ACO PHARMACY SERIES

PCMHs, ACOs, and Medication Management: Lessons Learned from Early Research Partnerships

BENEFIT MANAGEMENT

Evaluation of Increased Adherence and Cost Savings of an Employer Value-Based Benefits Program Targeting Generic Antihyperlipidemic and Antidiabetic Medications

Measuring Economic Impact of Applying Daily Average Consumption Limits

Discrepancies Identified with the Use of Prescription Claims and Diagnostic Billing Data Following a Comprehensive Medication Review

Incremental Health Care Resource Utilization and Economic Burden of Venous Thromboembolism Recurrence from a U.S. Payer Perspective

CLINICAL MANAGEMENT

Pharmacists’ Role in the Care of Patients with Heart Failure: Review and Future Evolution

BE EMPOWERED, A Specialty Pharmacy Education Program for Hemophilia B Patients, Impacts Adult Joint Bleeds and Pediatric Use of RICE

Analysis of Gastrointestinal Prophylaxis in Patients Receiving Dual Antiplatelet Therapy with Aspirin and Clopidogrel

Tolerability of Saxagliptin in Patients with Inadequately Controlled Type 2 Diabetes: Results from 6 Phase III Studies

Adherence to National Recommendations for Safe Methotrexate Dispensing in Community Pharmacies

Economic Burden of Urgency Urinary Incontinence in the United States: A Systematic Review
**JMCP Mission Statement and Editorial Policy**

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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 manuscript submissions except Commentaries and Letters should include an abstract and 1-3 takeaway bullet points in each of 2 sections that immediately follow the abstract for “what is already known about this subject” and “what this study adds.”

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

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**Research**

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

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**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 specific criteria used for inclusion and exclusion of information and the number of articles included and excluded by each criterion. Narrative reviews, defined as noncomprehensive reviews that cover only a portion of the literature on a topic, are not considered for publication by JMCP. However, articles of this type may be considered as Commentary.

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**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 generally include description and interpretation of clinical evidence and comparative cost information.

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**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.

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**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. Brief Communications may warrant an Abstract with the typical JMCP categories (Background, Objective, Methods, Results, Conclusion).

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**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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**Letters**

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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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 that include (a) full disclosure of all sources of potential bias and conflicts of interest, nonfinancial as well as financial; (b) full disclosure of potential conflicts of interest by reviewers as well as authors; and (c) accurate attribution of each author’s contribution to the article. Aggressive bias-management methods are necessary to ensure the integrity and reliability of published work.

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HEP C KILLS 15,000 AMERICANS EACH YEAR – MORE THAN HIV

By 2016, spending on medications for hepatitis C will exceed that of much more common conditions, including high blood pressure.

HISTORY OF TREATMENT OPTIONS

<table>
<thead>
<tr>
<th></th>
<th>Success Rate</th>
<th>Regimen</th>
<th>Doses Per Day</th>
<th>Side Effects</th>
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<tbody>
<tr>
<td>Past</td>
<td>&lt;50%</td>
<td>48 weeks</td>
<td>2</td>
<td>Long-term Severe</td>
</tr>
<tr>
<td>Present</td>
<td>70-90%</td>
<td>12-24 weeks</td>
<td>1-3</td>
<td>Short-term Milder</td>
</tr>
<tr>
<td>Future</td>
<td>&gt;90%</td>
<td>8-12 weeks</td>
<td>1</td>
<td>Short-term Well-tolerated</td>
</tr>
</tbody>
</table>

DISEASE-SPECIFIC COUNSELING AND INDIVIDUALIZED CARE

Hep C treatment is complex, and staying adherent to the prescribed medication can often be a major challenge. Specialty-trained pharmacists help identify potential safety concerns and provide disease-specific counseling to patients that can increase adherence and lower overall treatment costs. They prepare patients for treatment, provide guidance to mitigate side-effects and ensure appropriate use of medications – all of which boost adherence and improve health outcomes.

Patients exclusively using a specialty pharmacy:

60% MORE LIKELY TO ACHIEVE OPTIMUM ADHERENCE

15 FEWER THERAPY GAP DAYS
(Days without any available medication)

3.2M AMERICANS LIVE WITH CHRONIC HEP C
16,000 NEW CASES PER YEAR AND RISING
JMCP Author Guidelines

JMCP accepts for consideration manuscripts prepared according to the Uniform Requirements for Manuscripts Submitted to Biomedical Journals.1

■ Manuscript Preparation
Recommended maximum manuscript length is 3,500 words. Manuscripts should include, in this order: title page, abstract, text, references, tables, and figures (see Manuscript Submission Checklist for details).

JMCP abstracts should be carefully written narratives that contain all of the principal quantitative and qualitative findings, with the outcomes of statistical tests of comparisons where appropriate. Abstracts are required for all manuscript submissions except Commentaries and Letters. The format for the abstract is Background, Objective, Methods, Results, Conclusion. Reference numbering should begin in the text and should not be included in the abstract.

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/JMCPhome.aspx.
- A subsection in the Discussion labeled “Limitations” is required for all articles except Commentaries and Letters.
- Most articles 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/JMCPhome.aspx).
- 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/JMCPhome.aspx).

■ Reference Style
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 (hyperlink) addresses for all free access references. An access date should be included for every URL except links to JMCP articles. See examples 2 and 3 in the second column. Here are examples of the style format for common types of references:


■ Manuscript Submission
A complete list of documents needed for submission to JMCP appears on the Manuscript Submission Checklist at www.amcp.org/JMCPhome.aspx and the Supplement Submission Checklist at www.amcp.org/JMCPhome.aspx. Prior to peer review, all manuscripts are reviewed by the editors and/or members of the Editorial Advisory Board for appropriateness of the topic for JMCP, methodological transparency, and compliance with submission requirements. See Author Guidelines for description of the “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.

Disclosures and conflicts of interest: Manuscript submissions should (a) 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 (b) be accompanied by completed and signed author attestation forms for the principal author and each coauthor.

■ Manuscript Submission Checklist
Before submitting your manuscript to JMCP, please review the JMCP Author Guidelines and please check to see that your package includes all items in the JMCP Manuscript Submission Checklist. Both are available at www.amcp.org/JMCPhome.aspx.

REFERENCE
Steve Avey would be the first to say that he is a lucky man, although at first glance, it might not seem so.

He did not feel so lucky 8 years ago when he was diagnosed with a rare form of cancer. But, he did feel extremely fortunate when he beat it. A few years earlier, in 2000, Avey probably wondered more than once if he was lucky to be leading the effort to promote and educate P&T committees and manufacturers regarding the inaugural AMCP Format for Formulary Submissions. As the work progressed, however, he realized how fortunate he was to be involved in this great work.

Creating the AMCP Format involved “tremendous effort on the part of a lot of people,” Avey concedes, but it was for an important professional cause. “In the late 1990s, formularies were becoming more sophisticated. But the only information we had, as pharmacists in managed care trying to establish formularies, was the product labeling that health care professionals receive. We needed a lot more information than that, including financials and a pharmacoeconomic model, to help us determine the value of a new medication and where it belonged on a formulary.”

The Academy of Managed Care Pharmacy (AMCP) stepped up and asked the Format Executive Committee to create a tool that would provide consistent, standardized information for P&T committees to use when requesting information from pharmaceutical manufacturers. Those manufacturers initially balked at the use of such a tool, but through the efforts of Avey and others, they recognized that a standardized dossier could benefit them, as well, when they were called on to provide information to pharmacy benefit managers (PBMs) and health plans. Ultimately, the manufacturers responded positively when Avey requested funding to hold a series of 35 programs across the country to educate stakeholders in how to appropriately use the AMCP Format.

Today, the AMCP Format “is the standard for drug assessments,” Avey says. “PhRMA companies start preparing their dossiers well in advance of approval so the information is available soon after the product launches.”

It was also exciting for Avey to see the AMCP Format come into use as a teaching tool. He explains that every year, pharmacy schools across the country hold a student P&T committee competition. “Student chapters submit applications, and after local competitions, 8 schools are selected. Their teams are given AMCP Format dossiers on a medication, and then the teams review the clinical information, assess the value proposition, and present their conclusions. This is one of our biggest draws in bringing student chapters to our meetings, and it is extremely popular with the schools, students, and AMCP members.”

Creating the AMCP Format “involved tremendous effort” from everyone involved, Avey asserts, but “it is the most gratifying work I have been involved in. The AMCP Format Committee and those who helped in the education programs were highly committed, and we knew we were doing something very special for the profession.”

In 2005, Avey was extremely honored when the AMCP Board chose to change the name of its Lifetime Achievement Award to the Steven G. Avey Award in honor of his tireless work on getting the AMCP Format adopted nationally. He laughingly attributes the recognition to “everyone being concerned I was about to die,” but his luck held, and with great medical care, he not only survived the illness but has gone back to running half-marathons again. And, he recognizes that the AMCP Format he helped create and market stands as one of AMCP’s most critical accomplishments.

Today, as Vice President of Specialty Pharmacy Programs for MedImpact—the largest privately held PBM in the country—Avey has found another professional mission. Avey oversees his firm’s management of specialty pharmaceuticals for “rare chronic diseases that need considerable clinical management,” he explains. These medications treat rare conditions from Crohn’s disease and cystic fibrosis to multiple sclerosis and rheumatoid arthritis.

Specially pharmacies tailor clinical pathways that achieve optimal outcomes within each patient population. In fact, optimal outcomes often coincide with demonstrated financial savings for payers, patients, and physicians. Each program is designed to meet the needs of patients through education, reimbursement investigation, and ongoing clinical interaction and support.

When Avey looks into the future, specialty pharmacy looms large with promise and challenges. “Within 4 years, about half of this nation’s drug spend will be from 1%-3% of the population who need specialty drugs,” he explains. “This could tip over the prescription drug spend unless we find a way to appropriately manage these medications. We’ve got to get in front on this issue.”

The expertise of managed care pharmacists will be more important than ever, Avey says. “First, we must ensure that it is appropriate for a patient to take one of these medications; sometimes, prescribers will go right to a specialty medication, leaping over less expensive, first-line drugs. Second, we have to do everything we can to ensure adherence. Managed care organizations will have a big role to play and should offer programs to help pharmacists coach patients on the critical importance of adhering to their medication regimens.”

He also sees a leading role for AMCP in this and other important issues, such as government intervention in health care. “With Medicaid expansion and the Affordable Care Act, we’ll have more patients than ever with prescription benefits that are provided through managed care. And, government will definitely be very involved in how this plays out. AMCP has been a tremendous voice for us on Capitol Hill. They do this extremely well, and it will be critical, as these programs develop, for us to ensure that the right legislation is in place.”

But most of all, Avey believes, “AMCP can never forget its roots. When I first got involved, it was because a respected colleague told me the Academy would provide me with everything I needed. That was in 1992 when my company at the time was first setting up rudimentary formularies, and although it was technically managed care, we were not providing a lot of management. I needed AMCP to help me learn how to actually manage a client’s prescription benefit.”

According to Avey, AMCP still has a critical role in “nurturing managed care pharmacists, providing continuing education, and doing all the things it’s done so well over the past 25 years.”

Cover Impressions

About the JMCP February Cover

### Top 10 Drugs by Rx Claim Volume for December 2013 (Nonspecialty)

- **Levothyroxine Sodium**: 3.2%
- **Lisinopril**: 3.1%
- **Omeprazole**: 3.0%
- **Simvastatin**: 3.0%
- **Amlodipine Besylate**: 2.5%
- **Atorvastatin Calcium**: 2.3%
- **Metformin HCL**: 2.1%
- **Furosemide**: 1.8%
- **Hydrochlorothiazide**: 1.6%
- **Insulin Glargine**: 3.4%
- **Fluticasone/Salmeterol**: 2.2%
- **Rosuvastatin Calcium**: 2.1%
- **Tiotropium Bromide**: 1.7%
- **Duloxetine HCL**: 1.7%
- **Etanercept**: 1.5%
- **Adalimumab**: 1.5%
- **Aripiprazole**: 1.5%
- **Sitagliptin Phosphate**: 1.4%
- **Glatiramer Acetate**: 1.3%

### New Type 2 Drugs Q1 2014 (Pending FDA Approval)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Manufacturer</th>
<th>FDA Deadline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Forxiga (dapagliptin)</td>
<td>Bristol-Myers Squibb Company and AstraZeneca</td>
<td>PDUFA: January 11, 2014</td>
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<tr>
<td>Metreleptin</td>
<td>Bristol-Myers Squibb Company and AstraZeneca</td>
<td>PDUFA: February 27, 2014</td>
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<tr>
<td>Empagliflozin</td>
<td>Eli Lilly and Boehringer Ingelheim</td>
<td>PDUFA: March 25, 2014</td>
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<tr>
<td>Eperzan (albiglutide)</td>
<td>GlaxoSmithKline</td>
<td>Expected approval: April 15, 2014</td>
</tr>
<tr>
<td>Dulaglutide</td>
<td>Eli Lilly</td>
<td>Expected approval: Q4 2014</td>
</tr>
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### State Distribution of Medicare Rx Lives January 2014

- **U.S. Total**: 33.8 million
- **Median**: 425,060 (Colorado)

### States with the Most and Least Medicare Rx Lives

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<th>States</th>
<th>Rank</th>
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<tr>
<td>California</td>
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<td>Alaska</td>
<td>27,466</td>
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<td>3,943,697</td>
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<td>District of Columbia</td>
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<td>Florida</td>
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<td>Pennsylvania</td>
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Tolerability of Saxagliptin in Patients with Inadequately Controlled Type 2 Diabetes: Results from 6 Phase III Studies

Jaime A. Davidson, MD, FACP, MACE

ABSTRACT

BACKGROUND: Oral antihyperglycemic drugs used to treat type 2 diabetes mellitus (T2DM) vary in safety and tolerability. Treatment-related hypoglycemia and weight gain can exacerbate underlying disease.

OBJECTIVE: To evaluate the tolerability of saxagliptin using data from phase III clinical trials.

METHODS: Six 24-week randomized studies in 4,214 patients with T2DM were assessed. Saxagliptin 2.5 mg or 5 mg was compared with placebo in 2 trials of monotherapy in treatment-naive patients and in 3 trials of add-on therapy to metformin, glyburide, or a thiazolidinedione; initial combination therapy with saxagliptin 5 mg plus metformin was compared with metformin monotherapy in treatment-naive patients. Data from the monotherapy and add-on studies were pooled; data from the initial combination study were analyzed separately. No statistical analyses of between-group comparisons across studies were conducted for these safety analyses because of multiplicity of end points and relative lack of statistical power and because small differences not reaching statistical significance have the potential to be clinically relevant.

RESULTS: In the pooled analysis, incidence rates for adverse events (AEs) with saxagliptin 2.5 mg, 5 mg, and placebo were 72.0% (635/882), 72.2% (637/882), and 70.6% (564/799), respectively; rates for serious AEs (SAEs) were 3.5% (31/882), 3.4% (30/882), and 3.4% (27/799); rates of discontinuation due to AEs were 2.2% (19/882), 3.3% (29/882), and 1.8% (14/799). AEs reported in ≥2% of patients receiving saxagliptin and occurring ≥1% more frequently with saxagliptin than with placebo were sinusitis, gastrointestinal, abdominal pain, and vomiting. In the initial combination study, AE incidence rates with saxagliptin 5 mg plus metformin and metformin monotherapy were 55.3% (177/320) and 58.5% (192/328), respectively; incidence rates for SAEs were 2.5% (8/320) and 2.4% (8/328); and rates of discontinuation due to AEs were 2.5% (8/320) and 3.4% (11/328).

CONCLUSION: Saxagliptin 2.5 mg or 5 mg was generally well tolerated as monotherapy, add-on combination therapy with other oral antihyperglycemic drugs, and initial combination with metformin.

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What is already known about this subject

- Oral antidiabetic drugs (OADs) differ in their safety and tolerability profiles. For example, the sulfonylureas are associated with weight gain and risk of hypoglycemia, whereas metformin is associated with gastrointestinal intolerance, and its use is limited by renal impairment. Thiazolidinediones (TZDs) are associated with increased risk of bone fracture (mainly in women), edema, weight gain, congestive heart failure, and possibly myocardial infarction (rosiglitazone).

- Dipeptidyl peptidase-4 (DPP-4) inhibitors are a newer class of OADs. The DPP-4 inhibitor saxagliptin is approved as an adjunct to diet and exercise for improving glycemic control in patients with type 2 diabetes mellitus (T2DM) and has also been shown to be efficacious as add-on therapy to metformin, a sulfonylurea (glyburide), and a TZD, as well as in initial combination therapy with metformin. The current evaluation of saxagliptin tolerability is based on an analysis of the phase III clinical trial program, consisting of 6 phase III studies, all of which were 24-week randomized, double-blind, placebo- or active-controlled studies.

What this study adds

- The purpose of the pooled analysis of placebo-controlled monotherapy and add-on therapy trials was to identify any safety signals for saxagliptin that might not have been identified in the smaller populations of the individual trials. The initial combination study was reported separately because patients in that study had new-onset T2DM, and the comparison was of initial add-on rather than sequential add-on therapies.

- Across 6 double-blind phase III clinical trials, saxagliptin was generally well tolerated as monotherapy, as add-on combination therapy with metformin, glyburide, or a TZD, and as initial combination therapy with metformin in patients with T2DM. Incidence rates of adverse events were comparable with saxagliptin 2.5 mg, saxagliptin 5 mg, and placebo (pooled analysis) and with saxagliptin 5 mg plus metformin and metformin monotherapy (initial combination study).

Despite many available therapies, only 57% of patients with type 2 diabetes mellitus (T2DM) in the United States reach the American Diabetes Association (ADA) recommended glycated hemoglobin (HbA1c) goal of <7%, according to the 2003-2004 interval of the National Health and Nutrition Examination Survey. Even fewer patients with T2DM reach the American Association of Clinical Endocrinologists (AACE)/American College of Endocrinology (ACE) recommended goal of <6.5%.

In their recent position statement, the ADA and European Association for the Study of Diabetes recommend initial drug therapy with metformin or, if metformin cannot be used, another oral antidiabetic drug (OAD) such as a sulfonylurea/ glinide, pioglitazone, or a dipeptidyl peptidase-4 (DPP-4)
inhibitor for patients with T2DM. OADs differ in their safety and tolerability profiles. For example, the sulfonylureas are associated with weight gain and risk of hypoglycemia, whereas metformin is associated with gastrointestinal (GI) intolerance, and its use is limited by renal impairment. Thiazolidinediones (TZDs) are associated with increased risk of bone fracture (mainly in women), edema, weight gain, congestive heart failure, and possibly myocardial infarction (rosiglitazone). The Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes (RECORD) trial confirmed that rosiglitazone doubled the risk of heart failure and showed a nonsignificant trend for increasing the risk of myocardial infarction but found no increase in overall cardiovascular (CV) morbidity or mortality.

DPP-4 inhibitors represent a useful therapeutic approach for the management of T2DM. DPP-4 inhibitors prolong the activity of incretin hormones (glucagon-like peptide-1 and glucose-dependent insulinotrophic polypeptide), thereby promoting insulin production and suppressing glucagon secretion, which results in reduced blood glucose. A formal meta-analysis of 41 clinical trials has demonstrated that DPP-4 inhibitors are, as a class, weight neutral and carry essentially no risk of hypoglycemia. The DPP-4 inhibitors currently approved in the United States are sitagliptin, saxagliptin, linagliptin, and alogliptin; vildagliptin is available in Europe. The DPP-4 inhibitor saxagliptin is approved as an adjunct to diet and exercise for improving glycemic control in patients with T2DM. Saxagliptin monotherapy has been shown to improve glycemic control in patients with T2DM in both 12-week and 24-week studies. Saxagliptin has also been shown to be efficacious as add-on therapy to metformin, sulfonylurea (glyburide), and a TZD as well as in initial combination therapy with metformin. In phase III studies, adverse events (AEs) occurring in ≥ 8% of patients and more commonly with saxagliptin versus placebo were upper respiratory tract infection, urinary tract infection, and headache.

The current evaluation of saxagliptin tolerability is based on an analysis of the phase III clinical trial program, consisting of 6 phase III studies, all of which were 24-week, randomized, double-blind, placebo-, or active-controlled studies. The 6 phase III studies included 2 monotherapy studies; 3 add-on combination studies with metformin, glyburide, or a TZD; and an initial combination study of saxagliptin plus metformin. The evaluation includes a pooled analysis of the 5 placebo-controlled monotherapy and add-on therapy trials and separate presentation of the initial combination study. The purpose of the pooled analysis was to identify any safety signals for saxagliptin that might not have been identified in the smaller populations of the individual trials. Based on the mechanism of action and clinical profile of the DPP-4 inhibitors and risks associated with T2DM, certain types of AEs were of special interest, including hypoglycemia, skin and subcutaneous tissue disorders, hypersensitivity events, infections and infestations, lymphopenia, thrombocytopenia, localized edema, and CV AEs.

**Methods**

Table 1 presents an overview of the 6 phase III saxagliptin studies. Briefly, each study included a 1- to 4-week dietary and placebo lead-in period followed by a 24-week double-blind treatment period. Patients with T2DM, aged 18 to 77 years, were eligible if they had inadequate glycemic control (HbA1c: 7%-10%, 7.5%-10%, 7%-10.5%, or 8%-12%; study dependent) for at least 24 weeks, fasting C-peptide ≥ 1.0 nanograms per milliliter [ng/mL], and body mass index [BMI] ≤ 40 kilograms per square meter [kg/m2]; in the add-on to the TZD study, the BMI inclusion range was revised to ≤ 45 kg/m2.

Patients in the monotherapy and initial combination with metformin studies were treatment-naive, defined as not receiving medical treatment for diabetes for ≥ 6 months since original diagnosis (in the monotherapy studies), or as never having received medical treatment for diabetes or having received medical treatment for diabetes for a total period of < 1 month since original diagnosis (initial combination with metformin study). In each of these studies, patients were also not to have received antihyperglycemic therapy for > 3 consecutive days or for a total of 7 nonconsecutive days during the 8 weeks before screening. Patients in the add-on combination therapy studies did not achieve glycemic control despite a stable dose of metformin, glyburide (2 months before screening), or a TZD (3 months before screening). In these studies, comparisons were made between add-on saxagliptin versus placebo; however, the add-on to glyburide trial allowed glyburide up titration in the control arm.

