcher and educator in the area of medication safety. The goals of the fellowship involve 4 main areas—clinical practice, institutional service, education, and research (Table 1). The fellow is expected to collaborate with physicians, nurses, and pharmacists to ensure compliance with core measure and safety initiatives.

Moreover, the fellow is expected to gain experience in study protocol development including methodology and statistical design, budget preparation, and institutional review board submission. The fellow is also required to conduct inpatient drug utilization evaluations (DUE) to identify areas requiring corrective action to ensure patient safety. The fellow is involved in writing manuscripts for submission to peer-reviewed pharmacy and/or medical journals, and research projects are presented as posters or in podium sessions at national and/or regional meetings. The fellow’s experience is not limited to research and grantmanship, but is also expanded to include teaching directed to the medical staff at the hospital. The fellow participates in the designing and/or delivery of elective and core courses at the college of pharmacy and assists in precepting pharmacy students in their intermediate and advanced pharmacy practice experiences.
In addition to research and teaching, the fellow is expected to provide pharmaceutical care, on a limited basis, to patients admitted to the stroke team at the hospital (e.g., provision of pharmacotherapy recommendations during daily patient-care rounds). Innovative questions that arise during patient care rounds or quality improvement meetings (e.g., phytonadione dose and route of administration to reverse warfarin, unexplained increase in vancomycin extravasations) are used as a vehicle to identify potential research questions, and to develop and implement large-scale educational programs that are geared towards pharmacists, physicians, and nurses.

The fellow is also required to submit an end-of-year report citing all accomplishments and activities to the program directors, the hospital’s Education & Research Fund, and hospital senior administration. Upon review of the accomplishments and activities from year 1, hospital senior administration agreed to fully fund the second year of the fellowship and to maintain the funding for future recruitment. The decision was based on activities that included, but were not limited to, development and implementation of an anticoagulation service, standardization and timely reporting of adverse drug reactions and medication errors, hospital-wide protocol development to prevent vancomycin extravasations, and educational initiatives provided to medical, nursing and pharmacy staff. Currently, the fellow is a full-time hospital employee with an adjunct faculty appointment.

This pharmacy medication safety fellowship is one of the few programs of its kind in the United States and the first at this urban teaching hospital. Establishment of the fellowship was made possible because of strong dedication and commitment to patient safety and collaboration between the hospital and the college of pharmacy. The fellowship program is an avenue that allows hospitals to evaluate practices pertaining to medication and patient safety without exhausting economic resources.

Karyn M. Sullivan, BS Pharm, MPH
Assistant Professor of Pharmacy Practice
Massachusetts College of Pharmacy and Health Sciences
karyn.sullivan@mcphs.edu

Michael J. Ditoro, PharmD
Director of Pharmacy – Saint Vincent Hospital

Kristin A. Tuiskula, PharmD
Pharmacy Medication Safety Fellow – Saint Vincent Hospital

Linda M. Spooner, PharmD, BCPS
Associate Professor of Pharmacy Practice
Massachusetts College of Pharmacy and Health Sciences

Abir O. Kanaan, PharmD
Assistant Professor of Pharmacy Practice
Massachusetts College of Pharmacy and Health Sciences

### TABLE 1

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<td>Clinical Practice</td>
<td>• Improve performance with The Joint Commission Core Measures for Acute Myocardial Infarction/Congestive Heart Failure and Community Acquired Pneumonia¹</td>
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<td>• Initiate pharmacist involvement with inpatient rounds with the Stroke Team</td>
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<td></td>
<td>• Evaluate practice guidelines and develop drug utilization protocols</td>
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<td></td>
<td>• Evaluate and report U.S. Food and Drug Administration warnings</td>
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<tr>
<td>Institutional Service</td>
<td>• Analyze and report on medication errors and adverse drug reactions</td>
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<td></td>
<td>• Participate on the P&amp;T Committee as a member</td>
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<td></td>
<td>• Initiate and co-chair the Medication Safety Subcommittee of the P&amp;T Committee</td>
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<tr>
<td></td>
<td>• Participate on the Medicine Performance Improvement Committee as a member</td>
</tr>
<tr>
<td></td>
<td>• Participate on the Cardiology Performance Improvement Committee as a member</td>
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<tr>
<td>Education</td>
<td>• Implement an in-house drug information telephone line</td>
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<td></td>
<td>• Provide educational conferences for internal medicine residents and attending physicians</td>
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<tr>
<td></td>
<td>• Co-precept introductory and advanced pharmacy practice experience students</td>
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<tr>
<td></td>
<td>• Lecture in various courses at the college of pharmacy</td>
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<tr>
<td></td>
<td>• Facilitate laboratory sessions at the college of pharmacy</td>
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<tr>
<td>Research</td>
<td>• Conduct DUEs as identified by the P&amp;T Committee</td>
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<td>• Develop research protocols in medication safety areas</td>
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<td>• Develop abstracts and posters for presentation at regional and national pharmacy meetings</td>
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<tr>
<td></td>
<td>• Develop manuscripts for publication in peer-reviewed journals</td>
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DUE = drug usage evaluation; P&T = pharmacy and therapeutics.
A Letter to the Editor written by C. Venkata S. Ram and Thomas Giles included an inaccurate statement of Disclosures.¹ C. Venkata S. Ram, MD, MACP, FACC, reports the receipt of compensation including speaking fees related to serving on speakers’ bureaus for Advanced Health Media, COGENIX, and GENESIS, which conduct educational programs for companies that manufacture pharmaceuticals and medical devices. Thomas Giles, MD, FACC, reports the receipt of grants for clinical research from AstraZeneca, Amgen, Abbott, Novartis, and National Institutes of Health, as well as grants for educational activities from AstraZeneca, Novartis, Boehringer-Ingelheim, and Sankyo/Forest. Dr. Giles also discloses that he has served as an advisor or consultant for Novartis, Pfizer, Boehringer-Ingelheim, Bristol-Myers Squibb, and Sankyo/Forest.

REFERENCE