Exclusion criteria were symptoms of poorly controlled diabetes; history of diabetic ketoacidosis or hyperosmolar nonketotic coma; insulin therapy within 1 year of screening; significant CV event within 6 months of study entry or New York Heart Association stage III/IV congestive heart failure and/or known left ventricular ejection fraction ≤ 40%; significant history of renal or liver disease; psychiatric disorder; history of alcohol or drug abuse within the previous year; treatment with potent cytochrome (CYP) 3A4 inhibitors or inducers; immunocompromised individuals; and active liver disease or clinically significantly abnormal hepatic, renal, endocrine, metabolic, or hematologic screening tests. For all 6 studies used in this analysis, study protocols were approved by the institutional review board or independent ethics committee for each participating site and carried out in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

**Study End Points**

Safety and tolerability analyses included assessment of overall AEs, serious AEs (SAEs), discontinuations for AEs, most common AEs, subgroup analyses of AEs, and AEs of special
interest. As previously described, AEs of special interest were a predefined subset of AEs, which were selected based on their general importance for antihyperglycemic agents (e.g., hypoglycemia and CV AEs); findings observed in the saxagliptin nonclinical and clinical trial programs (e.g., lymphopenia and thrombocytopenia); safety-related concerns reported for other DPP-4 inhibitors (e.g., abnormal liver function tests, skin disorders, localized edema, and hypersensitivity reactions); or theoretical considerations related to the mechanism of action of saxagliptin (e.g., infections and infestations, localized edema, and skin disorders). AE intensity was defined as mild (awareness of event but easily tolerated), moderate (discomfort enough to cause some interference with usual activity), severe (inability to carry out usual activity), and very severe (debilitating, significantly incapacitates patient despite symptomatic therapy). AE reporting included investigator assessments for severity and relationship to study medication. Classification of AEs was based on the Medical Dictionary for Regulatory Activities (MedDRA) version 10.1 (MedDRA MSSO, McLean, VA). Safety was also assessed using data from physical examinations, vital signs, electrocardiograms (ECGs), and standard laboratory measurements (e.g., hematology, serum chemistry, urinalysis).17,20,23,25

Data Analysis
Two populations were assessed for the safety of saxagliptin. The first was the pooled safety population that participated in the placebo-controlled trials of saxagliptin as monotherapy20,25 and as add-on therapy to metformin,17 glyburide,21 or a TZD.22 Data for saxagliptin 2.5 milligrams (mg), saxagliptin 5 mg, and placebo were separately pooled across the 5 studies for analysis. The second population participated in the trial of saxagliptin 5 mg as initial combination therapy with metformin versus metformin monotherapy.23 In the analyses of these 2 populations, only doses of saxagliptin common to all studies (approved doses of 2.5 mg and 5 mg) were included; safety findings for saxagliptin 10 mg can be found in the publications for the primary study in which it was assessed.17,20,23

All safety data are presented for treated patients, defined as patients who received at least 1 dose of the study drug. The extent of exposure was defined as the time from the first day that a patient received the study drug to 1 day after the last day that a patient received the study drug. A pooled analysis was conducted of the placebo-controlled phase III studies with a duration of up to 24 weeks (including rescue therapy to avoid potential imbalances in exposure to study treatment) to
identify any safety signals that might not have been apparent in the context of the smaller populations of the 5 individual trials. However, due to multiplicity of end points and a lack of statistical power, formal statistical analyses of between-group differences across studies were not performed. Data collected after rescue therapy were excluded in the initial combination with metformin analysis; however, no formal statistical comparison of between-group differences in safety was performed. Rescue therapy (metformin or pioglitazone) was initiated in accordance with study protocols and was given in addition to blinded study medication if patients failed to meet prespecified glycemic goals. The analyses of AEs of special interest were performed on datasets obtained up to week 24, including safety data acquired after rescue. Data on hypoglycemia, an AE of special interest, are classified as “reported hypoglycemia” (signs or symptoms consistent with hypoglycemia with or without documented glucose levels) and “confirmed hypoglycemia” (fingertip glucose ≤50 milligrams per deciliter [mg/dL] with associated symptoms). AEs were tabulated; other safety-related variables were summarized using descriptive statistics. Clinical AEs were coded and grouped into System Organ Class (SOC), preferred term, and treatment using MedDRA version 10.1.

### Results

#### Study Population Characteristics and Patient Disposition

Baseline demographics and clinical characteristics in the pooled placebo-controlled and phase III initial combination study analysis populations are summarized in Table 2. In the placebo-controlled pooled safety analysis, mean age ranged from 54.4 to 54.8 years across groups, with 16% to 17% of patients aged ≥65 years. In the initial combination with metformin study, patients were younger, with a mean age of 51.8 to 52.0 years across groups and 10% to 11% of patients aged ≥65 years. Mean baseline HbA1c and fasting plasma glucose (FPG) were 8.2% and 169 to 170 mg/dL across groups, respectively, in the placebo-controlled pooled safety analysis, and 9.4% and 198 to 199 mg/dL across groups, respectively, in the initial combination with metformin study, consistent with the higher HbA1c entry criteria for the latter study. Mean duration of T2DM was 5.2 to 5.4 years across groups in the placebo-controlled pooled safety analysis and 1.7 to 2.0 years in the initial combination with metformin study, reflecting the expected longer T2DM duration for patients receiving add-on therapy compared with initial therapy.

#### TABLE 2 Baseline Demographic and Clinical Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Placebo-Controlled Pooled Analysis&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Initial Combination Study&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2.5 mg (n=882)</td>
<td>5 mg (n=882)</td>
</tr>
<tr>
<td>Age, years&lt;sup&gt;c&lt;/sup&gt;</td>
<td>54.8 (10.0)</td>
<td>54.4 (10.2)</td>
</tr>
<tr>
<td>Age ≥65 years&lt;sup&gt;c&lt;/sup&gt;</td>
<td>149 (17)</td>
<td>142 (16)</td>
</tr>
<tr>
<td>Gender&lt;sup&gt;d&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>422 (48)</td>
<td>427 (48)</td>
</tr>
<tr>
<td>Women</td>
<td>460 (52)</td>
<td>453 (52)</td>
</tr>
<tr>
<td>Race (self-reported)&lt;sup&gt;e&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>603 (68)</td>
<td>599 (68)</td>
</tr>
<tr>
<td>Asian</td>
<td>154 (18)</td>
<td>155 (18)</td>
</tr>
<tr>
<td>Black</td>
<td>30 (3)</td>
<td>46 (5)</td>
</tr>
<tr>
<td>Other</td>
<td>95 (11)</td>
<td>82 (9)</td>
</tr>
<tr>
<td>Weight, kg&lt;sup&gt;f&lt;/sup&gt;</td>
<td>82.6 (18.0)</td>
<td>82.7 (19.0)</td>
</tr>
<tr>
<td>BMI, kg/m&lt;sup&gt;2&lt;/sup&gt;</td>
<td>30.4 (5.1)</td>
<td>30.3 (5.0)</td>
</tr>
<tr>
<td>Duration of diabetes, years&lt;sup&gt;c&lt;/sup&gt;</td>
<td>5.2 (3.3)</td>
<td>5.0 (5.3)</td>
</tr>
<tr>
<td>HbA1c, %&lt;sup&gt;g&lt;/sup&gt;</td>
<td>8.2 (1.0)</td>
<td>8.2 (1.0)</td>
</tr>
<tr>
<td>&lt;8&lt;sup&gt;h&lt;/sup&gt;</td>
<td>408 (46)</td>
<td>382 (43)</td>
</tr>
<tr>
<td>≥8 to &lt;9&lt;sup&gt;i&lt;/sup&gt;</td>
<td>288 (33)</td>
<td>303 (35)</td>
</tr>
<tr>
<td>≥9&lt;sup&gt;j&lt;/sup&gt;</td>
<td>185 (21)</td>
<td>193 (22)</td>
</tr>
<tr>
<td>Not reported&lt;sup&gt;k&lt;/sup&gt;</td>
<td>1 (0.1)</td>
<td>2 (0.2)</td>
</tr>
<tr>
<td>FPG, mg/dL&lt;sup,l&lt;/sup&gt;</td>
<td>169 (44.6)</td>
<td>170 (45.0)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Included 2 saxagliptin monotherapy trials and 1 trial each of saxagliptin as add-on to metformin, thiazolidinedione, and glyburide.

<sup>b</sup> Values are expressed as mean (SD).

<sup>c</sup> Values are expressed as n (%).

<sup>d</sup> BMI = body mass index; FPG = fasting plasma glucose; HbA1c = glycated hemoglobin; kg/m<sup>2</sup> = kilogram per square meter; MET = metformin 500-2,000 mg/d; mg/dL = milligram per deciliter; SAXA = saxagliptin; SD = standard deviation.
Placebo-Controlled Pooled Analysis

As shown in Table 3, the overall frequency of AEs for saxagliptin 2.5 mg, 5 mg, and placebo was 72.0%, 72.2%, and 70.6%, respectively. AE frequency for saxagliptin 2.5 mg or 5 mg was comparable with placebo for each individual SOC, with the exception of GI disorders, which were more common with saxagliptin 2.5 mg (22.1%) than with saxagliptin 5 mg or placebo (18.4% and 19.1%, respectively). No other AEs by SOC occurred at a rate ≥2% higher with saxagliptin 2.5 mg or 5 mg compared with placebo. Respiratory, thoracic, and mediastinal disorders were more common with placebo than saxagliptin.

Few AEs occurred at a frequency ≥5%; these included upper respiratory tract infection (7.0%, 7.7%, 7.6%), urinary tract infection (5.1%, 6.8%, 6.1%), nasopharyngitis (5.7%, 5.6%, 6.8%), headache (6.5%, 6.5%, 5.9%), diarrhea (6.0%, 4.1%, 6.1%), and back pain (3.7%, 4.3%, 5.1%) for saxagliptin 2.5 mg, 5 mg, or placebo, respectively. The majority of AEs were mild to moderate in intensity and were considered unrelated to the study medication by the investigator. The AEs that occurred at a frequency of ≥2% with saxagliptin 2.5 mg or 5 mg and also occurred at a ≥1% higher frequency with saxagliptin compared with placebo were simitis, gastroenteritis, abdominal pain, and vomiting.

The frequency of SAEs for saxagliptin 2.5 mg, 5 mg, and placebo was 3.5%, 3.4%, and 3.4%, respectively. AEs leading to discontinuation occurred in 2.2%, 3.3%, and 1.8% of patients receiving saxagliptin 2.5 mg, 5 mg, or placebo, respectively. AEs leading to discontinuation included lymphopenia (1, 4, and 0 patients receiving saxagliptin 2.5 mg, 5 mg, and placebo, respectively); rash (2, 3, and 2); increased blood creatinine (3, 0, and 0); and increased blood creatine phosphokinase (1, 2, and 0).
Tolerance of Saxagliptin in Patients with Inadequately Controlled Type 2 Diabetes: Results from 6 Phase III Studies

**TABLE 4  Adverse Events of Special Interest**

<table>
<thead>
<tr>
<th></th>
<th>Placebo-Controlled Pooled Analysis* (Including Rescue)</th>
<th>Placebo-Controlled Pooled Analysis* (Excluding Rescue)</th>
<th>Initial Combination Study (Excluding Rescue)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SAXA 2.5 mg (n = 882) (%)</td>
<td>SAXA 5 mg (n = 882) (%)</td>
<td>SAXA 5 mg + MET (n = 320) (%)</td>
</tr>
<tr>
<td></td>
<td>SAXA 5 mg (n = 882) (%)</td>
<td>Placebo (n = 799) (%)</td>
<td>MET (n = 328) (%)</td>
</tr>
<tr>
<td>All reported hypoglycemia</td>
<td>67 (7.6)</td>
<td>69 (7.8)</td>
<td>11 (3.4)</td>
</tr>
<tr>
<td>Confirmed hypoglycemia</td>
<td>7 (0.8)</td>
<td>4 (0.5)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>82 (9.3)</td>
<td>63 (7.1)</td>
<td>11 (3.4)</td>
</tr>
<tr>
<td>Hypersensitivity events</td>
<td>13 (1.5)</td>
<td>13 (1.5)</td>
<td>2 (0.6)</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>321 (36.4)</td>
<td>317 (35.9)</td>
<td>73 (22.8)</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>4 (0.5)</td>
<td>13 (1.5)</td>
<td>8 (1.0)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>4 (0.5)</td>
<td>2 (0.2)</td>
<td>1 (0.1)</td>
</tr>
<tr>
<td>Localized edema</td>
<td>8 (0.9)</td>
<td>20 (2.3)</td>
<td>2 (0.6)</td>
</tr>
<tr>
<td>Cardiovascular AEs</td>
<td>5 (0.6)</td>
<td>2 (0.2)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

*Includes 2 saxagliptin monotherapy trials and 1 trial each of saxagliptin as add-on to metformin, thiazolidinedione, and glyburide.

AE = adverse event; MET = metformin; mg = milligram; SAXA = saxagliptin.

**Initial Combination Study**

The safety profile of saxagliptin in the initial combination with metformin study was generally consistent with observations in the placebo-controlled pooled safety analysis. The frequency of AEs was 55.3% for saxagliptin 5 mg plus metformin and 58.5% for metformin monotherapy (Table 3). No AEs by SOC had a >2% higher incidence in the saxagliptin 5 mg plus metformin group compared with the metformin monotherapy group, although vascular disorders approached this threshold (6.6% vs. 4.6%). AEs in the SOC of cardiac disorders were less frequent for saxagliptin 5 mg plus metformin than for metformin monotherapy (2.2% vs. 4.9%).

Few AEs occurred at a frequency ≥5%; these included nasopharyngitis (6.9% and 4.0%), headache (7.5% and 5.2%), and diarrhea (6.9% and 7.3%) for saxagliptin 5 mg plus metformin or metformin monotherapy, respectively. The majority of events were mild to moderate in intensity; most were considered unrelated to study medication by the investigator. The AEs that occurred at a frequency of ≥2% with saxagliptin 5 mg plus metformin and also occurred at a ≥1% higher frequency with saxagliptin compared with metformin monotherapy were nasopharyngitis, bronchitis, headache, upper respiratory tract infection, arthralgia, dyspepsia, and hypertension. The frequency of SAEs for saxagliptin 5 mg plus metformin and metformin monotherapy was 2.5% and 2.4%, respectively, and the frequency of AEs leading to discontinuation of study drug was 2.5% and 3.4%, respectively).

**Additional Safety Considerations**

Data on the occurrence of AEs of special interest in patients treated with saxagliptin or comparators are summarized in Table 4.

**Hypoglycemia.** In the placebo-controlled pooled safety analysis, the frequency of all reported hypoglycemic events, up to week 24 regardless of rescue status, was 7.6%, 7.8%, and 6.8% for saxagliptin 2.5 mg, 5 mg, and placebo, respectively; the frequency of confirmed hypoglycemic events was 0.8%, 0.5%, and 0.4%, respectively, and there was no evidence of a dose relationship for hypoglycemic risk. In the initial combination with metformin study, the frequency of reported hypoglycemic events up to week 24 was 3.4% with saxagliptin 5 mg plus metformin and 4.0% with metformin monotherapy; the frequency of confirmed hypoglycemia was 0% and 0.3%, respectively.

**Skin and Subcutaneous Tissue Disorders.** In the placebo-controlled pooled safety analysis, the frequency of skin-related AEs, up to week 24 regardless of rescue status, was 9.3%, 7.1%, and 7.3% for saxagliptin 2.5 mg, 5 mg, and placebo groups. A dose relationship was not evident for saxagliptin 2.5 mg or 5 mg in this analysis. In the initial combination with metformin study, the frequency of skin-related AEs up to week 24 excluding rescued patients was 3.4% and 2.7% in the saxagliptin 5 mg plus metformin and metformin monotherapy groups.

**Hypersensitivity Events.** In the placebo-controlled pooled safety analysis, the frequency of hypersensitivity AEs was 1.5%, 1.5%, and 0.4% for the saxagliptin 2.5 mg, 5 mg, and placebo groups, respectively. All hypersensitivity AEs in the saxagliptin groups were characterized by the investigator as mild or moderate in intensity, and none were SAEs. In the initial combination with metformin study, the frequency of hypersensitivity AEs was 0.6% in both of the saxagliptin 5 mg plus metformin and metformin monotherapy groups.

**Infections and Infestations.** Infections were the most common types of AEs across the phase III clinical trial program. In the placebo-controlled pooled safety analysis, the frequency of infection-related AEs was comparable across treatment groups up to week 24 regardless of rescue status (saxagliptin 2.5 mg,
TABLE 5 Changes from Baseline in Lymphocyte Counts in the Placebo-Controlled Pooled Analysis* at Week 24, Including Rescue

<table>
<thead>
<tr>
<th>Change from baseline (x 10^9 cells/µL)</th>
<th>Median</th>
<th>Change from baseline (x 10^9 cells/µL)</th>
<th>Median</th>
<th>Placebo (n = 394)</th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ± SE (95% CI)</td>
<td></td>
<td>Mean ± SE (95% CI)</td>
<td></td>
<td>Mean ± SE (95% CI)</td>
<td></td>
</tr>
<tr>
<td>0.00 ± 0.026 (-0.05, 0.05)</td>
<td>-0.04</td>
<td>-0.11 ± 0.025 (-0.16, -0.06)</td>
<td>-0.11</td>
<td>-0.01 ± 0.028 (-0.06, 0.05)</td>
<td>-0.02</td>
</tr>
<tr>
<td>3.06 ± 1.450 (0.21, 5.91)</td>
<td>-1.64</td>
<td>-2.23 ± 1.60 (-4.51, 0.05)</td>
<td>-5.10</td>
<td>2.90 ± 1.375 (0.19, 5.60)</td>
<td>-0.88</td>
</tr>
</tbody>
</table>

*Includes 2 saxagliptin monotherapy trials and 1 trial each of saxagliptin as add-on to metformin, thiazolidinedione, and glyburide.
CI = confidence interval; mg = milligram; SAXA = saxagliptin; SE = standard error, µL = microliter.

36.4%; saxagliptin 5 mg, 35.9%; placebo, 34.8%). The most frequent infection-related AEs across the placebo-controlled pooled safety analysis studies (≥2% in the saxagliptin 2.5 mg or 5 mg groups compared with placebo) were upper respiratory tract infection (7.0%, 7.7%, 7.6%), urinary tract infection (5.1%, 6.8%, 6.1%), nasopharyngitis (5.7%, 5.6%, 6.8%), influenza (3.9%, 3.4%, 4.4%), sinusitis (2.9%, 2.6%, 1.6%), gastroenteritis (1.9%, 2.3%, 0.9%), pharyngitis (2.5%, 2.3%, 2.3%), and bronchitis (2.7%, 2.2%, 1.8%). The only infection-related AEs with >1% difference in the saxagliptin 2.5 mg or 5 mg groups when compared with the placebo group were sinusitis and gastroenteritis. In the initial combination with metformin study, the frequency of infection-related AEs up to week 24, excluding events occurring after rescue, was 22.8% and 23.5% for saxagliptin 5 mg plus metformin versus metformin monotherapy.

Lymphopenia. In the placebo-controlled pooled safety analysis, the frequency of AEs of lymphopenia up to week 24, regardless of rescue status, was 0.5%, 1.5%, and 1.0% for saxagliptin 2.5 mg, 5 mg, and placebo groups, respectively. In the initial combination with metformin study, the frequency of lymphopenia up to week 24, excluding events occurring after rescue, was 0% and 0.3% for saxagliptin 5 mg plus metformin versus metformin monotherapy.

Absolute Lymphocyte Count. A reduction of lymphocyte count was observed in patients receiving saxagliptin 5 mg but not those receiving the 2.5 mg dose; however, the clinical relevance of this decline was not evident. The decline from baseline to week 24 was approximately 100 cells per microliter (µL; 5%) with saxagliptin 5 mg relative to placebo (mean baseline absolute lymphocyte count approximately 2,200 cells/µL; Table 5). No increase in the magnitude of this effect was discernable over time. Similar effects were observed when saxagliptin 5 mg was given in initial combination with metformin compared with metformin alone.

Thrombocytopenia. In the placebo-controlled pooled safety analysis, the frequency of AEs of thrombocytopenia was 0.5%, 0.2%, and 0.1% for the saxagliptin 2.5 mg, 5 mg, and placebo groups, respectively. No clinically meaningful or consistent effects on platelet counts were seen with saxagliptin 2.5 mg or 5 mg across the phase III clinical trial program. In the initial combination with metformin study, thrombocytopenia was not observed in the saxagliptin 5 mg plus metformin group; 1 event (0.3%) occurred in the metformin monotherapy group.

Localized Edema. The frequency of localized edema AEs in the placebo-controlled pooled safety analysis was 0.9%, 2.3%, and 1.1% in the saxagliptin 2.5 mg, 5 mg, and placebo groups, respectively. The frequency of localized edema AEs was 0.6% in the saxagliptin 5 mg plus metformin and metformin monotherapy group; no cases of edema were reported in the initial combination with metformin study.

Cardiovascular Adverse Events. In the placebo-controlled pooled safety analysis, the frequency of cardiovascular AEs up to week 24 regardless of rescue status was 0.6%, 0.2%, and 1.0% for the saxagliptin 2.5 mg, 5 mg, and placebo groups, respectively. In the initial combination with metformin study, the frequency of CV-related AEs was 0.9% in the metformin monotherapy group and 0% in the saxagliptin 5 mg plus metformin group.

Overall, there were no safety signals or trends identified for saxagliptin from vital signs, physical findings, or ECGs. Blood pressure minimally declined in all saxagliptin phase III studies; this was similar to the blood pressure reductions seen with placebo or comparator. Clinical laboratory values (e.g., liver function tests, creatine kinase levels, hematology, serum chemistries, hypoglycemia, and renal function) did not show any imbalances between saxagliptin and placebo or comparator.

Discussion

This safety analysis of the saxagliptin phase III clinical trial program demonstrated that saxagliptin was generally well tolerated as monotherapy; add-on combination with metformin, glyburide, or a TZD; or initial combination with metformin.17,20,23,25 Specifically, the placebo-controlled pooled safety analysis demonstrated that the overall frequency of AEs was comparable for patients who received saxagliptin 2.5 mg, 5 mg, or placebo. In addition, the overall safety of the initial combination of saxagliptin 5 mg plus metformin was comparable to that with metformin monotherapy.23 Analyses of AEs in
long-term extension trials of the phase III studies for which data are available have not revealed any differences in the AE profile when compared with analyses performed for the 24-week trials.²⁸,²⁹

The safety profile of saxagliptin reflects general observations within the class of DPP-4 inhibitors.⁴ The overall incidence of AEs with sitagliptin and vildagliptin was comparable to that reported with placebo in monotherapy trials.¹⁴,²⁷,³⁰–³² In a pooled analysis, AEs were similar between sitagliptin (100 mg/day) and placebo, and there was a low incidence of hypoglycemia and a small increase in the incidence of nasopharyngitis.²⁷ A meta-analysis by Amori et al. (2007)¹³ suggested that DPP-4 inhibitors are associated with increased risk for nasopharyngitis, urinary tract infections, and headache. In the current placebo-controlled pooled safety analysis, these AEs occurred at a frequency ≥5% in the saxagliptin 2.5 mg or 5 mg treatment groups, but none occurred at rates ≥1% higher than the rate in the placebo group. AEs that occurred at a frequency of ≥2% with saxagliptin 2.5 mg or 5 mg and also occurred at a ≥1% higher frequency with saxagliptin compared with placebo were sinusitis, gastroenteritis, abdominal pain, and vomiting. A 5% decrease from baseline to week 24 in absolute lymphocyte counts occurred in the pooled-study patients receiving saxagliptin 5 mg but not in patients receiving saxagliptin 2.5 mg or placebo. The decrease in lymphocytes was not statistically significant and did not appear to be clinically relevant. In the initial combination with metformin study, the only AEs that occurred at a frequency ≥5% in the saxagliptin plus metformin group when compared with the metformin monotherapy group were nasopharyngitis and headache.

The incidence of AEs of special interest was generally comparable among the treatment arms of saxagliptin 2.5 mg, 5 mg, and placebo in the placebo-controlled pooled safety analysis and between the treatment arms of saxagliptin 5 mg plus metformin and metformin alone in the initial combination study. However, there was a higher incidence of hyperglycemia-related events in saxagliptin-treated patients compared with placebo-treated patients in the placebo-controlled pooled safety analysis (1.5% vs. 0.4%). None of these AEs in saxagliptin-treated patients required hospitalization or were reported as life threatening by the investigator.

While there was a modest decrease in absolute lymphocyte count in patients receiving saxagliptin 5 mg, it was not associated with an increased frequency of infection-related AEs. The overall frequency of lymphopenia was low in each study and similar among all treatment groups in the placebo-controlled pooled safety analysis. Therefore, the observed decrease in lymphocyte count with saxagliptin 5 mg does not appear to be associated with adverse clinical consequences.

Treatment with glyburide has been associated with an increased frequency of hypoglycemia, both in monotherapy and in combination with other oral antidiabetic agents.⁶ The incidence of reported hypoglycemic events was not significantly increased when saxagliptin 2.5 mg or 5 mg was added to glyburide compared with up-titrated glyburide (13.3%, 14.6%, and 10.1%, respectively). Nevertheless, the frequency of reported hypoglycemic events was higher in the add-on glyburide study than in the other placebo-controlled trials. Therefore, an additional pooled analysis was conducted that excluded the add-on glyburide trial; it demonstrated no differences in hypoglycemic events between the saxagliptin and placebo groups. Similar results were obtained in the initial combination with metformin study. These findings suggest that saxagliptin does not increase the risk of hypoglycemia when used in nonsulfonylurea OAD combination regimens. Notably, the combination of saxagliptin and metformin may offer particular advantages over other combination regimens, such as complementary mechanisms of action that result in enhanced efficacy without increasing the risk of hypoglycemia. This reflects the glucose-dependent mechanism of action of DPP-4 inhibitors, in contrast with antihyperglycemic agents such as glyburide, which induce insulin secretion irrespective of circulating glucose concentrations.¹³,³³,³⁴

Assessment of hypoglycemia with the DPP-4 inhibitors sitagliptin and vildagliptin has demonstrated similar results in add-on and combination studies. For example, sitagliptin was well tolerated with no increased risk of hypoglycemia as an add-on to pioglitazone versus pioglitazone monotherapy (incidence rate: 1.1% vs. 0%),⁵ as add-on to metformin versus metformin monotherapy (1.3% vs. 2.1%),⁶ as add-on to metformin versus sitagliptin monotherapy (no hypoglycemia events in either group),⁵⁷ and as add-on to metformin versus glipizide plus metformin (4.9% vs. 32.0%).³⁸ Similarly, there was a low incidence of hypoglycemia with vildagliptin plus metformin compared with pioglitazone plus metformin (0.3% vs. 0%)³⁹ and compared with metformin monotherapy (0% vs. 0.7%).⁴⁰ The current analysis supports these findings, demonstrating that the DPP-4 inhibitors are well tolerated with a low risk of hypoglycemia when used as monotherapy or add-on to OAD therapy.

Limitations

Certain limitations should be considered when evaluating the data presented in this article. The purpose of the pooled analysis of placebo-controlled monotherapy and add-on therapy trials was to identify any safety signals that might not have been identified in the smaller populations of the individual trials; the initial combination study was reported separately because patients in that study had new-onset T2DM and the comparison was of initial add-on rather than sequential add-on therapies. However, because of a multiplicity of end points and a lack of statistical power, no formal statistical analysis of between-group differences across the studies (saxagliptin 2.5 mg vs. 5 mg, saxagliptin 2.5 mg vs. placebo, saxagliptin
Tolerability of Saxagliptin in Patients with Inadequately Controlled Type 2 Diabetes: Results from 6 Phase III Studies

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5 mg vs. placebo) was performed. Similarly, there was no formal analysis of differences between saxagliptin plus metformin versus metformin monotherapy in the initial combination study. These findings are nonetheless informative, as even differences not large enough to achieve statistical significance have the potential to be clinically relevant. In addition, the studies included in this analysis were of relatively short duration (i.e., 24 weeks) and, therefore, may not have revealed AEs that may occur with longer exposure to the study drug. A recent long-term analysis, however, demonstrated that there is no increase in AEs associated with administration of saxagliptin versus placebo for up to 102 weeks.28

Conclusion

Across 6 double-blind phase III clinical trials, saxagliptin was generally well tolerated as monotherapy; as add-on combination therapy with metformin, glyburide, or a TZD; and as initial combination therapy with metformin in patients with T2DM.

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References

Tolerability of Saxagliptin in Patients with Inadequately Controlled Type 2 Diabetes: Results from 6 Phase III Studies

Economic Burden of Urgency Urinary Incontinence in the United States: A Systematic Review

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ABSTRACT
BACKGROUND: The International Continence Society (ICS) identifies several urinary incontinence (UI) subtypes: urgency urinary incontinence (UUI), stress UI (SUI), and mixed UI (MUI). UUI is a common symptom of overactive bladder (OAB) syndrome. Based on the current ICS definition of OAB, all patients with UUI have OAB, whereas not all patients with OAB have UUI. Because UUI is a chronic condition that is expected to increase in prevalence as the population of elderly individuals grows, it is important to understand its economic burden on society and patients and its cost components.

OBJECTIVE: To summarize the published English language medical literature on estimates of the economic burden of UUI in the United States from a societal and patient perspective, including direct costs (diagnosis, treatment, routine care [including incontinence pads], and UUI-associated comorbidities/complications); indirect costs (lost wages by patients and caregivers and lost work productivity due to absenteeism and presenteeism); and intangible costs (pain, suffering, and decreased health-related quality of life).

METHODS: A PubMed search of the literature for articles on the economic burden of UUI in the United States was conducted using the search terms (urgency urinary incontinence OR urge incontinence OR mixed incontinence OR overactive bladder) AND (burden OR cost OR economic) AND (United States), with limits for English language, publication from 1991 to 2011, humans, and adults (19+ years). Only primary articles of non-neurogenic UUI in the United States were retained.

RESULTS: Seven studies were identified that included data on the economic burden of UUI in the United States from a societal and patient perspective. Although estimates of the total economic burden of UUI include direct, indirect, and intangible costs, none of the 7 U.S. studies included all of these cost components. Furthermore, the costs of UUI often could not be fully extracted from the costs of OAB, which include patients with and without UUI, or the costs of other types of UI. The most recent cost analysis incorporated OAB with UUI prevalence rates and data on use of each cost component to calculate the total annual direct costs in 2007 for adults aged ≥25 years. The estimated total national cost of OAB with UUI in 2007 was $65.9 billion, with projected costs of $76.2 billion in 2015 and $82.6 billion in 2020. This 2007 estimate was markedly higher than those reported in older studies. Direct costs are the main driver of the overall cost of UUI in the United States. Studies that assessed patient costs indicated that the personal costs of routine care items for UUI and MUI represent a meaningful contribution to the overall economic burden of these conditions. These substantial personal expenditures may explain why patients reported that they were willing to pay considerable amounts for a treatment that would reduce the frequency of their UUI episodes.

CONCLUSIONS: UUI in the United States is associated with a substantial economic burden from both a societal and patient perspective. Studies evaluating the impact of interventions that reduce the frequency of UUI episodes on the overall economic burden of UUI are warranted.

What is already known about this subject
• Urgency urinary incontinence (UUI) is a common chronic condition in men and women that increases in prevalence with increasing age and often remains undiagnosed and untreated.
• Estimates of the overall economic burden of UUI are dependent on the accuracy of prevalence data for UUI.

What this study adds
• A review of the literature indicates that detailed analyses of the total economic burden of UUI in the United States are limited and difficult to compare because of the different methodologies used.
• Overall, the available evidence demonstrates that UUI imposes a considerable economic burden on society and individual patients in the United States, with a substantial increase in societal costs projected to occur over the next several years with the aging of the population.
• Research on the impact of effective interventions on the economic burden of UUI is warranted.

The International Continence Society (ICS) identifies several urinary incontinence (UI) subtypes: urgency urinary incontinence (UUI), defined as the complaint of involuntary loss of urine associated with urgency; stress UI (SUI), defined as the complaint of involuntary loss of urine on effort or physical exertion or on sneezing or coughing; and mixed UI (MUI), defined as the complaint of involuntary loss of urine associated with urgency and with exertion, effort, sneezing, or coughing (i.e., UUI and SUI).1,2 UUI is a common symptom of overactive bladder (OAB) syndrome, defined by the ICS as urinary urgency, usually accompanied by frequency (typically defined in clinical trials as ≥8 micturitions per 24 hours) and nocturia (defined by the ICS as ≥1 micturition interrupting sleep), with or without UUI, in the absence of urinary tract infection or other obvious pathology.1,2 UUI is a highly bothersome symptom that affects many aspects of a patient’s health-related quality of life (HRQL).3-6 UUI is also a driver of health care-seeking behavior, although approximately 3 of 4 individuals with UUI do not receive treatment.6 Based on the current ICS definition of OAB, all patients with UUI have OAB, whereas not all patients with OAB have UUI.
## TABLE 1  
Studies of the Prevalence of UUI in the United States

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample</th>
<th>Survey (Response Rate)</th>
<th>UUI Definition/Questions</th>
<th>UUI Prevalence</th>
</tr>
</thead>
</table>
| Coyne et al. 2012; Coyne et al. 2011 (EpiLUTS Survey)               | 20,000 adults (9,416 men; 10,584 women) aged ≥ 40 years               | Population-based, cross-sectional, Internet survey in 2007-2008 (60%)                | 2002 ICS  
1. During past 4 weeks, did you leak urine in connection with sudden need to rush to urinate?  
   Response: yes/no  
2. During past 4 weeks, how often have you leaked urine in connection with a sudden need to rush to urinate?  
   Response: ≤ once a month/≥ a few times a month/≥ once a week/daily/many times a day  
UUI=(1) yes and (2) at least a few times a month                          | By gender: 14.2% for men; 30.8% for women  
Of subjects with OAB symptoms (prevalence: men 27.2%, women 43.1%), 52.3% of men and 71.5% of women reported UUI |
| Dooley et al. 2008 (NHANES)                                          | 4,229 white, black, and Mexican-American community-dwelling women aged ≥ 20 years | NHANES 2001-2004 representative-sample, interview survey                           | During the past 12 months have you leaked or lost control of even a small amount of urine with an urge or pressure to urinate and you could not get to the toilet fast enough?  
UUI=UUI only  
MUI=UUI and SUI                                                             | Women: UUI only 7.9%; MUI 17.0%  
By age: UUI: 4.6% for 20-39 years; 8.7% for 40-59 years; 11.7% for ≥ 60 years  
MUI: 7.7% for 20-39 years; 18.6% for 40-59 years; 28.7% for ≥ 60 years  
By race: UUI: 7.5% for whites; 11.0% for blacks; 7.5% for Mexican-Americans (white women significantly lower OR for UUI than black women after adjusting for age, BMI, live births, diabetes)  
MUI: 17.8% for whites; 14.3% for blacks; 13.2% for Mexican-Americans |
| Diokno et al. 2007 (NFO Survey)                                      | 21,590 male heads of household aged ≥ 18 years matched to 2000 U.S. Census for age, geographic region, income, household size | Cross-sectional mail survey in 2001 (67%)                                           | UUI=yes to ≥ 1 of 2 questions on leakage or loss of urine because of an urge to urinate with no advanced warning during last 30 days;  
MUI=reported ≥ 1 UUI and ≥ 1 SUI symptom                                      | Men: 4.3% of men aged ≥ 18 years reported UUI; 1.8% reported MUI  
By age: UUI and MUI prevalence rates increase with age in men (UUI: ~30% and 57%; MUI: ~15% and 22% for 18-35 years and >75 years) |
| Thom et al. 2006 (RRISK)                                            | 2,109 women aged 40-69 years as of 1999 with goal of ~20% black, ~20% Hispanic, ~20% Asian-American, ~40% white | Population-based cohort study with self-report questionnaires and interviews        | ≥ 1 episode in last 12 months (with a physical sense of urgency), by monthly, monthly, weekly, or daily frequency  
UUI=UUI only or MUI with the majority of episodes being urge (rather than stress) | Women: 9.7% (UUI only and MUI predominantly UUI ≥ weekly, adjusted for age)  
By race: UUI only (≥ weekly): 4.8% for whites; 7.6% for blacks; 5.8% for Hispanics; 3.0% for Asian-Americans (P=0.03)  
MUI (predominantly urge; ≥ weekly): 4.0% for whites; 6.0% for blacks; 4.2% for Hispanics; 4.4% for Asian-Americans (not significant)  
MUI (equal urge and stress; ≥ weekly): 3.3% for whites; 1.9% for blacks; 3.5% for Hispanics; 3.2% for Asian-Americans (not significant)  
UUI only or MUI with the majority of episodes being urge (≥ weekly); OR similar in black, Hispanic, and Asian-American women vs. white women after adjusting for age, parity, hysterectomy, estrogen use, BMI, menopausal status, diabetes |
| Jackson et al. 2004 (Health, Aging, and Body Composition Study)      | 1,558 white and black, community-dwelling, well-functioning women aged 70-79 years with UI question data | Cross-sectional analysis of longitudinal cohort study with enrollment in 1997-1998 | In the past 12 months: when does your leakage of urine usually occur?  
Response (UUI): when you have the urge to urinate and can’t get to the bathroom quick enough.  
Multivariate analyses: significantly higher adjusted ORs for white race (OR = 3.1), current estrogen use (OR = 1.7), arthritis (OR = 1.7), diabetes treated with insulin (OR = 3.5), depressive symptoms (OR = 2.7), and decreased lower extremity physical performance (OR = 1.6) for women with UUI ≥ weekly vs. those with no UI | Women: 8.9% (UUI ≥ weekly; 138 of 1,558 women) |
## TABLE 1  
**Studies of the Prevalence of UUI in the United States (continued)**

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample</th>
<th>Survey (Response Rate)</th>
<th>UUI Definition/Questions</th>
<th>UUI Prevalence</th>
</tr>
</thead>
</table>
| Stewart et al. 2003 (NOBLE Program)³ | 5,204 adults aged ≥18 years (2,469 men; 2,735 women) | Population-based, cross-sectional, telephone survey in 2000-2001 (68%) | 1. ≥4 urgency episodes in the last 4 weeks  
2. Either ≥8 micturitions/day or use of a coping strategy  
3. ≥3 episodes of urinary leakage in the past 4 weeks not due exclusively to SUI | Overall: 6.1% (2.6% for men; 9.3% for women; did not vary by race) for adults aged ≥18 years  
By age: significantly steeper age-related increase in women vs. men (e.g., 19.1% for women aged 65-74 years vs. 8.2% for men aged 65-74 years) |
| Espino et al. 2003 (Hispanic EPSE)¹¹ | 1,589 Mexican-American women aged ≥65 years | Community-based, in-home interview in 1993-1994 | Do you have a feeling of needing to urinate before you lose your urine? | Women: UUI 5.0%; MUI 6.3% |
| Sze et al. 2002¹² | 2,370 (932 white, 799 black, and 639 Hispanic) women aged 15-94 years from gynecology clinics | Clinic-based survey in 2000-2001 | Do you lose urine less than 5 minutes after you feel the urge to urinate more than once per week? | Women: UUI: 16% for whites; 19% for blacks; 16% for Hispanics (P=0.214)  
MUI: 15% for whites; 14% for blacks; 9% for Hispanics (P<0.001)  
By race: Nulliparous Hispanic women aged <30 years were significantly more likely to have UUI or MUI than black or white women (P=0.002); multiparous black women aged 30-50 years were significantly more likely to have UUI than Hispanic or white women (P=0.008); multiparous black or white women aged 30-50 years were significantly more likely to have UUI or MUI than Hispanic women (P=0.011) |
| Brown et al. 2000 (SOF)¹³ | 6,049 community-dwelling white women aged 72-99 years from population-based listings at 4 clinical centers who provided UI information and 1 follow-up on falls | Longitudinal survey in 1994-1996 | 1. During the last 12 months, have you ever leaked or lost control of your urine? If yes:  
2. How often does this leakage of urine usually occur: daily, ≥1 times per week but not every day, ≥1 times per month but not every week, <once per month?  
3. Under what circumstances does your leakage of urine usually occur: when I cough/sneeze/laugh/lift/stand up/exercise, etc. (SUI); when I have the urge to urinate and can’t get to the toilet last enough (UUI); when I am sleeping/napping/dozing (other)  
UUI=(1) yes and (2) ≥1 times per week but not every day; (3) UUI | Elderly women: 24.7% of women aged 72-99 years reported UUI; 11.7% reported MUI |
| Nygaard et al. 1996 (Iowa 65+ Rural Health Study of EPSE)¹⁴ | 2,025 women aged ≥65 years | 6-year, longitudinal, community-based survey in 1981-1982 (baseline) | How often do you have difficulty holding your urine until you can get to the toilet?  
Response: never, hardly ever, some of the time, most of the time, all of the time  
UUI= ≥some of the time | Elderly women: 36.3% at baseline (increased with increasing age; P=0.017) |

BM* = body mass index; EPSE = Establishment of Populations for Epidemiology Studies of the Elderly; EpiLUTS = Epidemiology of Lower Urinary Tract Symptoms; Health ABC = Health, Aging, and Body Composition; ICS = International Continence Society; MUI = mixed urinary incontinence; NFO = National Family Opinion; NHANES = National Health and Nutrition Examination Survey; NOBLE = National Overactive Bladder Evaluation; OAB = overactive bladder; OR = odds ratio; RRISK = Reproductive Risks of Incontinence Study at Kaiser; SOF = Study of Osteoporotic Fractures; SUI = stress urinary incontinence; UI = urinary incontinence; UUI = urgency urinary incontinence.
UUI-specific prevalence data can be difficult to locate in the medical literature because they are often embedded within OAB or overall UI prevalence data. To date, the prevalence of UUI among adults in the United States has been estimated in 10 studies conducted from 1981 to 2007 (Table 1). The overall prevalence of UUI (both UUI alone and MUI [i.e., UUI and SUI]) ranged from 2.6% to 14.2% in U.S. men and from 8.9% to 36.3% in U.S. women. As the population of older individuals increases, the number of affected individuals is expected to increase with the continued aging of the population. Because UUI is a prevalent condition, it is important to understand its economic burden to society and the individual patient and to identify the components contributing to this burden. A complete and up-to-date estimate of the economic burden of UUI is crucial to the proper allocation of health care resources.

Although variability exists in published prevalence rates, the overall evidence indicates that UUI is a common and chronic condition that affects millions of U.S. adults, and the number of affected individuals is expected to increase with the aging of the population. Because UUI is a prevalent condition, it is important to understand its economic burden to society and the individual patient and to identify the components contributing to this burden. A complete and up-to-date estimate of the economic burden of UUI is crucial to the proper allocation of health care resources.

The total economic burden of UUI includes 3 categories of expenditures: direct costs (diagnosis, treatment, routine care [including incontinence pads], and UUI-associated comorbidities/complications); indirect costs (lost wages by patients and caregivers and lost work productivity due to absenteeism and presenteeism); and intangible costs (pain, suffering, and decreased HRQL). Intangible costs are difficult to assess but can be estimated using quality-adjusted life years or the willingness-to-pay method. The purpose of this review is to summarize the published medical literature on estimates of the economic burden of UUI on society and patients in the United States.

**Methods**

A search of the literature on the economic burden of UUI in the United States was conducted using PubMed on March 17, 2012, and updated September 7, 2012, based on the recommendations in the PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analyses) statement. The following search terms were used to identify relevant articles: (urgency urinary incontinence OR urge incontinence OR mixed incontinence OR overactive bladder) AND (burden OR cost OR economic) AND (United States), with limits for English language, publication from 1991 to 2011 (electronic or print), humans, and adults (19+ years). Criteria for inclusion or exclusion of retrieved articles were determined a priori; article review was conducted independently by 3 reviewers. Articles reporting data on direct costs (diagnosis, treatment, routine care [including incontinence pads], and UUI-associated comorbidities/complications); indirect costs (lost wages by patients and caregivers and lost work productivity due to absenteeism and presenteeism); and/or intangible costs (pain, suffering, and decreased HRQL) were included if they provided costs specifically for adults with UUI only or MUI or adults with OAB with UUI. Articles were excluded if they were (a) non-U.S. studies; (b) reviews or comments; (c) primarily assessing neurogenic UUI, UUI diagnosis, UUI treatment/management outcomes, pregnancy-associated UUI, surgery-associated or surgically treated UUI, or questionnaire validity; (d) duplicate articles; or (e) updated in a more recent article. References cited in the retained articles were

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**FIGURE 1** PRISMA Flow Diagram of Article Identification, Inclusion, and Exclusion

<table>
<thead>
<tr>
<th>Records identified through database searching (n=63)</th>
<th>Records identified through other sources (n=2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Records after duplicates removed (n=65)</td>
<td>Full-text articles assessed for eligibility (n=65)</td>
</tr>
<tr>
<td>Articles included in qualitative synthesis (n=7)</td>
<td>Full-text articles excluded (n=58)</td>
</tr>
<tr>
<td>No UUI (n=32)</td>
<td>Surgery/treatment (n=14)</td>
</tr>
<tr>
<td>Review (n=11)</td>
<td>Neurogenic (n=1)</td>
</tr>
</tbody>
</table>

PRISMA = Preferred Reporting Items for Systematic Review and Meta-Analysis; UUI = urgency urinary incontinence.
### TABLE 2  
Studies Reporting Economic Burden of UUI in the United States

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample Description</th>
<th>Analysis Perspective/Design</th>
<th>Cost Components</th>
<th>Model and Data Used in Cost Assessments</th>
<th>Reported Costs (USD Year)</th>
<th>Adjusted Costs (USD 2012)*</th>
</tr>
</thead>
</table>
| Ganz et al. 201020           | All subjects aged ≥25 years with OAB (urgency with UUI) from community and institutions | Societal/prospective        | Directs costs: physician visits, diagnostic laboratory tests, anticholinergic medications, OTC medications, physical therapy, surgical procedures, ER visits, UUI treatment, falls/fractures costs, OAB-related depression costs, OAB-related nursing home costs, costs of panti-liners, pads, diapers, latex gloves, bedside toilet, skin protection  | Cost-of-illness, prevalence-based model, with costs based on administrative data, using NOBLE study age- and gender-specific prevalence data for OAB with UUI, U.S. Census Bureau data, usage data, and NOBLE study work productivity data; U.S. Census population projections were used to project the costs to 2015 and 2020  | Overall costs (USD 2007):  
  - Annual per capita: $1,925  
  - Total annual: $65.9 billion  
  - Direct costs (USD 2007):  
    - Annual per capita: $1,499  
    - Total annual: $51.4 billion  
  - Indirect costs (USD 2007):  
    - Annual per capita: $426  
    - Total annual: $14.6 billion  
  - Projected costs:  
    - Annual per capita: $1,944 in 2015, $1,969 in 2020  
    - Total annual: $76.2 billion in 2015, $82.6 billion in 2020  | Overall costs:  
  - Annual per capita: $2,132  
  - Total annual: $73.0 billion  
  - Direct costs: Annual per capita: $1,660  
  - Total annual: $56.9 billion  
  - Indirect costs: Annual per capita: $472  
  - Total annual: $16.2 billion  |
| Hu et al. 200421             | Adults aged ≥18 years with UI and/or OAB from community and institutions | Health care professionals and policy makers/prospective | Direct costs for UUI and MUI (community): pharmacologic treatment costs  
Direct costs for UUI and MUI (institution): diagnostic, pharmacologic, treatment, routine care, and consequence costs (skin, UTIs, falls/fractures) | Incremental cost-of-illness, prevalence-based model, with costs based on administrative data, using pooled daily UI prevalence data (men 5%, women 12%) and NOBLE prevalence data, study treatment data, consequence probabilities, cost estimates  
**Limitations:** only direct costs reported for UUI and MUI; intangible costs not included; only pharmacologic treatment costs reported by type of UI for community-based adults | Direct costs for UUI and MUI (community; USD 2000):  
  - Annual cost UUI and MUI treatment: $210 million  
Direct costs for UUI and MUI (institution; USD 2000):  
  - Total annual: $3.5 billion (diagnosis: $16.0 million; pharmacologic treatment: $3.7 million; routine care: $3.4 billion; consequence: $78.9 million) | Direct costs for UUI and MUI (community):  
  - Annual cost UUI and MUI treatment: $280 million  
Direct costs for UUI and MUI (institution):  
  - Total annual: $4.7 billion (diagnosis: $21.3 million; pharmacologic treatment: $4.9 million; routine care: $4.5 million; consequence: $105.2 million) |
| Hu et al. 200323             | Adults with OAB with UUI in a nursing home               | Societal/prospective        | Direct costs: diagnostic costs, treatment costs, routine care costs, and consequence costs (skin, UTIs, bone fractures) | Cost-of-illness, prevalence-based model, with costs based on administrative data, using method of aggregating individual-level data pertaining to the average cost of treatment or supply use, multiplied by the average amount of health care use | Direct costs of OAB+UUI (institution; USD 2000):  
  - Total annual: $2.85 billion  
  - Routine care: $2.77 billion  
  - Other: $0.08 billion  
  - Annual per capita: $5,635  | Direct costs of OAB+UUI (institution):  
  - Total annual: $3.80 billion  
  - Routine care: $3.69 billion  
  - Other: $0.11 billion  
  - Annual per capita: $7,513 |
| Wilson et al. 200124         | Adults of all age groups from community and institutions | Societal/prospective        | Direct costs: routine care, diagnostic evaluation, treatment (surgical, behavioral, pharmacologic), consequences (skin, UTIs, falls), nursing home admission | Prevalence-based model, with costs based on administrative data, using UI prevalence data from published studies, U.S. Census Bureau data, diagnosis and treatment algorithms, and mean Medicare reimbursement data  
**Limitations:** assumptions regarding those residing in community vs. institution and type of UI in community, indirect and intangible costs not included; only pharmacologic treatment cost reported by type of UI | Total treatment (USD 1995):  
  - $1.3 billion (SUI 82%; MUI 12%; UUI 4%)  | Total treatment: $2.0 billion |
TABLE 2
Studies Reporting Economic Burden of UUI in the United States (continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample Description</th>
<th>Analysis Perspective/Design</th>
<th>Cost Components</th>
<th>Model and Data Used in Cost Assessments</th>
<th>Reported Costs (USD Year)</th>
<th>Adjusted Costs (USD 2012)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subak et al. 2007 (RRISK)27</td>
<td>Population-based study conducted from 1999 to 2003 of 528 community-dwelling women aged 40–69 years with ≥ weekly UI, MUI, or SUI</td>
<td>Patient/prospective</td>
<td>Direct costs: routine care (pads, diapers, laundry, dry cleaning, other)</td>
<td>Direct costs of routine care of UI were calculated using actual prevalence data, actual resource use, and mean national unit costs</td>
<td>Direct costs of routine care (USD 2005): Mean cost/wk: $6.35 for MUI; $6.02 for UUI; $3.91 for SUI</td>
<td>Direct costs of routine care: Mean cost/wk: $7.47 for MUI; $7.08 for UUI; $4.60 for SUI</td>
</tr>
<tr>
<td>Subak et al. 2006 (DAISy)28</td>
<td>Cross-sectional survey of 293 community-dwelling women aged ≥40 years with ≥3 UI episodes/wk, seeking treatment, not treated in prior 3 months conducted in 2005 at 5 sites</td>
<td>Patient/prospective</td>
<td>Direct costs: routine care (pads, diapers, toilet paper, paper towels, laundry, dry cleaning) Intangible costs: WTP for improvement in incontinence episode frequency</td>
<td>Direct costs of routine care of UI were calculated using actual resource use and national resource cost data, patient-reported WTP for UI improvement were assessed by UI type, with proportion of patients WTP plotted according to cost and stratified by percent improvement expected</td>
<td>Intangible costs (USD 2005): Women WTP mean of $28/mo ($336/year) for 25% improvement, $39/mo ($468/year) for 50% improvement, $49/mo ($588/year) for 75% improvement, $70/mo ($840/year) for 100% improvement in UI frequency (P&lt;0.001) WTP not significantly associated with UI subtype</td>
<td>Intangible costs: Women WTP mean of $33/mo ($395/year) for 25% improvement, $46/mo ($550/year) for 50% improvement, $58/mo ($691/year) for 75% improvement, $82/mo ($988/year) for 100% improvement in UI frequency (P&lt;0.001)</td>
</tr>
<tr>
<td>O’Conor et al. 199829</td>
<td>257 non-randomly selected patients with UI or MUI who completed a self-administered mail survey in 1997</td>
<td>Patient/prospective</td>
<td>Intangible costs: WTP for reduction in micturitions and urine leakages</td>
<td>Contingent valuation method, with relation between hypothetical costs and proportion of patients agreeing to purchase at given costs generating a demand curve Limitations: nonrandom sample; WTP can be sensitive to survey methodology and statistical analyses used</td>
<td>Intangible costs (USD 1997): For a 25% reduction in UUI/MUI symptoms, 70% of respondents willing to pay $10/month and 4% willing to pay $400/month. For a 50% reduction in UUI/MUI symptoms, 95% of respondents willing to pay $10/month and 13% willing to pay $400/month. Median willingness to pay was $27/month for 25% reduction and $76 for 50% reduction in symptoms.</td>
<td>Intangible costs: For a 25% reduction in UUI/MUI symptoms, 70% of respondents willing to pay $14/month and 4% willing to pay $572/month. For a 50% reduction in UUI/MUI symptoms, 95% of respondents willing to pay $14/month and 13% willing to pay $572/month. Median willingness to pay was $39/month for 25% reduction and $109 for 50% reduction in symptoms.</td>
</tr>
</tbody>
</table>

*Adjusted costs for 2012 were calculated using Consumer Price Index inflation calculator from U.S. Department of Labor, Bureau of Labor Statistics.29

CI = confidence interval; DAISy = Diagnostic Aspects of Incontinence Study; ER = emergency room; MUI = mixed urinary incontinence; NOBLE = National Overactive Bladder Evaluation; OAB = overactive bladder; OTC = over the counter; RRISK = Reproductive Risks of Incontinence Study at Kaiser; SUI = stress urinary incontinence; UI = urinary incontinence; USD = U.S. dollars; UTI = urinary tract infection; UUI = urgency urinary incontinence; wk = week; WTP = willingness to pay.
reviewed for additional articles. It was planned a priori that the 3 reviewers would discuss any inclusion/exclusion discrepancies; no such discrepancies occurred. Overall, of 63 articles retrieved by the PubMed search and 2 articles that were cited in the retrieved articles, 7 peer-reviewed articles that included U.S. cost data for UUI were retained (Figure 1). Data were qualitatively summarized. Cost data reported in the retained articles were adjusted to 2012 U.S. dollars (USD) using the Consumer Price Index inflation calculator from the U.S. Department of Labor, Bureau of Labor Statistics.19

Results

Seven national and patient-based studies that estimate the economic burden of UUI in the United States are summarized in Table 2.

U.S. National Studies

The most recent prevalence-based model by Ganz et al. (2010) incorporated age- and sex-specific prevalence rates of OAB with UUI, data on the use of various cost components, and work productivity data from the NOBLE study to calculate annual per capita and total U.S. costs (i.e., direct and indirect costs) for 2007 among community-dwelling and institutionalized adults aged ≥ 25 years. In addition, U.S. Census forecasts were used to project the costs for 2015 and 2020.20 The average annual per capita cost (USD in 2007) of OAB with UUI was estimated to be $1,925 ($1,433 direct medical costs, $66 direct nonmedical costs, and $426 indirect costs). After applying these costs to the total number of adults in the United States with OAB with UUI, the total national cost was $65.9 billion ($49.1 billion direct medical costs, $2.3 billion direct nonmedical costs, and $14.6 billion indirect costs). The average annual per capita cost in 2015 and 2020 is projected to be $1,944 and $1,969, respectively. The total national cost is projected to be $76.2 billion in 2015 and $82.6 billion in 2020, with the highest costs incurred by patients aged 75-84 years (Figure 2).20 These cost projections suggest that the total cost of OAB with UUI will increase by 25% from 2007 to 2020 in the United States, largely because of the aging of the population, and will be driven by direct costs rather than indirect costs. As a result, these increasing costs will be borne primarily by patients and private health insurance enrollees.20

In 2004, Hu et al.21 reported costs for OAB with UUI in community-dwelling and institutionalized adults aged ≥ 18 years using an incremental cost-of-illness, prevalence-based model that was based on prevalence data for daily UI22 and NOBLE study3 prevalence data, treatment data, consequence probabilities, and cost estimates based on USD in 2000. Because it was often not possible to separate costs for UI and OAB due to data limitations (i.e., UI costs included the costs for patients with OAB and UUI, and OAB costs included costs for UUI), the annual cost for pharmacologic treatment in community-dwelling adults ($210 million) and the total annual direct cost for institutionalized adults ($3.5 billion) were the only UUI-specific cost data reported.21 The cost of routine care, including absorbent pads, was $3.4 billion, which represented the primary contributor to the total annual direct cost of UUI and MUI.21 An annual direct cost for UUI and MUI in institutionalized adults of $2.9 billion (based on USD in 2000) was reported by Hu et al. in 2003 (Table 2).23 A high annual direct cost of UI in the United States was also reported in an analysis using a prevalence-based model and diagnostic and treatment algorithms from published clinical practice guidelines, UI prevalence data from published studies, and Medicare reimbursement data.24 The annual direct cost (USD in 1995) of UI was $16.3 billion ($12.4 billion for women, $3.8 billion for men). Among women, the annual direct cost was $8.6 billion for those in the community versus $3.8 billion for those who were institutionalized. The annual direct cost was higher for women aged ≥ 65 years ($7.6 billion) than for those aged < 65 years ($3.6 billion). Overall, the largest direct cost category was routine care ($11.3 billion; 70% of total direct costs), followed by nursing home admissions ($2.4 billion), treatment ($1.3 billion), complications ($1.0 billion), and diagnosis/evaluations ($0.2 billion). However, only the cost of treatment (behavioral, pharmacologic, and surgical) was analyzed according to UI subtype. For women, 85% of the total UI treatment cost was for SUI, 12% was for MUI, and 2% was for UUI; for men, the corresponding percentages were 55%, 14%, and 22%.24 Thus, the treatment costs for UUI and MUI combined contribute less to overall UI treatment costs than the treatment cost for SUI.

![Figure 2](https://www.amcp.org)
U.S. Patient-Based Studies

The cost of routine care (e.g., pads, diapers, laundry, and dry cleaning) from the patient perspective accounts for the majority of direct nonmedical costs associated with UUI in community dwellers. Routine care costs, especially for community-dwelling adults, are often borne by the individual patient or family members because patients frequently do not discuss their symptoms with or seek treatment from health care providers.

In a population-based study conducted from 1999 to 2003, 528 racially diverse, community-dwelling women aged 40-69 years (mean age, 57 years) with UUI (UUI alone or MUI with UUI predominant), SUI (SUI alone or MUI with SUI predominant), or MUI (neither UUI or SUI predominant) with ≥1 event per week were assessed as part of the Reproductive Risks for Incontinence Study at Kaiser (RRISK). Annual out-of-pocket costs (in 2005 USD) for routine care (i.e., pads, diapers, laundry, dry cleaning, other) were notably higher for women with UUI ($313 per year) or MUI ($330 per year) than for those with SUI ($204 per year). In a multivariate analysis model that included women with UI-related costs, the cost of routine care was higher for MUI than for SUI ($219 per year) for a 25% improvement, $39 per month ($468 per year) for a 50% improvement, $49 per month ($588 per year) for a 75% improvement, and $70 per month ($840 per year) for a 100% improvement in their UI frequency (P<0.001; Figure 3). In a multivariate logistic regression model, the willingness to pay for a 50% and 100% improvement was not significantly associated with the subtype of UI.

A total of 293 women (mean age, 56 years) reported that they were willing to pay a mean of $28 per month ($336 per year) for a 25% improvement, $39 per month ($468 per year) for a 50% improvement, $49 per month ($588 per year) for a 75% improvement, and $70 per month ($840 per year) for a 100% improvement in their UI frequency (P<0.001; Figure 3). As willingness to pay is a hypothetical assessment, the amounts that patients actually would pay are unknown.

The indirect cost of lost wages for patients with UUI or their caregivers was not estimated in any of the patient-based studies.

Discussion

Current studies reporting the total national cost of UUI in the United States are based on different analysis models, different populations, different cost components, and different prevalence estimates. However, the evidence consistently indicates that UUI places a substantial economic burden on society. Because the prevalence of UUI increases with age and the number of individuals aged ≥65 years will increase over the next decade, the prevalence rates of UUI alone and MUI are also expected to increase. The most recent analysis of direct costs for OAB plus UUI among adults aged ≥25 years estimated an annual national cost of $82.6 billion in 2020.

The results of patient-based studies indicate that the personal costs of routine care items for patients with UUI or...
MUI in the United States represent a meaningful contribution to the overall economic burden of these conditions. Perhaps because of these personal expenditures, patients reported that they would be willing to pay substantial additional amounts for a treatment that would reduce the frequency of their UUI episodes. Of note, the cost of lost wages for patients and caregivers associated specifically with UUI was not estimated in any study.

Possible approaches to reducing the significant economic burden of UUI are worthy of discussion. Toward this end, an accurate understanding of the cost components and their relative contribution to the overall costs of UUI are crucial. Direct costs are the main driver of the overall cost of UUI in the United States, with the cost of routine care items (e.g., diapers, incontinence pads) borne largely by the patient accounting for the majority (70%) of direct costs, followed by the costs of nursing home stays (14%), treatment (9%), complications (6%), and diagnosis/evaluations (1%).

Similar results for the breakdown of the contributors to the direct costs of OAB (incontinence pads, 63%; physician visits, 20%; drugs, 10%; and complication treatment, 7%) in 5 European countries were reported by Reeves et al. (2006), with the direct costs for patients with UUI representing 70% of the direct costs of the overall OAB population. Of note, the cost of treatment (behavioral, pharmacologic, and surgical) of UUI and MUI in the United States in 2001 was markedly less than that of SUI for the majority (70%) of direct costs, followed by the costs of nursing home stays (14%), treatment (9%), complications (6%), and diagnosis/evaluations (1%).

The first-line pharmacologic treatment for OAB symptoms, including UUI, is antimuscarinic therapy. U.S. Food and Drug Administration (FDA)-approved antimuscarinics indicated for the treatment of OAB symptoms include darifenacin (Enablex), fesoterodine (Toviaz), oxybutynin (Ditropan; Oxytrol), solifenacin (Vesicare), tolterodine (Detrol), and trospium (Sanctura), with oxybutynin and tolterodine available as generic products. Oxybutynin (Oxytrol) was approved by the FDA in 2013 as an over-the-counter treatment for women with OAB symptoms. Other recently licensed drugs for the treatment of OAB symptoms include onabotulinumtoxinA (Botox), an acetylcholine release inhibitor and neuromuscular blocker, and mirabegron (Myrbetriq), a β3-adrenoceptor agonist.

Based on the relative contribution of the costs of incontinence pads and nursing home stays versus the cost of treatment, it has been suggested that effective treatment of UUI and its complications may lessen the direct costs and economic burden of UUI.

The results of other studies suggest that effective treatment of UUI may lead to a reduction in resource utilization and result in cost containment. A study of 441 adults aged ≥18 years with diagnosed OAB, including 76% reporting UUI, who were followed up from the U.S. National Health and Wellness Survey found that patient-reported treatment success with prescription medications for OAB was associated with significantly lower rates of health care resource consumption (health care provider visits, P < 0.02; incontinence pad use, P < 0.001) and fewer complications (urinary tract infections, P < 0.013; skin infections, P < 0.034; falls, P < 0.017) compared with unsuccessful management. In a cohort study of 43,367 subjects aged ≥18 years who had at least 1 OAB symptom (i.e., UUI, urinary frequency, nocturia, bladder dysfunction) or were taking an antimuscarinic medication, annual direct medical costs (medications and all other pharmacy claims); outpatient care costs (emergency department visits, physician visits, laboratory tests, all outpatient services); and inpatient hospitalization costs were estimated in 2007 USD and compared with 43,367 matched nonpharmacologically managed patients. As expected, patients treated with pharmacologic medication had significantly higher mean annual pharmacy costs ($2,796) compared with nonpharmacologically managed patients ($2,150; P < 0.001). However, patients treated with pharmacologic medication had significantly lower annual OAB-related outpatient care costs ($176 vs. $277; P < 0.001) and inpatient costs ($47 vs. $93; P < 0.001) than nonpharmacologically managed patients. Finally, the results of a longitudinal cohort study of 275 patients aged ≥65 years with OAB symptoms, including UUI, and taking antimuscarinic medication indicated that increased antimuscarinic adherence was the most significant predictor of decreased annual costs for health care services in a managed care setting.

Overall, these results suggest that successful treatment can result in lower costs for health care services. Future research is needed to evaluate the impact of early diagnosis on the overall economic burden of UUI. In addition, controlled studies are needed to assess the impact of long-term treatment with drug therapy and behavioral modification on UUI costs. Finally, the effects of patient age and disease severity on national and patient costs of UUI need to be evaluated.

Limitations

There are several limitations of published articles that estimate the economic burden of UUI in the United States and, thus, of this review of those articles. First, the estimation of the economic burden of UUI is directly related to UUI prevalence data used in the cost analysis model; however, there is considerable variability in estimates of the prevalence of UUI, which is likely attributable to methodological differences among prevalence studies. As a result of the variability in UUI prevalence data, estimates of the economic burden of UUI also are highly variable. Second, few studies have estimated the economic burden of UUI in the United States without confounding from costs for OAB without UUI or other subtypes of UI. Third, cost estimates from different studies are not standardized to comparable U.S. dollar amounts. Because UUI is a large cost driver for patients with OAB, it is important to have accurate and up-to-date data on the costs that are attributable specifically to UUI. Recent studies of prevalence, which is a key component in many analysis models used for estimating economic burden of UUI.
burden, provide data for UUI, MUI, and SUI, thereby allowing a distinction among the different subtypes of UI. Future economic analyses will need to incorporate this same approach to improve the accuracy and our understanding of the costs specific to UUI, as well as the other UI subtypes.

Conclusions

UUI is a chronic and age-related condition that imposes a substantial economic burden on society and individual patients in the United States. Estimates of the overall costs of UUI are highly dependent on the accuracy of prevalence data and the cost components included in the analysis model, making it difficult to ascertain the true cost of UUI based on the limited number of available studies. Controlled studies of the impact of effective interventions that reduce the frequency of UUI episodes on the economic burden of UUI are warranted.

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DISCLOSURES

Funding for this study was provided by Pfizer Inc.

Coyne is an employee of United BioSource Corporation who was a scientific consultant to Pfizer. Wein consults/advises for Astellas, Allergan, Endo, Medtronic, Theravida, Pfizer, Ferring, Opko, Ethicon, Uroplasty, and Merck. Nicholson has been a consultant to Pfizer in connection with developing economic models of the costs associated with diabetes, cardiovascular disease, smoking, and urinary incontinence and has received grant support from Pfizer, Merck, J&J, and AstraZeneca. Kvasz was an employee of Pfizer PIO at the time this study was conducted. Chen is currently employed by Pfizer China. Milsom is a scientific consultant for Pfizer Inc. and United BioSource Corporation; has been an investigator for Pfizer and Astellas and a lecturer for Pfizer, Astellas, Recordati, SCA and Novartis; and has received grant support from Pfizer and Astellas.

All authors contributed equally to study concept and design, data interpretation, and writing and revision of the manuscript. Kvasz, Chen, and Coyle were responsible for data collection.

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REFERENCES


Evaluation of Increased Adherence and Cost Savings of an Employer Value-Based Benefits Program Targeting Generic Antihyperlipidemic and Antidiabetic Medications

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ABSTRACT

BACKGROUND: A major employer implemented a change to its employee health benefits program to allow beneficiaries with diabetes or high cholesterol to obtain preselected generic antidiabetic or generic antihyperlipidemic medications with a zero dollar copayment. To receive this benefit, plan beneficiaries were required to participate in a contracted vendor’s case management and/or wellness program.

OBJECTIVE: To assess changes in medication adherence and the costs for generic antidiabetic and generic antihyperlipidemic medications resulting from participation in a zero copay (ZCP) program.

METHODS: This was a retrospective pre-post comparison group study, evaluating adherence and cost. Participants using an antihyperlipidemic and/or antidiabetic medication during the study identification period and post-implementation period for the program were considered eligible for the study. Eligible beneficiaries who enrolled in the ZCP program during the post-implementation period were considered participants, while those who did not enroll during this period were considered nonparticipants. ZCP program participants and nonparticipants were matched via a 1-to-1 propensity scoring method using age, gender, comorbidity count, medication type (antihyperlipidemic, antidiabetic, or both), and baseline adherence as matching criteria. The proportion of days covered (PDC) metric expressed as a mean percentage was used to assess adherence to medication therapy, while payer cost was examined using prescription drug utilization expressed as per member per year (PMPY) and cost change per 30 days of medication expressed in dollars.

RESULTS: Among participants who were users of antidiabetic medications, the mean adherence rate was sustained from pre- to post-implementation (81.8% vs. 81.9%); however, it decreased in the matched nonparticipant group (81.9% vs. 73.1%). This difference in mean adherence over time between the participants and nonparticipants was statistically significant (0.1% vs. -8.8, P<0.001). Similar results were found among users of antihyperlipidemics. The mean adherence rate was sustained over time for participants (77.7% vs. 78.3%) but declined over time for nonparticipants (77.6% vs. 70.8%). The difference in mean change over time was statistically significant between participants and nonparticipants (0.6% vs. -6.8, P<0.001). Average prescription costs PMPY increased for participants of the ZCP program during the post-implementation period; however, the increase was not larger than the cost increase among nonparticipants ($581 vs. $584, P=0.95). Furthermore, among antihyperlipidemics the cost increase post-implementation was actually significantly less for participants than nonparticipants ($51 vs. $143, P<0.001).

CONCLUSIONS: Plan sponsors are increasingly evaluating the use of value-based benefit design (VBBD) to change member behavior. This ZCP program used a reduction in cost sharing to incentivize members to use more generic drugs and to enroll in a case management coaching program. The study also demonstrated that a VBBD program can have a positive impact on adherence and cost outcomes among those who participate compared with nonparticipants.

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What is already known about this subject

- Nonadherence to medication therapy is associated with increased risk for all-cause hospitalization (OR=1.58, 95% CI=1.38-1.81, P<0.001) and increased risk for all-cause mortality (OR=1.81, 95% CI=1.46-2.23, P<0.001).
- Copayment reductions are associated with improvements in medication adherence to antidiabetic therapy as measured by the medication possession ratio (MPR), which increased 4.9% (P<0.001) for the value-based benefit design (VBBD) group and decreased 2.3% (P<0.001) for the comparison group.

What this study adds

- Introduction of a VBBD targeting beneficiaries with diabetes and/or hyperlipidemia using a zero-dollar generic copayment as an incentive for participation can result in a large and statistically significant difference in adherence change over time between participants and nonparticipants of the program. In the antidiabetic and antihyperlipidemic medication groups, program participants exhibited statistically higher absolute mean changes in proportion of days covered from the pre-period to the post-period compared with the comparison group (antidiabetics: 0.1% vs. -8.8%, P<0.001; antihyperlipidemics: 0.6% vs. -6.8%, P<0.001). Increased drug utilization and reduced member cost sharing were achieved without increasing the plan sponsor’s cost for participants relative to nonparticipants. While average cost PMPY increased during the post-implementation period, it was not larger than the increase among nonparticipants ($581 vs. $584, P=0.95). Furthermore, among antihyperlipidemics, the cost increase was actually significantly less among participants than nonparticipants ($51 vs. $143, P<0.001).
Evaluation of Increased Adherence and Cost Savings of an Employer Value-Based Benefits Program Targeting Generic Antihyperlipidemic and Antidiabetic Medications

Value-based benefit design (VBBD), also known as value-based insurance design (VBID), refers to employer-based incentives designed to “encourage enrollee adoption of one or more of the following:

- appropriate use of high-value services, including certain prescription drugs and preventive services;
- adoption of healthy lifestyles, such as smoking cessation or increased physical activity; and
- use of high performance providers who adhere to evidence-based treatment guidelines. 

Enrollee incentives can include rewards, reduced premium share, adjustments to deductible and copay levels, and contributions to fund-based plans such as health savings accounts.

The focus of VBBD is on the relationship of beneficiary cost share to the value of, rather than to the cost of, clinical services. VBBD has been discussed as a way to improve employee health and productivity through enhanced consumer engagement. There is a high level of interest in VBBD among larger employers. A survey conducted in 2010 showed that 14% of employers with more than 500 employees and 25% of employers with more than 20,000 employees have implemented VBBD programs.

Nonadherence to medication therapy is a significant problem across chronic disease states. Nonadherence may be driven by myriad factors, including personal, sociodemographic, disease, comorbidity, health status, and cost, as well as beneficiary perception of drug therapy value, factors related to drug regimen complexity and side effects, and poor communication with health professionals. An inverse relationship between copayment and adherence to medication therapy has been documented across beneficiary disease states and severity of illness. A similar relationship has been documented between lower cost sharing for prescription drugs and increased adherence to therapy. In a retrospective cohort study of older adults with employer-sponsored drug coverage, higher copayments for prescription drugs were found to be associated with delayed initiation of therapy. As an example of VBBD, copayments for prescription drugs could be selectively eliminated to encourage beneficiary adherence to prescribed drug therapy.

A positive correlation between nonadherence, adverse outcomes, and medical cost has also been documented. A 2003 retrospective cohort study of beneficiaries enrolled in the Kaiser Permanente of Colorado diabetes registry determined that nonadherence to medication therapy was associated with increased risk for all-cause hospitalization as measured by odds ratio (OR = 1.58, 95% confidence interval [CI] = 1.38–1.81; P < 0.001) and increased risk for all-cause mortality (OR = 1.81, 95% CI = 1.46–2.23; P < 0.001). This study found that incremental improvements in medication adherence of at least 25% were associated with improved outcomes, including reduced systolic and diastolic blood pressure, reductions in hemoglobin A1c (HbA1c), reductions in low-density lipoprotein cholesterol (LDL-C) levels, reductions in all-cause hospitalization, and reductions in all-cause mortality.

Another study of insured beneficiaries enrolled in a health maintenance organization diagnosed with diabetes, hypercholesterolemia, and hypertension in the period 1999 through 2001 showed a positive correlation between nonadherence and HbA1c and LDL-C levels. Benefits of higher drug adherence may include improved beneficiary health status, improved worker productivity, reduced medical consequences of disease, and/or avoidance of costly medical interventions, although there is insufficient documentation of these benefits at the present time.

A recent pre-post study compared adherence to antidiabetic therapy for continuously eligible plan participants 1 year before and after their pharmacy benefit plan modified its copayment structure to incentivize certain behaviors. Copayments for the generic and insulin therapies dropped from $15 to $0; copayments for the preferred brands dropped from $30 to between $10 and $15; and copayments for the nonpreferred brands remained at $35. This resulted in higher treatment initiation rates (2.3% vs. 1.4%, P < 0.001) and lower discontinuation rates for metformin (OR = 1.7, 95% CI = 1.2–2.2; P < 0.01), antidiabetic combinations (OR = 2.5, 95% CI = 1.5–4.3; P < 0.01), and insulin (OR = 1.9, 95% CI = 1.3–2.9; P < 0.01) for the VBBD group compared with the comparison group in the year following the benefit design change. Adherence to antidiabetic therapy as measured by the medication possession ratio (MPR) increased 4.9 percentage points (P < 0.001) for the VBBD group and decreased 2.3 percentage points (P < 0.001) for the comparison group.

This article presents an analysis of a zero copay (ZCP) program implemented in January 2010 for a major employer’s employees, dependents, and retirees enrolled in the employee health plan with a diagnosis of diabetes or hyperlipidemia. Using a study design similar to that used in the Chang et al. (2010) study, the current research effort implements a less dramatic reduction in copayments to ascertain the VBBD program’s impact on adherence and cost. Eligibility for the ZCP program was contingent on beneficiary participation in a contracted vendor’s case management and/or wellness program. The research objective of this study was to assess the impact on beneficiary adherence and plan sponsor cost of offering generic antidiabetic and antihyperlipidemic medications without cost sharing.

### Methods

#### Program Description

A major employer’s employee benefits program was changed on January 1, 2010, to allow members to obtain certain generic diabetic and antihyperlipidemic medications with zero copay, provided that the beneficiary participated in a disease management and/or wellness program. This is referred to as the ZCP
program. The employer’s plan provided 3 tiers of cost sharing, as shown in Table 1. The ZCP program was designed to incentivize patients to continue using generic drugs (if already a user) or to switch to a generic drug (if a brand user).

Eligible participants included active employees, dependents, and retired plan participants who had coronary artery disease, hyperlipidemia, and/or diabetes and met the terms of enrollment and participation in 1 or more programs, including disease management and wellness programs addressing diabetes, cardiac conditions, weight management, stress management, exercise, and nutrition. Specific drugs covered by the ZCP program are shown in Table 2.

As part of the program, the vendor invites a beneficiary to complete an initial assessment of need and to participate in 1 or more wellness or disease management programs appropriate for the member’s condition or lifestyle. If the beneficiary agrees, he or she is flagged in the vendor’s database and is considered “enrolled” on acceptance of 1 or more phone calls or interactions with a vendor health coach or nurse and completion of the initial member assessment. Once enrolled, the beneficiary becomes eligible for the ZCP program, and eligibility continues through the benefit year unless the beneficiary drops out of all disease management and wellness programs or cannot be reached for scheduled coaching, at which time the beneficiary is terminated from the ZCP program. If the beneficiary is terminated from the program, the member’s copay reverts to the plan level.

In granting the organization’s request to remain anonymous, we have not included any further information.

**Study Design**

This was a retrospective pre-post comparison group study. The study had 3 main time periods: (a) identification period, (b) pre-implementation period, and (c) post-implementation period. A 6-month identification period was used to determine which beneficiaries were taking a medication for treatment of diabetes and/or hyperlipidemia and were existing users. The pre-implementation period was the 18 months after the

### TABLE 1 Prescription Drug Plan Copay Rates (2009-2011)

<table>
<thead>
<tr>
<th>Year</th>
<th>Generic ($)</th>
<th>Preferred Brand ($)</th>
<th>Nonpreferred Brand</th>
</tr>
</thead>
<tbody>
<tr>
<td>2009</td>
<td>Up to 30-day supply</td>
<td>5.00</td>
<td>29.00</td>
</tr>
<tr>
<td></td>
<td>30- to 90-day supply</td>
<td>12.00</td>
<td>72.50</td>
</tr>
<tr>
<td>2010</td>
<td>Up to 30-day supply</td>
<td>5.00</td>
<td>30.00</td>
</tr>
<tr>
<td></td>
<td>30- to 90-day supply</td>
<td>12.00</td>
<td>75.00</td>
</tr>
<tr>
<td>2011</td>
<td>Up to 30-day supply</td>
<td>5.00</td>
<td>30.00</td>
</tr>
<tr>
<td></td>
<td>30- to 90-day supply</td>
<td>12.00</td>
<td>75.00</td>
</tr>
</tbody>
</table>

### TABLE 2 Generic Medications Covered by the Zero Copay Program

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>GPI 10&lt;sup&gt;a&lt;/sup&gt; Code</th>
<th>GPI 10 Code</th>
<th>Generic Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antihyperlipemics</td>
<td></td>
<td>Antiabetes</td>
<td></td>
</tr>
<tr>
<td>Chlorpropamide</td>
<td>2720002000</td>
<td>3910001000</td>
<td>Cholestyramine</td>
</tr>
<tr>
<td>Glimepiride</td>
<td>2720002700</td>
<td>3910001010</td>
<td>Cholestyramine light</td>
</tr>
<tr>
<td>Glipizide</td>
<td>2720003000</td>
<td>3910002010</td>
<td>Colestipol HCl</td>
</tr>
<tr>
<td>Glyburide</td>
<td>2720004000</td>
<td>3920002500</td>
<td>Fenofibrate</td>
</tr>
<tr>
<td>Glyburide micronized</td>
<td>2720004010</td>
<td>3920003000</td>
<td>Gemfibrozil</td>
</tr>
<tr>
<td>Tolazamide</td>
<td>2720005000</td>
<td>3940005000</td>
<td>Lovastatin</td>
</tr>
<tr>
<td>Nateglinide</td>
<td>2723405000</td>
<td>3940006510</td>
<td>Pravastatin sodium</td>
</tr>
<tr>
<td>Metformin HCl</td>
<td>2725005000</td>
<td>3940007500</td>
<td>Simvastatin</td>
</tr>
<tr>
<td>Acarbose</td>
<td>2750001000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glipizide-metformin HCl</td>
<td>2799700235</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glyburide-metformin</td>
<td>2799700240</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metformin HCl-nutritional supplement</td>
<td>2799900250</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>GPI is Generic Product Identifier, a segmented numeric drug code assigned by Medi-Span, using a hierarchical classification scheme encompassing drug group, class, subclass, name, name extension, and dosage.
identification period and before the implementation of the program. The post-implementation period was the 18 months after the start of the ZCP program and included rolling enrollment into the ZCP program. Figure 1 depicts the study period broken down into the 3 time periods with accompanying date ranges for each period. The study used a difference-in-difference analysis with propensity score matching to examine changes in adherence and cost for diabetes and/or hyperlipidemia medications between the pre-implementation period and the post-implementation period, comparing those who participated in the ZCP program and those who did not. We analyzed the impact of the ZCP program separately for users of antidiabetes and antihyperlipidemics. It was possible that some eligible beneficiaries were users of both classes of medications. In this case, the beneficiary was considered for both analyses.

**Beneficiary Selection**

Selection criteria required that beneficiaries (a) were continuously enrolled in benefits during the identification, pre-implementation, and post-implementation periods, and (b) had at least 1 brand or generic medication claim for the treatment of diabetes and/or hyperlipidemia during the identification and post-implementation periods (Figure 2). Beneficiaries who enrolled in the program during the post-implementation period were considered “ZCP users,” while those who did not enroll during this period were considered “ZCP nonusers.” We identified users of medications for each of these conditions by mapping prescription drug claims data to the Medi-Span Generic Product Index (GPI). Beneficiaries who had a prescription drug claim that mapped to GPI 27 “antidiabetics” or GPI 39 “antihyperlipidemics” were considered to be on a medication used to treat these conditions. To identify whether beneficiaries enrolled in the ZCP program during the first 12 months of the post-implementation period, we used a designation in their prescription claims records that indicated enrollment.

**Propensity Score Matching**

ZCP users were matched to ZCP nonusers to reduce the effects of self-selection bias. Propensity scoring was used to obtain 1:1 matches of participants and nonparticipant group members using a “greedy” matching algorithm. Propensity scores were obtained by fitting covariates, which included age, gender, comorbidity count, medication class (antidiabetic, antihyperlipidemic, or both), and pre-implementation adherence into a logistic regression model. Comorbidity count reflects the number of unique medical conditions identified for beneficiaries during the identification period (calendar year 2009). Inferred conditions were based on the mapping of prescriptions provided in the Medispan Drug Indications Database, which imputes a diagnosis to a patient based on the specific drugs in the patient’s profile. This algorithm first matched ZCP program participants to nonparticipants on 5 digits of the propensity score. This was repeated for those who did not match using 4 digits of the propensity score and continued down to a 1-digit match.

**Outcomes Measures**

**Adherence.** Medication adherence was measured using proportion of days covered (PDC) and gaps in medication therapy. PDC was calculated as the sum of the days covered divided by 365 (the number of follow-up days), where days covered is based on the fill date and days supply, as indicated in the prescription claim. In the event a patient had a prescription fill for more than 1 drug within the same therapeutic group, causing overlapping fills, overlapping days were included once.

**Medication Refill Gap.** Medication refill gap, which is calculated for refill prescriptions, was the number of days between the assumed depletion date of 1 claim (the claims fill date plus days supply) and the fill date of the next refill. A refill gap of greater than 180 days was interpreted as an indication that the patient had an interruption in the therapy.

**Cost.** The impact of the ZCP program on pharmacy benefit cost for the payer reflected the net effect of 3 factors: (a) the cost of the waived copays; (b) the cost of induced demand for
Evaluation of Increased Adherence and Cost Savings of an Employer Value-Based Benefits Program Targeting Generic Antihyperlipidemic and Antidiabetic Medications

**FIGURE 2** Beneficiary Selection for Zero Copay Program Evaluation

Users of oral antibiotics, antihyperlipidemics, or both during the identification period* and post-implementation period* (N=11,296)*

- **Users of Antidiabetics** (n=5,274)
  - ZCP users (n=891)
  - ZCP nonusers (n=4,383)
  - 1:1 propensity matching
  - Matched ZCP users (n=870)
  - Matched ZCP nonusers (n=870)

- **Users of Antihyperlipidemics** (n=10,355)
  - ZCP users (n=1,449)
  - ZCP nonusers (n=8,906)
  - 1:1 propensity matching
  - Matched ZCP users (n=1,428)
  - Matched ZCP nonusers (n=1,428)

* *Identification period (January 1, 2008, to June 30, 2008); post-implementation period (January 1, 2010, to June 30, 2011).*

**Results**

There were 5,274 users of antidiabetic medications and 10,355 users of antihyperlipidemic medications who met the eligibility criteria for this study (Figure 2). In all there were 891 users of antidiabetics and 1,449 users of antihyperlipidemics enrolled in the ZCP program during the first 12 months of the post-implementation period. ZCP users and nonusers within each medication class were then matched using 1:1 propensity score matching. There were 21 beneficiaries using antidiabetics and 21 beneficiaries using antihyperlipidemics who enrolled in the ZCP program during the post-implementation period for whom a match could not be found. Thus, these 42 beneficiaries were eliminated from the analysis. The final sample consisted of 870 matched pairs of antidiabetic users and 1,428 matched pairs of antihyperlipidemic users (Figure 2). Table 4 shows baseline characteristics for ZCP users and nonusers within each medication class after matching. There are no statistically significant differences in age, gender, comorbidity count, dual medication class users, or pre-implementation period adherence between matched pairs for either medication class.

Adherence to medication therapy, as measured by PDC, is presented in Table 5 for the matched ZCP users and nonusers within each medication class. Among users of antidiabetics, the
### TABLE 3  
Zero Copay Program Cost Benefit Component Work Sheet

<table>
<thead>
<tr>
<th>Utilization and Cost Component</th>
<th>Antidiabetics</th>
<th>Antihyperlipidemics</th>
<th>Combined</th>
</tr>
</thead>
<tbody>
<tr>
<td>PDC&lt;sup&gt;a&lt;/sup&gt; for the comparison group in the baseline period (A)</td>
<td>81.9%</td>
<td>77.6%</td>
<td>79.2%</td>
</tr>
<tr>
<td>PDC for the comparison group in the post-period (B)</td>
<td>73.1%</td>
<td>70.8%</td>
<td>71.7%</td>
</tr>
<tr>
<td>PDC for zero copay group in the baseline period (C)</td>
<td>81.8%</td>
<td>77.7%</td>
<td>79.3%</td>
</tr>
<tr>
<td>PDC for zero copay group in the post-period (D)</td>
<td>81.9%</td>
<td>78.3%</td>
<td>79.7%</td>
</tr>
<tr>
<td>Estimated PDC for ZCP in the absence of program</td>
<td>73.0%</td>
<td>70.9%</td>
<td>71.8%</td>
</tr>
<tr>
<td>Converted into 30-day fills equivalent</td>
<td>8.9</td>
<td>8.6</td>
<td>8.7</td>
</tr>
<tr>
<td>Converted into annual cost based on $5 copay per generic Rx as (b1)</td>
<td>$44.41</td>
<td>$43.13</td>
<td>$43.67</td>
</tr>
<tr>
<td>Induced demand (D-[B/A×C]) in PDC</td>
<td>8.89%</td>
<td>7.41%</td>
<td>7.91%</td>
</tr>
<tr>
<td>Converted into days supply (E)</td>
<td>32.4</td>
<td>27.0</td>
<td>28.9</td>
</tr>
<tr>
<td>The cost per generic 30-day script in the intervention period (before copay) (F)</td>
<td>$9.69</td>
<td>$9.69</td>
<td>$9.69</td>
</tr>
<tr>
<td>Cost of induced demand ([E/30×F] as (b2))</td>
<td>$10.48</td>
<td>$8.73</td>
<td>$9.32</td>
</tr>
<tr>
<td>Total cost due to induced demand (b1+b2)</td>
<td>$54.89</td>
<td>$51.86</td>
<td>$53.00</td>
</tr>
<tr>
<td>Overall saving of the ZCP program PMPY as (a)</td>
<td>($36)</td>
<td>($60)</td>
<td>$24</td>
</tr>
<tr>
<td>Net cost benefit of switching from brand to generic (a+[b1-b2])</td>
<td>$18.89</td>
<td>$111.86</td>
<td>$77.00</td>
</tr>
</tbody>
</table>

<sup>a</sup>The value reflects average PDC for antihyperlipidemic and antidiabetic medications.  
PDC = proportion of days covered, PMPY = per member per year, Rx = prescription, ZCP = zero copay.

### TABLE 4  
Characteristics of Propensity Matched<sup>a</sup> Zero Copay Users and Nonusers

<table>
<thead>
<tr>
<th>Patient Group</th>
<th>Metric</th>
<th>ZCP Users Mean (95% CI)</th>
<th>ZCP Nonusers Mean (95% CI)</th>
<th>P Value&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antidiabetic users (n = 1,740)</td>
<td>Age</td>
<td>56.0 (55.3, 56.7)</td>
<td>56.3 (55.5, 57.0)</td>
<td>0.577</td>
</tr>
<tr>
<td></td>
<td>Male gender</td>
<td>0.5 (0.4, 0.5)</td>
<td>0.5 (0.4, 0.5)</td>
<td>1.000</td>
</tr>
<tr>
<td></td>
<td>Comorbidity count&lt;sup&gt;d&lt;/sup&gt;</td>
<td>4.2 (4.1, 4.3)</td>
<td>4.2 (4.0, 4.3)</td>
<td>0.313</td>
</tr>
<tr>
<td></td>
<td>Ratio of patients using both therapy classes</td>
<td>0.7 (0.7, 0.8)</td>
<td>0.7 (0.7, 0.8)</td>
<td>0.860</td>
</tr>
<tr>
<td></td>
<td>Pre-period&lt;sup&gt;c&lt;/sup&gt; PDC</td>
<td>81.8 (80.3, 83.2)</td>
<td>81.9 (80.4, 83.3)</td>
<td>0.930</td>
</tr>
<tr>
<td>Antihyperlipidemic users (n = 2,856)</td>
<td>Age</td>
<td>57.4 (56.9, 58.0)</td>
<td>57.1 (56.5, 57.6)</td>
<td>0.298</td>
</tr>
<tr>
<td></td>
<td>Male gender</td>
<td>0.5 (0.5, 0.5)</td>
<td>0.5 (0.5, 0.5)</td>
<td>0.965</td>
</tr>
<tr>
<td></td>
<td>Comorbidity count&lt;sup&gt;d&lt;/sup&gt;</td>
<td>3.8 (3.7, 3.9)</td>
<td>3.8 (3.7, 3.9)</td>
<td>0.332</td>
</tr>
<tr>
<td></td>
<td>Ratio of patients using both therapy classes</td>
<td>0.4 (0.4, 0.4)</td>
<td>0.4 (0.4, 0.4)</td>
<td>0.321</td>
</tr>
<tr>
<td></td>
<td>Pre-period&lt;sup&gt;c&lt;/sup&gt; PDC</td>
<td>77.7 (76.5, 79.0)</td>
<td>77.6 (76.4, 78.8)</td>
<td>0.842</td>
</tr>
</tbody>
</table>

<sup>a</sup>Propensity score was used to obtain 1:1 matches of ZCP users and nonusers.  
<sup>b</sup>No values are statistically significant.  
<sup>c</sup>Pre-period reflects the pre-implementation period.  
<sup>d</sup>Comorbidity count reflects the number of unique medical conditions identified for beneficiaries during the pre-implementation period.

The mean PDC in the pre-period for ZCP users having a significantly higher mean PDC compared with ZCP nonusers (81.9% vs. 73.1%, P<0.001). The change between the 2 periods was also significantly different between ZCP users and nonusers, whereby adherence among users remained relatively steady but adherence for nonusers declined (0.1% vs. -8.8%, P<0.001). Among users of antihyperlipidemics, there was no significant difference in mean PDC between groups in the pre-period (77.7% vs. 77.6%, P=0.84); however, there was a significant difference in the post-period between ZCP users and nonusers (78.3% vs. 70.8%, P<0.001). The mean PDC change over time between the antihyperlipidemic ZCP user and nonuser groups was also significant (0.6% vs. -6.8%, P<0.001) with adherence among users remaining relatively stable and adherence declining in the post-period for nonusers (Table 5).

The proportion of beneficiaries with greater than 180 gap days by ZCP user status is also presented in Table 5. Among antidiabetic users, there was a significant difference in the proportion of beneficiaries with more than 180 gap days between the ZCP users and nonusers in the pre-period (8.3% vs. 5.5%, P=0.02) and post-period (10.0% vs. 19.1%, P<0.001). The change over time in the ZCP users group was also significantly smaller compared with the ZCP nonusers group, which actually increased substantially in the post-period (1.7% vs. 13.6%, P<0.001). The proportion of beneficiaries with gap days
Evaluation of Increased Adherence and Cost Savings of an Employer Value-Based Benefits Program Targeting Generic Antihyperlipidemic and Antidiabetic Medications

### TABLE 5

<table>
<thead>
<tr>
<th>Patient Group</th>
<th>Outcomes Metric</th>
<th>ZCP Users Mean (95% CI)</th>
<th>ZCP Nonusers Mean (95% CI)</th>
<th>Difference (95% CI)</th>
<th>P Value&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antidiabetic users (n = 1,740)</strong></td>
<td>Pre-period PDC&lt;sup&gt;a&lt;/sup&gt; (A)</td>
<td>81.8 (80.3, 83.2)</td>
<td>81.9 (80.4, 83.3)</td>
<td>-0.1 (1.7, -1.9)</td>
<td>0.930</td>
</tr>
<tr>
<td></td>
<td>Post-period PDC (B)</td>
<td>81.9 (80.1, 83.8)</td>
<td>73.1 (71.2, 74.9)</td>
<td>8.8 (11.3, 6.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>PDC change (B-A)</td>
<td>0.1 (-1.6, 1.9)</td>
<td>-8.8 (-10.5, -7.0)</td>
<td>8.9 (11.4, 6.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Pre-period % with gap&lt;sup&gt;b&lt;/sup&gt; &gt; 180 days (C)</td>
<td>8.3 (6.6, 10.0)</td>
<td>5.5 (3.8, 7.2)</td>
<td>2.8 (5.0, 0.5)</td>
<td>0.017</td>
</tr>
<tr>
<td></td>
<td>Post-period % with gap &gt; 180 days (D)</td>
<td>10.0 (7.7, 12.3)</td>
<td>19.1 (16.8, 21.4)</td>
<td>-9.1 (-12.3, -5.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Change (D-C)</td>
<td>1.7 (-0.9, 4.4)</td>
<td>13.6 (10.9, 16.2)</td>
<td>-11.8 (-15.5, -8.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Antihyperlipidemic users (n = 2,856)</strong></td>
<td>Pre-period PDC&lt;sup&gt;a&lt;/sup&gt; (A)</td>
<td>77.7 (76.5, 79.0)</td>
<td>77.6 (76.4, 78.8)</td>
<td>0.2 (1.6, -1.3)</td>
<td>0.842</td>
</tr>
<tr>
<td></td>
<td>Post-period PDC (B)</td>
<td>78.3 (76.9, 79.8)</td>
<td>70.8 (69.3, 72.3)</td>
<td>7.5 (9.5, 5.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>PDC change (B-A)</td>
<td>0.6 (-0.8, 1.5)</td>
<td>-6.8 (-8.1, -5.4)</td>
<td>7.4 (9.2, 5.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Pre-period % with gap &gt; 180 days (C)</td>
<td>10.9 (9.2, 12.5)</td>
<td>10.8 (9.2, 12.4)</td>
<td>0.1 (2.3, -2.1)</td>
<td>0.950</td>
</tr>
<tr>
<td></td>
<td>Post-period % with gap &gt; 180 days (D)</td>
<td>12.0 (10.0, 13.9)</td>
<td>22.0 (20.1, 23.9)</td>
<td>-10.0 (-12.7, -7.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Change (D-C)</td>
<td>1.1 (-1.3, 3.3)</td>
<td>11.2 (9.0, 13.4)</td>
<td>-10.1 (-13.2, -7.0)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

<sup>a</sup>PDC indicates the proportion of days in the measurement period “covered” by prescription claims for the same medication or another in its therapeutic category.

<sup>b</sup>% with gap > 180 days” measures the percentage of patients with a gap greater than 180 days in their medication utilization coverage.

<sup>c</sup>Paired t-tests were used to compute P values for continuous level variables, and McNemar’s test was used for proportions. The Bonferroni step-down adjustment was used to control the family-wise error rate (FWER).

Cl = confidence interval, PDC = proportion of days covered, ZCP = zero copay.

### TABLE 6

Prescription Utilization Pre-implementation to Post-implementation Trend: Antidiabetic and Antihyperlipidemic Medications

<table>
<thead>
<tr>
<th>Patient Group</th>
<th>Outcomes Metric</th>
<th>ZCP Users Mean (95% CI) S</th>
<th>ZCP Nonusers Mean (95% CI) S</th>
<th>Difference (95% CI) S</th>
<th>P Value&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antidiabetic users (n = 1,740)</strong></td>
<td>Pre-period PMPY&lt;sup&gt;a&lt;/sup&gt; (A)</td>
<td>773 (700, 846)</td>
<td>993 (920, 1,066)</td>
<td>-220 (-117, -323)</td>
<td>&lt;0.001</td>
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<tr>
<td></td>
<td>Post-period PMPY (B)</td>
<td>1,354 (1,235, 1,472)</td>
<td>1,577 (1,458, 1,695)</td>
<td>-223 (-57, -389)</td>
<td>0.009</td>
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<tr>
<td></td>
<td>PMPY change (B-A)</td>
<td>581 (507, 654)</td>
<td>584 (510, 657)</td>
<td>-3 (99, -106)</td>
<td>0.951</td>
</tr>
<tr>
<td></td>
<td>Cost change per 30 days supply of Rx</td>
<td>3 (1.5)</td>
<td>10 (8.12)</td>
<td>-7 (-4.10)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Antihyperlipidemic users (n = 2,856)</strong></td>
<td>Pre-period PMPY&lt;sup&gt;a&lt;/sup&gt; (A)</td>
<td>220 (200, 241)</td>
<td>346 (326, 367)</td>
<td>-126 (-98, -155)</td>
<td>&lt;0.001</td>
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<tr>
<td></td>
<td>Post-period PMPY (B)</td>
<td>271 (237, 304)</td>
<td>489 (456, 523)</td>
<td>-219 (-172, -265)</td>
<td>&lt;0.001</td>
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<tr>
<td></td>
<td>PMPY change (B-A)</td>
<td>51 (31, 70)</td>
<td>143 (123, 163)</td>
<td>-93 (-65, -120)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Cost change per 30 days supply of Rx</td>
<td>-5 (-6.4)</td>
<td>0 (-1.1)</td>
<td>-5 (-4.6)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

<sup>a</sup>Refers to count of unique beneficiaries within therapy class.

<sup>b</sup>Paired t-test was used to assess cost changes.

Cl = confidence interval; PMPY = per member per year; Rx = prescription; ZCP = zero copay.

Greater than 180 was virtually equal between the antihyperlipidemic ZCP users and nonusers during the pre-period (10.9% vs. 10.8%, P = 0.95). However, in the post-period and when examining the difference over time (post-period minus pre-period), there was significant difference between the groups (post: 12.0% vs. 22.0%, P < 0.001; change: 11.1% vs. 11.2%, P < 0.001; Table 5). Similar to antidiabetics, this metric did not change much over time for ZCP users; however, the proportion of nonusers with a significant gap in days coverage increased significantly in the post-period compared with the pre-period.

Table 6 displays the total cost PMPY incurred by ZCP users and nonusers during the pre-period to the post-period within each medication class. Antidiabetic ZCP users had significantly lower pre- and post-period PMPY costs compared with nonusers (pre-period: $773 vs. $993, P < 0.001; post-period: $1,354 vs. $1,577, P = 0.009). There was no significant difference in the change pattern in PMPY between antidiabetic ZCP users and nonusers (P = 0.95; Table 3). However, the cost change per 30 days of medication differed significantly between the 2 groups, whereby ZCP users had a significantly lower rise in cost compared with nonusers ($3 vs. $10, P < 0.001). Among antihyperlipidemics, ZCP users had significantly lower PMPY costs pre- ($220 vs. $346, P < 0.001) and post-implementation ($271 vs. $489, P < 0.001). They also had a significantly smaller increase in PMPY over time compared with nonusers ($51 vs. $143, P < 0.001). Furthermore, the cost change per 30 days of medication was significantly lower for ZCP users compared with nonusers ($-5 vs. $0, P < 0.001; Table 6).

We further analyzed the sources of gain and loss to the employer from the different effects of the program. We
estimated the effect of the employer’s cost of implementing the ZCP as the sum of 3 components (Table 3): (a) the cost of waiving the $5 generic copay; (b) the cost of the induced demand for additional days supply, and (c) the savings due to members switching from brand to generic drugs.

To estimate the cost of the waiver of the $5 copay for a 30-day supply, we used the experience of the comparison group to estimate the PDC for all ZCP members in the absence of the program. PDC for the comparison group in the baseline year was 0.792. The PDC fell to 0.717 in the comparison group in the following year, or a reduction of 9.5%. The baseline PDC in the zero copay group was 0.793; the estimated PDC for this group in the absence of the ZCP program was (0.717/0.792) × (0.793) = 0.718, or 8.70 30-day fills. Thus, we estimated that the cost of the copay waiver (assuming no induced demand) was $5 × 8.7, or $43.67 (Table 3).

The cost of induced demand (additional generic drugs dispensed to the ZCP population) represents an increase in cost to the employer. The difference between the expected PDC for the participating group and the actual PDC for this group was (0.797 − 0.718) = 0.079. Applying this difference in PDC to 365 days supply, we derived an induced demand for 28.9 additional days supply. The cost per generic 30-day prescription in the intervention period was $9.69 before copay. Hence, the estimated cost of the induced demand was (28.9/30.0) × ($9.69) or $9.32 (Table 3).

We previously calculated the overall effect of the ZCP program as a net cost reduction of $24.00 PMPY. The effect of generic switching is a reduction in the employer’s cost, which we estimate as the difference between the net cost reduction of $24.00 PMPY and the increase in cost due to the 2 factors above ($53.00), or $77.00 PMPY (Table 6).

## Discussion
This VBBD program was an opt-in program consisting of a disease management component with a reduction in medication copayment as an incentive for participation. This study adds to an existing body of literature concerning other VBBD programs that have used an opt-in design with a disease management component using the zero copay mechanism as an incentive.37–41 However, this program was unique from other published opt-in studies because it only lowered the copayment for generic medications used to treat the 2 conditions as an incentive. The other opt-in studies did not specify that they restricted the copayment reduction to a specific medication type (i.e., generic only).37–41

This ZCP program achieved an enrollment rate of 17% among eligible beneficiaries taking antidiabetic medications and 14% among eligible beneficiaries taking antihyperlipidemic medications during the first 12 months of the 18-month post-implementation period. This is a smaller proportion than the only other study we found that included enrollment statistics, The Asheville Project. The Asheville Project’s diabetes management program enrolled 43% of those eligible for the program with a similar time frame.41 It is possible that a higher proportion enrolled in The Asheville Project because of the incentives it provided. For example, the project provided persons that opted into the program a free glucometer and waived copayments for diabetic supplies. Furthermore, to our knowledge, all diabetes medications were eligible for copayment reductions, not just generic medications.41

The current study found a PDC change for ZCP users of 0.1 percentage points for antidiabetics and an increase of 0.6 percentage points in antihyperlipidemias from pre- to post-implementation of the ZCP program. Two other studies that examined a 1-year change in adherence after implementation of the VBBD program targeting medications for chronic conditions found increases in adherence ranging from 0.9-4.0 percentage points.17,42 However, the design of the other studies differed from the current study in several ways. First, these studies did not include an opt-in process—beneficiaries received the benefits of the program without an enrollment process. Furthermore, they did not limit the reduction in copayment exclusively for generic medications and did not require participation in a disease management program.17,42 It should also be noted that these comparison studies used medical possession ratio, as opposed to PDC, to measure adherence. Taken together, the differences in study design and measurement between previous studies and the current study limit our ability to draw any conclusions based on the differences found.

Perhaps the most striking result of this study was the impact of participation on adherence between ZCP users and nonusers. Among ZCP users, the program appeared to sustain the pre-implementation adherence rate into the post-implementation period, whereas the adherence rate for the nonusers declined in the post-implementation period. This result suggests that the program may serve to prevent reductions in adherence over time. Another study found similar results. A retrospective pre-post study conducted by Choudhry et al. (2010) evaluated the impact of a VBBD program that reduced the copay for statins and a medication to treat clotting disorders.16 This study found that the VBBD program served to prevent the decline in adherence post-implementation for the intervention beneficiaries, while adherence for the comparison group continued to decline in the post-implementation period.16 Furthermore, our study found through the difference-in-difference analysis that the percentage of change over time differed between ZCP users and nonusers for both medication classes, with a more positive adherence among ZCP users relative to nonusers. Other VBBD studies with a difference-in-difference study design have reported similar results.16,18,30,43–45

Even with the increase in mean per-beneficiary prescription cost for the payer after the implementation of the program for both participants and nonparticipants, the increase was generally smaller for participants and statistically smaller among ZCP users of antihyperlipidemias compared with nonusers.
Furthermore, the mean per-beneficiary cost change from pre- to post-implementation per 30 days of medication for the payer was significantly smaller when comparing the ZCP users in both classes with nonusers. In fact, for anti-hyperlipidemics, ZCP users saw a decrease in mean per-beneficiary 30-day medication cost over time. Other studies have generally found VBID programs to either be cost neutral or to provide modest savings for payers, although the costs being measured and methods of measurement varied across studies. 37-40,46

Limitations

Given that beneficiaries could enroll in the program during the first 12 months of the post-implementation period, it is possible that the amount of time during the post-implementation period when a beneficiary was a ZCP user could have varied. The effect of this limitation is likely to bias results toward the null and lead to a conservative estimate of findings between the ZCP users and nonusers. While program users and nonusers were propensity matched, there were factors that we were not able to control. For example, ZCP users may have been more willing to change from a brand name to a generic equivalent or more likely to have already been on a generic medication prior to program implementation. In addition, due to the limitations of the data (limited variables), it was not possible to adjust for all potential predictors of adherence, such as socioeconomic factors. We also only examined one aspect of cost, namely prescription drug costs. It is possible that the economic effects of positive impact on adherence reach beyond these savings to savings in other medical and productivity costs, which were not examined in the current study. Finally, we were unable to determine if it was the reduction in copay or the disease management program, or both, that accounted for the sustained adherence among participants over time.

Conclusions

This VBBD program (case management/wellness program combined with the zero copay incentive) had the intended effect of positively impacting adherence to medications used to treat diabetes and high cholesterol for program participants compared with nonparticipants. This difference was mostly via a sustained adherence level among participants in the post-implementation period compared with a decline in adherence among nonparticipants. The program was also associated with a relative cost savings for payers among participants compared with nonparticipants, even though adherence (i.e., prescription drug utilization) among participants was higher compared with nonparticipants. Given the low rate of enrollment into the program, an analysis of reasons for low participation rates is warranted. It is possible that with a higher rate of enrollment, the project’s effects could be even more far-reaching.

Authors

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DISCLOSURES

All authors except Rubinstein are paid employees of Walgreens Co. Rubinstein is a paid consultant to Walgreens Co.

Clark, Hou, and Duncan were responsible for concept and design and data interpretation. McMurray was responsible for data collection. Clark, DuChane, Rubinstein, and Duncan wrote the manuscript, and Clark, DuChane, and Hou revised the manuscript.

REFERENCES

Evaluation of Increased Adherence and Cost Savings of an Employer Value-Based Benefits Program Targeting Generic Antihyperlipidemic and Antidiabetic Medications


BE EMPOWERED, A Specialty Pharmacy Education Program for Hemophilia B Patients, Impacts Adult Joint Bleeds and Pediatric Use of RICE

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ABSTRACT

BACKGROUND: Traditional education about hemophilia B in hemophilia treatment centers (HTCs) and episodic contact with HTCs limit the amount of education patients and their caregivers receive. Specialty care providers have frequent, continuing contact with patients. Each contact with a specialty care provider (e.g., coordinating a refill or addressing a patient inquiry) is another opportunity to support patient self-management of the disease and to give counsel on appropriate medication administration. The role of specialty pharmacy in improving patient self-management and supporting medication management and adherence is well established and reported with rheumatoid arthritis, multiple sclerosis, and renal transplant. With hemophilia, specialty pharmacies can support educational reinforcement of HTCs as well as support patient self-management and education of medication therapy. Utilization of patient education materials and programs can facilitate such a role. BE EMPOWERED, a specialty pharmacy education program for hemophilia B patients, is a multimodule education program coupled with frequent telephonic outreach.

OBJECTIVE: To provide education about hemophilia B, based upon discrete curriculum modules, facilitated by a specialty pharmacy-based nurse educator.

METHODS: Patients with hemophilia B (or, for children, their caregivers) were enrolled in the BE EMPOWERED program, and data were prospectively collected regarding bleeding and hemophilia-specific quality of life (QoL) outcomes (n = 21 caregivers, n = 17 adults).

RESULTS: BE EMPOWERED was associated with a statistically significant impact on the use of RICE (rest, ice, compression, and elevation) by caregivers whose utilization increased from 81% to 95% (P = 0.05). Adults in the BE EMPOWERED program experienced a statistically significant drop in the annualized bleeding rate (ABR), decreasing from 4.7 to 2.5 for total bleeds and decreasing from 3.5 to 1.7 for joint bleeds (P ≤ 0.02). For children with hemophilia B, bleeds were less common overall, as reported by their caregivers, with a mean ABR of 1.1 before and 1.2 following the program. Regarding QoL scores, adults had lower scores compared with children enrolled in the program.

CONCLUSIONS: Completion of the BE EMPOWERED program was associated with a decrease in total and joint bleeds in adults and with increased RICE utilization in children, as reported by caregivers.

What is already known about this subject

• Educational programs are often delivered by health care professionals during hemophilia treatment center visits.
• Adequate management of factor therapy entails knowledge assessment, tailored educational interventions, and behavior modification techniques.
• Some approaches have sought to establish patients with hemophilia as educators (“patient tutors”) who help educate their peers through an interactive framework.

What this study adds

• Customized programs that reinforce adherence to appropriate hemophilia management may have beneficial results on multiple hemophilia outcomes.
• Completing the BE EMPOWERED program was associated with a decrease in total and joint bleeds in adults and with increased RICE utilization in children, as reported by caregivers.

Hemophilia comprises 2 distinct inherited X-linked disorders that result in prolonged bleeding. Hemophilia A is a deficiency of functional clotting factor VIII, while hemophilia B is a deficiency of clotting factor IX. Hemophilia B occurs in approximately 1 in 10,000 male births, comprising 15% to 20% of cases of all races and economic groups. Both hemophilia A and B are classified as mild, moderate, or severe based on the individual’s factor activity, and those with either disorder have similar bleeding tendencies. People with severe hemophilia (<1% of normal clotting factor activity) often experience spontaneous bleeds into joints and muscles. People with moderate hemophilia (1%-5% of normal clotting factor activity) occasionally experience spontaneous bleeding but more often have prolonged bleeding after minor insults, while those with mild hemophilia (5%-40% of normal activity) rarely bleed and usually experience bleeding only in response to severe trauma or surgery. Repeated bleeding into joints and muscles often leads to progressive deterioration and long-term disability. Because treatment consists of intravenous infusions of the missing clotting factor, extensive patient and family education is required to help prevent long-term complications.
Comprehensive care for people with hemophilia B involves ongoing education and reinforcement of adherence to prescribed factor therapy, including bleeding episode management. Educational programs are often delivered by health care professionals during hemophilia treatment center (HTC) visits. The HTCs comprehensively approach the case of the patient and the patient’s family by attempting to address the ongoing medical, physical therapy, and psychosocial aspects of hemophilia, which can include educational and emotional support. The HTC is the primary point of education, with goals to deepen the patient’s and family members’ understanding of the disease and to facilitate development of independence in leading a full life. A multimedia approach that includes patient outreach when a patient or family is not at their HTC provides an additional opportunity to support the educational activities of the HTC toward appropriate factor therapy and bleeding management. Specialty pharmacy providers are well positioned to deliver educational programs that reinforce physician-prescribed hemophilia care management.

Adequate management of factor therapy entails knowledge assessment, tailored educational interventions, and behavior modification techniques provided by specialist pharmacists and nurses. Historically, the medical literature has not included evaluation of specialty pharmacy providers as a mode of delivering this information to hemophilia patients. Some approaches have sought to establish patients with hemophilia as educators (“patient tutors”) who help educate their peers through an interactive framework. Other interventions have included informal self-learning programs on the Internet. However, additional programs supporting enhanced knowledge and self-management skills are needed.

Customized programs that reinforce adherence to appropriate hemophilia management may have beneficial results on multiple hemophilia outcomes. Examples of such outcomes include joint bleeds, emergency department visits, hospitalizations, surgeries, enhanced adherence to a prescribed drug regimen, and healthy lifestyle. Although not an educational intervention, the Joint Outcome Study found that adherence to therapy improved joint health and function. The BE EMPOWERED program, a specialty pharmacy education program for hemophilia B patients, provides an educational experience based upon discrete curriculum modules that were facilitated by a specialty pharmacy-based nurse educator. The results of this proof-of-concept, structured educational program are reported here.

## Methods

The BE EMPOWERED educational program, jointly developed by Accredo Health Group and Pfizer, Inc., was based on the Health Belief Model, which assumes healthy behaviors will increase with a better understanding of a patient’s disease state and treatment. Educational modules were developed by clinicians familiar with hemophilia B and the barriers faced in therapy regimen adherence. Each module had a specific educational focus, and a summary of each module is provided in Table 1. All materials and the informed consent document were reviewed and approved by the Western Institutional Review Board, as well as relevant Accredo and Pfizer committees.

Patients were eligible for inclusion if they were male hemophilia B patients receiving recombinant factor IX (nonacog alfa; BeneFIX, Pfizer Inc, Philadelphia, PA) through Accredo’s Hemophilia Health Services for 12 months prior to study participation (between June 1, 2009, and May 30, 2010); were caregivers of patients with hemophilia B aged 4 to 17 years; or were adults aged 18 years or older with hemophilia B who had received nonacog alfa from Accredo for 12 months prior to participation. Patients were excluded if they were female, were affiliated with a client of Accredo who had opted out of any type of mail education information materials, or resided in Florida.

Informed consent was obtained by the study nurse coordinator, who also recorded baseline information during the telephonic interactions. Nonacog alfa was selected as the factor to evaluate during this program because at the time it was the only recombinant factor IX currently on the market and has the highest utilization among hemophilia B patients. In all, 438 hemophilia B patients were identified and invited to participate in the BE EMPOWERED program, and 179 volunteered to participate. Their participation involved completion of the educational modules and completion of a voluntary baseline and follow-up survey.

### Table 1: BE EMPOWERED Module Description

<table>
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<th>Title</th>
<th>Content Description</th>
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| Module 1: Managing Your Hemophilia | • Identifying and managing bleeds  
• Treating the bleed  
• Identifying bleeding patterns and how best to maintain a journal  
• Goal setting  
• What to discuss with your health care professional; empowering the patients to dialogue with their health care professional by using prompted questions |
| Module 2: Reducing Your Risk | • Tips for maintaining an active and healthy lifestyle for patients with hemophilia B  
• Maintaining a healthy weight  
• Patient awareness of habits and patterns: set of questions to support patient identification of habits and promote healthy lifestyle with health care provider  
• Openly and honestly answering questions about thoughts, feelings, and overall behavior  
• Providing facts about risk level of certain activities |
| Module 3: Creating Healthy Environments | • Suggestions for creating a healthy environment by identifying triggers that disrupt a typical routine and suggestions to get back on track  
• Positive reinforcement and recognizing success  
• Suggestions for additional training |
A welcome packet sent out to eligible patients included a baseline survey and a treatment journal with a postage pre-paid envelope for returning completed surveys. See Table 2 for details of the baseline and follow-up surveys. Three BE EMPOWERED educational pamphlets were mailed 1 month apart, with follow-up counseling telephone calls approximately 1 week after each module to discuss the content. The study nurse coordinator followed a structured format for reviewing module topics with each patient, ensuring consistency between patients. The calls were approximately 15 to 20 minutes in duration, which allowed time to address patient questions on the modules in addition to allowing the nurse educator to highlight key hemophilia management concepts and address medication adherence. Subsequent to the third module call, a follow-up voluntary survey was mailed with a postage prepaid envelope for returning completed surveys. The total study period was approximately 6 months, which included 1 month of enrollment, 3 months of educational intervention, and 2 months for return of surveys for data collection.

Data collected included the baseline and follow-up surveys; prescription refill data and infusion logs; self-reported (or caregiver-reported) adherence to regimen prescribed by the patient’s physician; self-reported (or caregiver-reported) bleeding events; factor usage (prescription refill history); school participation (absenteeism, arriving late, leaving early, visiting the school nurse); social and physical activities; and use of RICE (rest, ice, compression, and elevation) for adjunctive therapy for addressing bleeds. RICE is part of the recommended comprehensive approach to treating bleeding events and is included in the guidelines for the management of hemophilia. A welcome packet sent out to eligible patients included a baseline survey and a treatment journal with a postage pre-paid envelope for returning completed surveys. See Table 2 for details of the baseline and follow-up surveys. Three BE EMPOWERED educational pamphlets were mailed 1 month apart, with follow-up counseling telephone calls approximately 1 week after each module to discuss the content. The study nurse coordinator followed a structured format for reviewing module topics with each patient, ensuring consistency between patients. The calls were approximately 15 to 20 minutes in duration, which allowed time to address patient questions on the modules in addition to allowing the nurse educator to highlight key hemophilia management concepts and address medication adherence. Subsequent to the third module call, a follow-up voluntary survey was mailed with a postage prepaid envelope for returning completed surveys. The total study period was approximately 6 months, which included 1 month of enrollment, 3 months of educational intervention, and 2 months for return of surveys for data collection.

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for perfect adherence.\textsuperscript{9} The MPR metric as defined here is only applicable to medication regimens that have regularly scheduled doses.

Nonacog alfa dosing is variable when used to control or prevent bleeds and is based on several considerations, including severity of factor IX deficiency, individual patient pharmacokinetics, age, and the severity and location of bleeds. In general, 1 international unit (IU) of factor IX increases the plasma level by 1%. Dosing for minor bleeds is in the range of 20 to 30 IU per kilogram (IU/kg) given intravenously every 12 to 24 hours for 1 to 2 days, while the dose for major bleeds is in the range of 50 to 100 IU/kg intravenously every 12 to 24 hours for 7 to 10 days.\textsuperscript{10} Because nonacog alfa does not follow a regularly dosing schedule, an adjusted MPR was developed due to the episodic nature of factor infusion that incorporated patient- or caregiver-reported information, specifically the number of doses of factor used to treat bleeds.\textsuperscript{11}

Patient- or caregiver-reported persistence to prescribed treatment of bleeds with prompt factor infusion and utilization of adjunctive therapies, such as RICE, was defined as excellent (76%-100% of bleeds), good (51%-75% of bleeds), fair (26%-50% of bleeds), or poor (0%-25% of bleeds).\textsuperscript{12,13} This assessment was done at baseline and at follow-up. Patients were considered to be adherent if their MPRs were $\geq 1$, or “persistence” to prescribed treatment was categorized as excellent.

All categorical variables were compared using the chi-square test and continuous variables using the independent samples t-test, with $P \leq 0.05$ indicating significance. Survey responses between adherent and poorly adherent patients were examined in relation to QoL. In particular, differences between HAEMO-QoL-A scores were explored between the adherent and nonadherent patients (using t-tests). Statistical analyses were performed using SAS version 9.3 (SAS Institute, Inc., Carey, NC).

\section*{Results}

Of 438 patients identified receiving nonacog alfa, 179 (41%) patients or caregivers met the inclusion criteria and
voluntarily enrolled in the BE EMPOWERED educational program. Seventy-one baseline voluntary surveys were completed, evenly split between caregivers (n = 39) and adults with hemophilia B (n = 32). Of those who completed the voluntary baseline survey, 38 participants also completed the voluntary follow-up survey (caregivers, n = 21; adults, n = 17, Figure 1). Overall, 8.7% of the initial 438 patients identified completed the entire program.

The majority of participants completing the study were white and included 71% of caregiver and 94% of adult participants. The mean ages of caregivers and adults with hemophilia B completing the study were similar, at 43 and 44 years, respectively (Table 3). The mean age of children receiving nonacog therapy was 10 years. Many of the caregivers completing the study had high education levels (48% associate’s or bachelor’s degrees), while most adults completing the study had some college education but no degree (47%).

Caregivers were split between on-demand and regular therapeutic regimens (48% vs. 52%, respectively), while adults were more commonly using on-demand treatment compared with children (94% vs. 6%, respectively). Most of caregivers’ children had either moderate or severe hemophilia B (62%), and the majority of adults with hemophilia B had either moderate or severe disease (88%).

The BE EMPOWERED educational intervention was scored on a 5-point scale, with 1 being extremely unlikely and 5 being extremely likely for patients to engage in the activity. Responses indicated that BE EMPOWERED had a statistically significant impact on the use of RICE by caregivers, the utilization of which in children rose from 17 (81%) to 21 (95%), as listed in Table 4. There was little change in adults with hemophilia, who may have already been familiar with this approach. Both before and after the BE EMPOWERED program, most caregivers were likely to infuse as soon as symptoms were noted (81% at baseline; 95% at follow-up), while fewer adults were likely to infuse as soon as symptoms were noted (70% at baseline; 76% at follow-up; P = not significant). With regard to seeking assistance when a bleeding event occurred, caregivers were more likely to seek assistance (71% at baseline; 67% at follow-up) than were adults (41% at baseline; 24% at follow-up). No statistical difference was noted in seeking assistance based on the BE EMPOWERED intervention for either caregivers or adults.

The BE EMPOWERED program did not impact the recognition of pain, stiffness, redness, difficulty moving, or sensation of a pulled muscle as signs of a bleed for either caregivers or adults with hemophilia. However, caregivers reported more improvement in joint bleed recognition through warmth/tingling (71% at baseline; 95% at follow-up) compared with adults (94% at baseline; 94% at follow-up; P ≤ 0.02). Recognition of swelling as a symptom of a joint bleeding event improved among caregivers (81% at baseline; 100% at follow-up; P < 0.05) but not adults (94% before and 94% at follow-up). This suggests a positive correlation with educational intervention for the caregiver group.
Among adults, the annualized bleeding rate (ABR) for total bleeds went from 4.7 to 2.5 and, for joint bleeds, improved from 3.5 to 1.7 (P ≤ 0.02) but did not improve among caregiver responses, wherein they were less common overall, with an ABR of 1.1 to 1.2 (Table 4; Figures 2 and 3).

When baseline HEAMO-QoL scores were compared between adherent and nonadherent patients, no statistically significant differences were found between adherent (TSS 76 ± 13) and nonadherent (TSS 67 ± 18) adults. The TSSs in children aged 4 to 7 years (adherent, TSS 30; nonadherent, TSS 41; P = 0.83) and those aged 8-17 (adherent, TSS 23; nonadherent, TSS 21; P = 0.62) were lower than those of adults; indicating overall higher QoL scores in the pediatric group (Table 5).

When comparing baseline and follow-up HAEMO-QoL scores, no statistically significant changes were noted. Adults maintained high scores (78 at baseline; 76 at follow-up; P = 0.35). Both pediatric groups maintained similar, nonsignificant HAEMO-QoL scores from baseline to follow-up: 22 at baseline and 23 at follow-up (P = 0.97) for ages 4 through 7 and 23 at baseline and 23 at follow-up for ages 8 through 17.

**Discussion**

Education about hemophilia classically occurs in the HTC setting. Social media (e.g., the Internet) and national organizations also offer educational information. This is the first report of the use of specialty pharmacy as a source of education to complement these existing resources. In contrast to HTCs, wherein contact with the patient is often episodic (e.g., annual visit), specialty pharmacies have multiple and continuing interactions with patients and caregivers throughout the year. Therefore, this existing infrastructure offers an opportunity for enhanced education and patient counseling efforts. It is encouraging to document that this pilot project positively impacted clinical outcomes (e.g., lower ABR for total bleeds and joint bleeds in adults). This may pave the way for expansion of similar efforts in the future, using specialty pharmacies as key participants in the care team, providing patient education, and potentially improving clinical outcomes.

One of the more striking outcomes noted from this pilot evaluation centers around the statistically significant drop in both the total number of bleeds in adults (4.7 at baseline; 2.6 at follow-up) and joint bleeds (3.5 at baseline; 1.7 at follow-up; P ≤ 0.02). This may indicate that young patients and their caregivers, being relatively new to dealing with hemophilia, have a higher level of understanding of the disease and the importance of treatment. The authors surmise that adults may have forgotten some of the specifics and may have been more distracted by the challenges and responsibilities of adult life. It could also be that caregivers were more vigilant in taking care of their children’s hemophilia than adult patients would be in taking care of themselves. It is encouraging that refocusing their attention to the fundamentals of hemophilia in an educational program such as BE EMPOWERED results in memory refreshment that translates into statistically significant and clinically meaningful lower bleed rates.

Adult baseline Haemo-Qol. TSS of 67 and 76 in this evaluation were substantially higher than those previously reported by Mercan et al. (2010), indicating more impairment among U.S. adults than Turkish adults, although there are no specific norms for U.S. versus Turkish patients. Pediatric TSS in this study (21-23 in ages 4-7; 21-30 in ages 8-17) were comparable with those in European reports by Gringeri et al. (2004).
16-25 in ages 4-7 and 21-25 in ages 13-16) but much lower than those reported by Mercan et al. (40 in ages 4-7; 40 in ages 13-16). Therefore, the lower TSS in this program and in Europe are indicative of better QoL scores. Potential reasons for this may include the presence of HTCs, as well as the more developed socioeconomic conditions in the United States and Europe than in Turkey.

It is also important to note the comparison of individual pediatric domain scores obtained in this study with those from Turkish pediatric hemophilia patients in a recently published study by Mercan et al. U.S pediatric patients had substantially lower TSS and, thus, higher QoL scores in physical health, feelings, view, family, and dealing with hemophilia, while scores were similar in the domains of friends, sports/schools, and treatment. The children included in the Mercan et al. Turkish study did not have the benefit of nationally organized HTCs on a scale such as that currently available in the United States, and only about one-half infused at home, which may indicate less ready access to medical care. Educational programs such as BE EMPOWERED specifically emphasize routine and prudent physical activities. The BE EMPOWERED Module 2 stressed reducing bleeding risk with tips for maintaining an active and healthy lifestyle, maintaining a healthy weight, and practicing habits that promote a healthy lifestyle. Child and family awareness of these may have led to high QoL in Family, Others, and Dealing domains as children felt more empowered and encouraged to pursue fulfilling life activities, and families were more at ease with allowing their children such opportunities.

The data reported by Gringeri et al. are more difficult to compare with those of the current report, since the Gringeri et al. study broke TSS out by number of bleeding events in the past 12 months. Using the <3 ABR as a comparison (ABR in this report was 1), BE EMPOWERED scores were substantially lower, reflecting higher QoL than Gringeri et al.’s report in the dealing domain but substantially higher scores, and thus a lower QoL, in sports and school. This suggests that BE EMPOWERED modules may provide information to better integrate hemophilia into everyday life. For example, Module 3, Creating Healthy Environments, provides suggestions for creating a healthy environment with techniques to address triggers that may disrupt a typical routine and provide positive reinforcement. Gringeri et al.’s cohort of Western European patients clearly perceived sports and school with a higher QoL compared with Mercan et al.’s Turkish group or with the current U.S. cohort. The reasons for this disparity are unclear and merit further investigation in future studies.

Limitations
These findings should be considered in light of some study limitations. These limitations include the small number of patients completing the pilot program. No effort was made to assess baseline knowledge and to tailor the educational program to meet identified deficits so the BE EMPOWERED modules may not have had a substantial impact, since it may have included material with which the participants were already familiar.

We also found that many of the caregivers completing the study had high education levels (48% associate’s or bachelor’s degrees), while most adults completing the study had some college education but no degree (47%). Due to the small number of patients in the program and study evaluation, the authors were not able to stratify the data to assess the potential effect that baseline education may have had on the comprehension of the pamphlets. Future studies should attempt to take this into consideration.

Factor usage does not necessarily equal prescription refill history, and baseline inventories of nonacog alfa were not surveyed. Additionally, the short duration of observation may have led to bias in the ABR. There was no long-term follow-up, so it is unknown how durable the lowering of ABR in adults may be. It should also be noted that no control group was used and

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**TABLE 5** HAEMO-QoL Pediatric Comparison by Age

<table>
<thead>
<tr>
<th>Domain, TSS [SD]</th>
<th>BE EMPOWERED 8-16 Years</th>
<th>Mercan et al.13 8-12 Years</th>
<th>13-16 Years</th>
<th>Gringeri et al.14 (ABR &lt; 3) 8-12 Years</th>
<th>13-16 Years</th>
</tr>
</thead>
</table>

ABR = annualized bleeding rate; HAEMO-QoL = short version of the Hemophilia QoL Questionnaire for Children; QoL = quality of life; SD = standard deviation; TSS = transformed scale score.
that the study utilized patient self-reported measures. While patient-reported outcomes are often and increasingly utilized in research, it is recognized that a certain level of bias may have been introduced through this method. In addition, at the time of program and study development, the VERITAS (Validated Hemophilia Regimen Treatment Adherence Scale) tool was not yet available. Therefore, the study team developed and utilized a survey that would be appropriate and applicable in a real-world setting for hemophilia B patients. Future work will take into consideration the validation of survey tools developed for this program or will utilize the now available VERITAS tools.

Conclusions
This is the first report that documents the educational impact that a specialty pharmacy can have in the hemophilia B population. The BE EMPOWERED program in adults was associated with a statically significant reduction in the ABR of all bleeds and joint bleeds. The program was also associated with a statistically significant increase in the use of RICE among caregivers of children with hemophilia B. Further work should be performed to extend and expand this pilot program and explore the use of specialty pharmacies in hemophilia B education.

Study concept and design were contributed by all authors. Blankenship was a study investigator and enrolled patients. All authors were responsible for the collection and assembly of data and for data analysis and interpretation. All authors participated in manuscript preparation, review, and revisions and granted final approval of the manuscript.

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REFERENCES

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Measuring Economic Impact of Applying Daily Average Consumption Limits

Bridget M. Flavin, PharmD; Lynn M. Nishida, RPh; Sean H. Karbowicz, PharmD; Mark E. Renner; and Ruth J. Leonard, PharmD

ABSTRACT

BACKGROUND: Health plans may achieve cost savings by limiting the daily average consumption (DACON) of certain medications and encouraging members and prescribers to select lower cost dosing options. Various strengths of a given medication may be similarly priced per unit; therefore, a single unit of a higher-strength medication may cost less than multiple lower-strength units that provide the same dose. For instance, a single 10 mg tablet may cost less than two 5 mg tablets.

OBJECTIVE: To measure the economic impact of implementing DACON limits for selected medications.

METHODS: RegenceRx prescription claims data for the top 200 brand and select generic medications from the first quarter of 2011 were searched for DACON limit opportunities. DACON limits were placed on medications that were available in multiple strengths that were similar in cost, and at least one strength was double another (e.g., 5 mg and 10 mg).

Phase 1 of the program occurred in December 2011 and consisted of messaging to dispensing pharmacies (either electronic or direct contact). In Phase 2 (effective January 1, 2012), the claims system was coded to prevent payment for prescription claims in quantities exceeding DACON limits (>1.9 tablets/day). During this phase, dispensing pharmacists received electronic messaging at the point of service recommending a transition to the least costly dosing option. If the dispensing pharmacist determined transition was not clinically appropriate, the pharmacy was able to contact RegenceRx customer service for an override.

Impact was determined by analyzing prescription claims for the selected medications for the 3 months following implementation of DACON limits (January–March 2012). Specific measurements analyzed included number of claims not paid because of exceeding DACON limits, health plan administrative burden, and cost avoidance.

RESULTS: DACON limits were placed on 41 medications for commercial lines of business and 35 medications for Medicare Part D lines of business, based on the medication selection criteria (DACON limits were not placed on classes of clinical concern for Medicare Part D). A total of 5,100 claims across both commercial and Medicare Part D lines of business for January to March 2012 were impacted by implementation of DACON limits at the point of service. Duloxetine, niacin CR, and generic temazepam were responsible for more than 60% of the DACON limit claims volume. Implementing DACON limits resulted in a total cost avoidance of approximately $730,000 across both commercial and Medicare Part D lines of business for January to March 2012. Duloxetine, niacin CR, and aripiprazole were responsible for nearly 60% of the total aggregate cost avoidance. After adjustment for health plan administrative costs, the total cost avoidance was just under $720,000.

CONCLUSION: Implementing DACON limits on selected medications provided a cost avoidance of approximately $720,000 over a 3-month period with limited interruption to patient access and relatively low administrative burden. This reduction could result in annualized savings of nearly $3 million.

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What is already known about this subject

• Programs to promote the least costly dosing option (dose optimization; dose consolidation) result in cost savings to health plans.
• Interventions that notify at the point of service in an integrated health system, or those involving direct contact with the prescriber or patient, achieve greater savings than written interventions.

What this study adds

• An intervention implemented by a stand-alone pharmacy benefit manager at the point of service can result in even greater cost savings and less health plan administrative burden.

Health plans are charged with the difficult balance of ensuring affordable health care coverage for members without limiting access to necessary services. For medication costs, this balance is often accomplished with utilization management strategies such as prior authorization and medication quantity limits. These utilization management strategies can be implemented with varying levels of administrative burden. For instance, prior authorization requires a request to be submitted from a prescriber and then a review by the health plan staff, whereas quantity level limits can often be resolved at the point of service.

The most successful utilization management strategies are those that provide cost savings with minimal member impact and administrative cost to health plans and providers.1,2

Impacting daily average consumption (DACON) of medications is a utilization management strategy that encourages the least costly dosing option. Because various tablet strengths of a medication are often similarly priced per unit, taking multiple units of a medication at its lower strength is often more expensive than taking a single unit at its higher strength. For instance, taking two 5 milligram (mg) tablets per day may cost more than taking one 10 mg tablet. Therefore, by prompting dispensing pharmacists to transition members to the higher strength when they deem it clinically appropriate, overall cost savings may be achieved.

Prompting review at the point of service and allowing dispensing pharmacists to resolve the claim without prior authorization has several advantages. These include reducing member impact and decreasing the administrative burden for...
providers, pharmacies, and health plans. This process ensures that members continue to receive high quality care and benefit from any cost savings achieved.

Methods

RegenceRx handles prescription claims for just over 1.2 million members in Oregon, Washington, Idaho, and Utah. RegenceRx prescription claims data for the top 200 brand and select generic medications from the first quarter of 2011 were searched for DACON opportunities. DACON limits were placed on medications that met the following predefined criteria: the medication must have been available in multiple strengths that were similar in cost according to average wholesale price, and at least 1 available strength was double another (e.g., 5 mg and 10 mg).

Following selection of medications, implementation of the program occurred in 2 phases. Phase 1 occurred during December 2011. For commercial lines of business, dispensing pharmacies received electronic messaging at the point of sale when adjudicated claims exceeded DACON limits. The messaging directed the dispensing pharmacy to transition the member to the least costly dosing option. Because of time constraints on coding submissions for Medicare Part D lines of business, electronic messaging was not provided to pharmacies dispensing medications to Medicare Part D members. Instead, following a retrospective claims review, RegenceRx contacted the dispensing pharmacies of Medicare Part D members receiving prescriptions in quantities that exceeded DACON limits and requested the dispensing pharmacy to transition the member to the least costly dosing option. Phase 1 also included RegenceRx customer service staff training on the DACON limit program and the procedure for administering override requests.

Phase 2 became effective January 1, 2012. During this phase, the claims system was coded to prevent payment for prescription claims in quantities exceeding DACON limits (>1.9 tablets/day). Dispensing pharmacists received electronic messaging at the point of service to transition the member to the least costly dosing option (Table 1). If the dispensing pharmacist determined that transition was not clinically appropriate, the pharmacy was able to contact RegenceRx customer service for an override. Examples of override reasons include twice daily dosing or intermittent (as-needed) use.

Impact was determined by analyzing prescription claims for the selected medications for the 3 months following implementation of DACON limits (January-March 2012). Specific measurements analyzed for both commercial and Medicare Part D lines of business included (a) the number of claims not paid because of exceeding DACON limits; (b) health plan administrative burden as determined by the number of overrides multiplied by the cost of a customer service call; and (c) the cost avoidance in dollars per month and dollars per member per month.

Additional analysis was performed on DACON limit claims that were not resubmitted for the same medication within the allowed 10-day period to detect potential barriers to care. Each member’s profile was searched with predetermined parameters to identify reasons why a claim may not have been resubmitted. The parameters included (a) the member was not eligible within 30 days of the DACON reject; (b) a paid claim for the same medication occurred more than 10 days from the DACON reject; or (c) there was a paid claim for an alternative drug in the same therapeutic class (based on Medi-Span assigned generic product indicator [GPI] level 4). If a medication had 25 or more claims from January-March 2012 to which one of these parameters did not apply, the claims were manually searched to determine other possible scenarios. The medications that required such searching included generic temazepam, niacin CR, duloxetine, milnacipran, and aripiprazole.

Results

DACON limits were placed on 41 medications for commercial lines of business and 35 medications for Medicare Part D lines of business based on the medication selection criteria (DACON limits were not placed on classes of clinical concern for Medicare Part D; Table 1). Two of the selected medications were generic. In general, the medications selected are dosed once daily.

A total of 5,100 claims across both commercial and Medicare Part D lines of business for January-March 2012 were reviewed at the point of service as a result of implementing DACON limits (Table 2). Duloxetine, niacin CR, and generic temazepam were responsible for more than 60% of the DACON limit claims (Figure 1).

Implementing DACON limits resulted in a cost avoidance of approximately $730,000 across both commercial and Medicare Part D lines of business for January-March 2012 (Table 2). Duloxetine, niacin CR, and aripiprazole were responsible for nearly 60% of the total cost avoidance (Figure 2). Of the selected medications, prasugrel, sirolodin, and sertraline provided no cost avoidance because of low claims volume.

Overrides were identified for 1,283 claims. Assuming each override required the dispensing pharmacy to call RegenceRx customer service, and estimating the cost of a customer service call at $7.73, these overrides represent an administrative cost of $9,918 to the health plan. The total cost avoidance adjusted for health plan administrative burden was $717,515, which results in a weighted per member per month cost avoidance of $0.19 (Table 2).

There were 1,370 claims not resubmitted for the same medication within 10 days of the initial DACON limit claim (26.9% of total DACON limit claims). Of these, 58 were claims for patients who were no longer plan members after 30 days; 601 had claims for the same medication beyond 10 days; and 126 had subsequent claims for another medication with the
### TABLE 1 Medications Selected for DACON Limits

<table>
<thead>
<tr>
<th>Medication Name, Submitted Strength (mg)</th>
<th>Point of Service Messaging</th>
<th>Medication Name, Submitted Strength (mg)</th>
<th>Point of Service Messaging</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arpiprazole 5a</td>
<td>For 10 mg dose, use 10 mg tablet</td>
<td>Milnacipran HCL 12.5</td>
<td>For 25 mg dose, use 25 mg tablet</td>
</tr>
<tr>
<td>Arpiprazole 10a</td>
<td>For 20 mg dose, use 20 mg tablet</td>
<td>Milnacipran HCL 25</td>
<td>For 50 mg dose, use 50 mg tablet</td>
</tr>
<tr>
<td>Arpiprazole 15a</td>
<td>For 30 mg dose, use 30 mg tablet</td>
<td>Milnacipran HCL 50</td>
<td>For 100 mg dose, use 100 mg tablet</td>
</tr>
<tr>
<td>Aliskiren 150</td>
<td>For 150 mg dose, use 150 mg tablet</td>
<td>Metoprolol succinate 25</td>
<td>For 50 mg dose, use 50 mg tablet</td>
</tr>
<tr>
<td>Bupropan XL 150a</td>
<td>For 300 mg dose, use 300 mg tablet</td>
<td>Metoprolol succinate 50</td>
<td>For 100 mg dose, use 100 mg tablet</td>
</tr>
<tr>
<td>Candesartan 8</td>
<td>For 16 mg dose, use 16 mg tablet</td>
<td>Metoprolol succinate 100</td>
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<tr>
<td>Candesartan 16</td>
<td>For 32 mg dose, use 32 mg tablet</td>
<td>Nebivolol 2.5</td>
<td>For 5 mg dose, use 5 mg tablet</td>
</tr>
<tr>
<td>Carvediolol ER 10</td>
<td>For 20 mg dose, use 20 mg tablet</td>
<td>Nebivolol 5</td>
<td>For 10 mg dose, use 10 mg tablet</td>
</tr>
<tr>
<td>Carvediolol ER 20</td>
<td>For 40 mg dose, use 40 mg tablet</td>
<td>Nebivolol 10</td>
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</tr>
<tr>
<td>Carvediolol ER 40</td>
<td>For 80 mg dose, use 80 mg tablet</td>
<td>Niacin CR 500</td>
<td>For 1,000 mg dose, use 1,000 mg tablet</td>
</tr>
<tr>
<td>Darifenacin 7.5</td>
<td>For 15 mg dose, use 15 mg tablet</td>
<td>Pantoprazole 20</td>
<td>For 40 mg dose, use 40 mg tablet</td>
</tr>
<tr>
<td>Desvenlafaxine 50a</td>
<td>For 100 mg dose, use 100 mg tablet</td>
<td>Pregabalin 150</td>
<td>For 50 mg dose, use 50 mg tablet</td>
</tr>
<tr>
<td>Dextansoprazole 30</td>
<td>For 60 mg dose, use 60 mg capsule</td>
<td>Prasugrel 5</td>
<td>For 10 mg dose, use 10 mg tablet</td>
</tr>
<tr>
<td>Duloxetine 30a</td>
<td>For 60 mg dose, use 60 mg capsule</td>
<td>Saxagliptin 2.5</td>
<td>For 5 mg dose, use 5 mg tablet</td>
</tr>
<tr>
<td>Esomeprazole 20</td>
<td>For 40 mg dose, use 40 mg capsule</td>
<td>Sitagliptin 25a</td>
<td>For 50 mg dose, use 50 mg tablet</td>
</tr>
<tr>
<td>Eszopiclone 1</td>
<td>For 2 mg dose, use 2 mg tablet</td>
<td>Sitagliptin 50</td>
<td>For 100 mg dose, use 100 mg tablet</td>
</tr>
<tr>
<td>Ezetimibe/simvastatin 10/20</td>
<td>For 40 mg dose, use 40 mg tablet</td>
<td>Sitaglin 25</td>
<td>For 50 mg dose, use 50 mg tablet</td>
</tr>
<tr>
<td>Ezetimibe/simvastatin 10/40</td>
<td>For 80 mg dose, use 80 mg tablet</td>
<td>Sitagliptin 50</td>
<td>For 100 mg dose, use 100 mg tablet</td>
</tr>
<tr>
<td>Flotteperone fumarate 4</td>
<td>For 8 mg dose, use 8 mg tablet</td>
<td>Sitagliptin 50</td>
<td>For 100 mg dose, use 100 mg tablet</td>
</tr>
<tr>
<td>Generic mirtazpine 7.5</td>
<td>For 15 mg dose, use 15 mg tablet</td>
<td>Solifenacn succinate 5</td>
<td>For 10 mg dose, use 10 mg tablet</td>
</tr>
<tr>
<td>Generic mirtazpine 15</td>
<td>For 30 mg dose, use 30 mg tablet</td>
<td>Tapentadol ER 50</td>
<td>For 100 mg dose, use 100 mg tablet</td>
</tr>
<tr>
<td>Generic temazepam 7.5</td>
<td>For 15 mg dose, use 15 mg tablet</td>
<td>Tapentadol ER 100</td>
<td>For 200 mg dose, use 200 mg tablet</td>
</tr>
<tr>
<td>Generic temazepam 7.5</td>
<td>For 30 mg dose, use 30 mg tablet</td>
<td>Telmisartan 20</td>
<td>For 40 mg dose, use 40 mg tablet</td>
</tr>
<tr>
<td>Guanfacine ER 1</td>
<td>For 2 mg dose, use 2 mg tablet</td>
<td>Telmisartan 40</td>
<td>For 80 mg dose, use 80 mg tablet</td>
</tr>
<tr>
<td>Guanfacine ER 2</td>
<td>For 4 mg dose, use 4 mg tablet</td>
<td>Milnacipran HCL 25</td>
<td>For 50 mg dose, use 50 mg tablet</td>
</tr>
<tr>
<td>Irbesartan 75</td>
<td>For 150 mg dose, use 150 mg tablet</td>
<td>Milnacipran HCL 50</td>
<td>For 100 mg dose, use 100 mg tablet</td>
</tr>
<tr>
<td>Irbesartan 150</td>
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<td>Tolterodine tartrate ER 2</td>
<td>For 4 mg dose, use 4 mg capsule</td>
</tr>
<tr>
<td>Lansoprazole 15</td>
<td>For 30 mg dose, use 30 mg capsule</td>
<td>Valsartan 40</td>
<td>For 80 mg dose, use 80 mg tablet</td>
</tr>
<tr>
<td>Lansoprazole dispersible tablet 15</td>
<td>For 30 mg dose, use 30 mg tablet</td>
<td>Valsartan 80</td>
<td>For 160 mg dose, use 160 mg tablet</td>
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<tr>
<td>Lidexametamine dimesylate 20</td>
<td>For 40 mg dose, use 40 mg capsule</td>
<td>Valsartan 160</td>
<td>For 320 mg dose, use 320 mg tablet</td>
</tr>
<tr>
<td>Lidexametamine dimesylate 40</td>
<td>For 80 mg dose, use 80 mg capsule</td>
<td>Venlafaxine ER 37.5</td>
<td>For 75 mg dose, use 75 mg capsule</td>
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<tr>
<td>Losartan 25</td>
<td>For 50 mg dose, use 50 mg tablet</td>
<td>Venlafaxine ER 75</td>
<td>For 150 mg dose, use 150 mg capsule</td>
</tr>
<tr>
<td>Losartan 50</td>
<td>For 100 mg dose, use 100 mg tablet</td>
<td>Zolpidem tartrate 5</td>
<td>For 10 mg dose, use 10 mg tablet</td>
</tr>
<tr>
<td>Memantine 5</td>
<td>For 10 mg dose, use 10 mg tablet</td>
<td>Zolpidem tartrate ER 6.25</td>
<td>For 12.5 mg dose, use 12.5 mg tablet</td>
</tr>
</tbody>
</table>

*DACON limits were not placed on protected therapeutic classes for Medicare Part D. DACON = daily average consumption; mg = milligram.

The unaccounted for claims of any medication that had ≥5 total claims over the 3-month period (aripiprazole, duloxetine, milnacipran, niacin CR) were then manually searched to attempt to determine a reason for lack of resubmission. One exception was generic temazepam, which had 143 claims over the 3-month period. This drug was excluded from further search because we surmised that claims data would not accurately reflect the actual outcome of the DACON limit claim for one of 2 reasons: patients may or may not have chosen to fill their prescription at a later time because of intermittent or temporary use, or patients may have chosen to pay out-of-pocket for their prescription because of the relatively low cost of generic temazepam.

Following the manual search, additional scenarios for unaccounted for claims were identified, which accounted for another 134 claims. These included multiple claims for the same member, claims for the same therapeutic class based on GPl 2; and a subsequent reversed claim for the same medication (Table 3). Overall, the reason for lack of resubmission could not be determined for 167 DACON limit claims (3% of total DACON limit claims).

### Discussion

Previous studies based on promoting transition to the least costly dosing option have reached different conclusions. One
Measuring Economic Impact of Applying Daily Average Consumption Limits

**TABLE 2** DACON Limit Impact and Cost Avoidance (January-March 2012)

<table>
<thead>
<tr>
<th>Commercial (n = 41 Medications)</th>
<th>Medicare Part D (n = 33 Medications)</th>
<th>Totals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Claims exceeding DACON limits (not paid)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of claims</td>
<td>2,056</td>
<td>1,095</td>
</tr>
<tr>
<td>Potential cost ($)</td>
<td>641,284</td>
<td>355,249</td>
</tr>
<tr>
<td>Resubmitted claims (paid)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of claims (%)</td>
<td>1,599 (77.8%)</td>
<td>764 (69.8%)</td>
</tr>
<tr>
<td>Amount resubmitted ($)</td>
<td>$376,269 (58.7%)</td>
<td>$161,122 (45.6%)</td>
</tr>
<tr>
<td>Cost avoidance ($)</td>
<td>265,016</td>
<td>192,128</td>
</tr>
<tr>
<td>Cost avoidance (SPMPM)</td>
<td>0.24</td>
<td>0.17</td>
</tr>
</tbody>
</table>

*Amount paid without DACON limit.

*Resubmitted for the same medication within 10 days of the original claim.

*Amount paid for resubmitted claims.

*Potential cost minus amount resubmitted.

*Cost avoidance per month divided by the number of plan members.

*Weighted average adjusted for administrative burden.

DACON = daily average consumption; SPMPM = dollars per member per month.

**FIGURE 1** Top DACON Limits by Claims Volume

**FIGURE 2** Top DACON Limits by Cost Avoidance

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*Includes both commercial and Medicare Part D lines of business for January-March 2012.

DACON = daily average consumption.

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study done within an integrated health care system used their own therapeutic intervention application to flag potential dose consolidation opportunities. Following the flag, an automatically generated form was provided to the clinician to determine whether the switch was appropriate. Of 927 opportunities, 454 (49%) were switched, resulting in an estimated annualized drug cost savings of $390,662 ($1.67 per member per year). The authors’ conclusion was that a dose consolidation program was a relatively simple way to manage costs without sacrificing care.¹

Another study employed a written intervention to achieve potential dose consolidation. Prescribers were randomized into one of 2 treatment arms. In one arm, prescribers received a letter with information regarding the inefficient dosing regimen and the suggested dose consolidation. In the other arm, both the prescriber and the patient received a letter. Both intervention arms had higher consolidation rates than the control arm and resulted in savings of $0.02 to $0.03 per member per month. The authors concluded that the savings were not significant enough to justify continuation of the program.²

Wheeler and Butitta (2003) also contacted both the member and prescriber; however, they contacted them directly and found a 60% decrease in drug spend for prescriptions with an optimized dose during a 6-month follow-up period (P < .01). Additionally, 97% of patients indicated they were receptive to the optimized regimen. Wheeler and Butitta concluded that...
dose optimization presents an opportunity for decrease in drug spend with low impact to patients.3

The present study, done by a stand-alone pharmacy benefit manager, confirms that DACON limits achieve the goal of health plans of providing cost avoidance with little interruption to member access and relatively low administrative burden.

While this study shows that DACON limits can achieve cost avoidance, it also provides additional research opportunities. For instance, general selection criteria were used for this study, but more specific criteria could be developed to target medications with the greatest cost savings potential. For example, medications that require dose titration, such as niacin CR, are often initiated with a prescription for more tablets at a lower strength. This practice allows for a gradual increase in dose but may not be replaced by fewer tablets of a higher strength once the dose titration is complete. The potential for this type of cost avoidance was demonstrated in this study with niacin CR, as it was one of the top DACON medications both by claims volume and dollar amount. Another area for future research may include determining whether adherence was increased by transitioning the member to fewer tablets.

**Limitations**

The current study did not attempt to quantify the administrative burden on dispensing pharmacists, though we assume that burden was low because of phase 1 notification and the ability of the dispensing pharmacist to call RegenceRx for an override rather than requiring prior authorization.

The cost avoidance calculation may have underestimated actual cost avoidance because it assumed claim resubmission within a 10-day period.

A reason for lack of resubmission could not be identified for 3% of total DACON limit claims. It is unclear what the outcomes of these claims were.

**Conclusion**

Implementing DACON limits on selected medications provided a cost avoidance of approximately $720,000 over a 3-month period with limited interruption to patient access and relatively low administrative burden. This reduction could result in annualized savings of nearly $3 million.
ACKNOWLEDGMENTS

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REFERENCES


DISCLOSURES

There was no external funding for this study. Flavin, Nishida, Renner, and Karbowicz were primarily responsible for the concept and design of the study. Data were primarily collected by Renner, with assistance from Leonard. Flavin, Renner, and Leonard did data interpretation, and the manuscript was written by Flavin. Revision was primarily from Flavin, with assistance from Karbowicz.

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Discrepancies Identified with the Use of Prescription Claims and Diagnostic Billing Data Following a Comprehensive Medication Review

Terese E. Roane, PharmD, BCACP; Vinita Patel, PharmD; Heather Hardin, PharmD, BCACP; and Martha Knoblich, PharmD

ABSTRACT

BACKGROUND: The University of Florida College of Pharmacy’s Medication Therapy Management Communication and Care Center (UF MTMCCC) provides medication therapy management (MTM) services to patients enrolled in a State of Florida Medicaid Waiver Program: Medicaid for the Aged and Disabled. To provide these services, UF MTMCCC was given access to patients’ prescription claims data and diagnostic billing data in the form of ICD-9 codes. Prior to calling a patient, a precomprehensive medication review (CMR) work-up was performed to identify potential medication-related problems (MRPs) and/or health-related problems (HRPs). Based on information provided by the patient in relation to comorbidities, medications, and medical history during the interactive telephone conversation, problems were either confirmed or eliminated. All of the reported information was also assessed to identify any new MRPs or HRPs. Accordingly, telephonic MTM services have the potential to bridge the gap between pharmacy claims data and patient self-reported information, since the MTM services provided rely on the accuracy of both informational resources.

OBJECTIVE: To determine the degree of discrepancy in patient-reported information regarding chronic comorbidities and medications versus diagnostic billing data (ICD-9 codes for chronic comorbidities) and pharmacy claims data (medications) when providing MTM services during an interactive telephonic comprehensive medication review.

METHODS: A retrospective chart review (n = 147 patients) was performed for patients who received a telephonic CMR. Pharmacy claims data and diagnostic billing data, in conjunction with the pre-CMR work-up data, were used to identify discrepancies in information obtained from the patient during the CMR. During the chart review, identified MRPs or HRPs were categorized as “confirmed” (patient reported the problem exists and/or it was deduced from the presence/absence of a medication that the problem does exist); “eliminated” (patient reported the problem does not exist and/or it was deduced from the presence/absence of a medication that the problem does not exist); or “new” (a problem that was not identified during precall identification of problems, but following the CMR interaction, it was determined that a problem now exists). The study evaluated the discrepancies before and after a CMR telephonic interaction in the following categories: medications, chronic comorbidities, level 1 drug-drug interactions, level 2 drug-drug interactions, gaps in therapy, therapeutic duplications, lack of therapy, preferred drug list alternatives, combination products, and tobacco use. Percent discrepancy was calculated as the sum of new and eliminated data elements divided by the total number of data elements for each MRP or HRP.

RESULTS: The percent discrepancy observed was 42% for medications, 41% for chronic comorbidities, 77% for level 1 drug-drug interactions, 93% for level 2 drug-drug interactions, 35% for gaps in therapy, 87% for therapeutic duplications, 26% for lack of therapy, 36% for preferred drug list alternatives, 42% for combination products, and 54% discrepancy for report of tobacco use. Overall, 4,441 data elements were identified as confirmed, eliminated, or new across the 147 CMRs. Among those data elements, 56% of the data was confirmed; 23% was eliminated; and 21% was discovered as new.

CONCLUSIONS: The study met its objective in determining the degree of discrepancies that existed when prescription claims data and ICD-9 billing data were used to identify MRPs and/or HRPs versus using patient-reported data. Data revealed that the presence of discrepancy is relatively large depending on the category, indicating a difficulty in accurately making recommendations with incomplete data or solely based on prescription claims and billing data. MTM services with patient interaction are vital in identifying information that allows for more appropriate decision making.

What is already known about this subject

- The congruence of medication information from patient self-reporting and pharmacy claims data is variable and dependent on the time interval for claims data surveillance.
- Telephonic services have been used for providing general patient care and assessing the accuracy of pharmaceutical claims data.
- Electronic pharmacy records have been used for the assessment of medication compliance and adherence to disease state guideline recommendations.
- Drug use review using prescription database information and inferred diagnoses is widely used to trigger medication-related interventions.
- The combination of electronic medical record assessment with telephonic services has been employed for the provision of MTM services.

What this study adds

- Using the patient’s electronic record and a telephone interview, data analyzed were the change in medications and perceived medication- and/or health-related problems between pre-CMR and post-telephonic CMR assessment.
- Results indicate that an assessment of the electronic medical record (prescription and billing claims) coupled with telephonic services leads to a more thorough medication review and assessment when providing MTM services.
Medication therapy management (MTM) is “a distinct service or group of services that optimize therapeutic outcomes for individual patients.” MTM is further defined as patient-centered services that evaluate the patient’s complete medication regimen rather than focusing on an individual medication. The American Pharmacists Association and the National Association of Chain Drug Stores Foundation developed a model framework for implementing effective MTM services. The intent of this framework is to help improve collaboration among health care professionals, enhance communication between patients and the patients’ health care team, and to optimize medication use for improved patient outcomes. Using the elements of the framework, the pharmacist, or other qualified health care professional, provides MTM services to patients to help enhance patients’ knowledge of their medications and obtain the most benefit from those medications, as well as empower patients to assume a more active role in managing their medication therapy and their health conditions.

There are 5 core elements identified in the MTM service model framework. The first core element is the medication therapy review (MTR), also commonly referred to as a comprehensive medication review (CMR). The MTR/CMR is a systematic method of gathering patient-specific information using prescription claims data and information obtained during an interactive consultation with the patient or the patient’s caregiver. The MTR/CMR also consists of gathering information on all of the medications the patient is currently taking that is not captured in the prescription claims data, including over-the-counter products, herbal therapies, homeopathic remedies, sample medications, and dietary supplements. All of the information gathered is then assessed to identify medication-related problems (MRPs) and/or health-related problems (HRPs), followed by the generation of a plan to resolve those problems that includes collaboration with the pharmacist, patient, caregiver, and/or the prescriber.

The second core element is the personalized medication record (PMR). The PMR is a comprehensive record, or medication list, containing all of the patient’s prescription and nonprescription medications and is intended to be given to, and used by, the patient. The third core element is the medication action plan (MAP). The MAP is a document that is also intended for use by the patient and contains beneficial information for the patient to help in self-management of medications and conditions. The fourth element is intervention and/or referral. This element defines the pharmacist’s role in providing consultation services and interventions to address medication-related problems with a referral to the appropriate health care provider when the pharmacist deems necessary. The final core element of the service model framework is the use of documentation with follow-up reviews and/or appointments. Documentation and follow-up are necessary components to maintain consistency throughout the process of providing MTM services, as well as to ensure the continuity of care for the patient. The method of providing MTM services using the core element framework involves using interactive encounters between the pharmacist and the patient and/or the patient’s caregiver. The interactive encounter may be face-to-face, telephonic, or a combination of both methods.

The University of Florida College of Pharmacy established an MTM Communication and Care Center (UF MTCCC) in March 2010. The center uses the fundamentals of the MTM service model framework to provide MTM services to patients. MTM services provided by UF MTCCC used information obtained from prescription claims data and diagnostic billing data as well as patient self-reported data obtained during the CMR. The UF MTCCC relies on patient self-reporting of information to confirm, eliminate, and identify new MRPs and/or HRPs during the provision of MTM services.

The agreement between pharmacy data and self-reported data has been investigated in various settings. One study found that among chronic glucocorticoid users enrolled in a managed care program, agreement between self-report and osteoporosis care was high but was dependent on the time interval for pharmacy data review (Table 1). Specifically, the investigators reported an optimal interval of pharmacy data surveillance of 120-180 days to distinguish between current and past bisphosphonate users. Similarly, self-reported information was found to be more reliable than pharmacy claims data when the focus was on assessing patients’ medications at a specific point in time. A patient’s self-reported medical history is assumed to be accurate, and the validity of the reported medical information beyond medication lists has been investigated. In particular, an evaluation of the congruence of medical record information and self-reported history of preeclampsia found validity was only moderate. In addition, literature regarding the accuracy of self-reported history among autoimmune disease, schizophrenia, and chronic pain suffers is also available (Table 1).

Telephonic MTM services have the potential to bridge the gap between pharmacy claims data and patient self-reported information, as they rely on the accuracy of both informational resources. Telephonic interventions have also been employed to investigate the accuracy of available medication information. A 2004 assessment of the accuracy of computerized medication histories included patients aged at least 65 years who were receiving 5 medications or more. Only 5.3% of patients included in the assessment had complete agreement between the computer-generated medication list and the patient-reported medication history taken during the telephonic interview. Of all medications, 65% were prescription; 23% were over the counter (OTC); and 12% were vitamins/herbals. The average number of drug omissions was 3.1 per patient. Also, 25% of the total number of medications reported by patients as actually being taken was found to be omitted.
from the electronic medical record. Likewise, an investigation of the agreement between medication lists, from telephonic self-reports versus claims data in Australia, reported that the agreement between the telephone self-reports and pharmacy claims data declined significantly as retrieval periods increased (7, 30, 60, and 90 days). The authors reported sensitivity and predictive values specific to classifications, with a marked decline in sensitivity being observed with increasing retrieval period for benzodiazepines (88%, 80%, and 74% for 30-, 60-, and 90-day retrieval periods, respectively).

Assessing data received from pharmacy claims alone is not enough when providing MTM services. In today’s world, patients are receiving medications from many different sources, including samples from their provider’s office, through patient assistance programs, mailed in from other countries, or through their local pharmacy’s free or low-cost medication programs. The interactive component of the CMR is vital in fully assessing the accuracy and completeness of a patient’s medication history. The purpose of this study was to determine the degree of discrepancy between diagnostic billing codes (indicating chronic conditions/comorbidities), combined with pharmacy claims data (indicating active medications that were available prior to the patient interaction) and patient-reported health conditions and actual medication use data, obtained from the patient when MTM services were provided through an interactive telephonic consultation.

### Methods

#### Data Source

A retrospective study was performed on 147 patients who received an interactive telephonic CMR consultation provided by the UF MTMCCC from June to August in 2011 as part of the patients’ enrollment in the State of Florida Medicaid Waiver Program: Florida Medicaid for the Aged and Disabled (MEDS-AD) and MTM programs. This study received institutional review board approval from the University of Florida. Pharmacy claims data and diagnostic billing data were provided by the Agency for Health Care Administration. The pharmacy claims data provided a list of medications that were billed to and paid for by Florida Medicaid as a part of the patients’ pharmacy benefits. The diagnostic billing data, in the form of the International Statistical Classification of Diseases and Related Health Problems, 9th Revision codes (ICD-9 codes), provided a list of conditions and services for the patient that

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**Table 1: Literature Regarding Patient Self-Reporting and Telephonic Services for General Care**

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Population</th>
<th>Sample Size</th>
<th>Method</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Curtis et al, 2006&lt;sup&gt;4&lt;/sup&gt;</td>
<td>Chronic glucocorticoid users from a National Managed Care Organization database</td>
<td>2,363</td>
<td>Compared self-reported current use of alendronate, risedronate, calcitonin, and raloxifene with different intervals of pharmacy data to determine agreement.</td>
<td>The 6-month interval of pharmacy data failed to capture &gt;25% of self-reported current bisphosphonate users. The optimal interval for surveillance to distinguish between current and past users was 120-180 days.</td>
</tr>
<tr>
<td>Caskie et al, 2006&lt;sup&gt;5&lt;/sup&gt;</td>
<td>Subset of individuals tested during the seventh wave of the Seattle Longitudinal Study</td>
<td>1,430</td>
<td>Compared brown bag data collection information with pharmacy database claims for the previous 4 months.</td>
<td>More than half the sample (58%) had complete agreement on all 16 of the chosen drug classes. Chronic disease status was a significant predictor of agreement between brown bag and pharmacy data for all age groups.</td>
</tr>
<tr>
<td>Bourgeois et al, 2007&lt;sup&gt;6&lt;/sup&gt;</td>
<td>Patients and parents presenting to an ED waiting room in a tertiary care children’s hospital</td>
<td>936</td>
<td>Measured the sensitivity and specificity of 3 data sources for assigning patients to disease categories.</td>
<td>Disease category assignment based on patient-reported information was significantly more sensitive in correctly identifying as disease category than data used by national disease surveillance systems.</td>
</tr>
<tr>
<td>Don and Carragee, 2008&lt;sup&gt;7&lt;/sup&gt;</td>
<td>Cohort of consecutive patients with persistent axial pain after an MVA from 5 spine specialists’ outpatient clinics</td>
<td>335</td>
<td>Determined the validity of self-reported history in patients with pain in a retrospective, multilocal study.</td>
<td>The self-reported rates of alcohol abuse, illicit drug use, psychological diagnosis, and prior axial pain were significantly lower than seen in the medical records.</td>
</tr>
<tr>
<td>Brill et al, 2007&lt;sup&gt;8&lt;/sup&gt;</td>
<td>Schizophrenic or schizoaffective disorder males, healthy males</td>
<td>131</td>
<td>Compared contemporaneous and retrospective reports from a behavioral functioning assessment.</td>
<td>No overall significant differences found in accuracy of reporting between persons with schizophrenia and those without.</td>
</tr>
<tr>
<td>Kaboli et al, 2004&lt;sup&gt;9&lt;/sup&gt;</td>
<td>Iowa VA Medical Center primary care patients aged ≥65 receiving at least 5 prescriptions</td>
<td>493</td>
<td>Assessed accuracy of computerized medication lists, allergies and ADR records using telephonic interviews with patients.</td>
<td>Patients were taking a mean of 12.4 medications: 65% prescription, 23% OTC, and 12% vitamin/herbals. Complete agreement between computer medication list and what patient was taking was found for only 5.3% of patients.</td>
</tr>
<tr>
<td>Pit et al, 2008&lt;sup&gt;10&lt;/sup&gt;</td>
<td>Community-dwelling, general practice patients aged ≥65</td>
<td>566</td>
<td>Compared self-reported use of medicines with pharmaceutical claims data for different retrieval periods using an agreement study.</td>
<td>Kappa coefficients showed good to very good agreement (≥0.75) with retrieval periods of 30, 60, and 90 days for BZDs, low-risk NSAIDs, thiazide diuretics, and most other drugs.</td>
</tr>
</tbody>
</table>

ADR = adverse drug reactions; BZD = benzodiazepine; ED = emergency department; HF = heart failure; MVA = motor vehicle accident; NSAID = nonsteroidal anti-inflammatory drug; OTC = over the counter; VA = Veterans Affairs.
were also billed to Florida Medicaid. These 2 sets of data were used together to identify a variety of plausible problems related to the patient’s health care and were assessed prior to the telephone interactive consultation with the patient. The billed data were then compared with the patient-reported information obtained during the interactive CMR to identify discrepancies in the data.

Patient Population
The patients included in this study received MTM services provided by the UF MTMCCC and were enrolled in MEDS-AD. To be enrolled in the MEDS-AD program, patients were required to reside in the state of Florida, be Medicaid recipients assigned to the MEDS-AD Waiver program, and have an annual income at, or below, 88% of the federal poverty level with assets at, or below, $5,000 for an individual (or $6,000 for a couple).12 Also as part of the enrollment criteria, these patients could not be enrolled in a health maintenance organization plan.12

Pharmacy Claims Data
Prior to conducting a telephonic CMR, pharmacy claims data were used to generate a list of medications in the patient’s chart. The prevalent medication list included any medications filled by the pharmacy and billed to Florida Medicaid for the patient from January 1, 2011, to the date of the actual CMR call. Medications excluded from this list included short-term antibiotic and antifungal regimens, prescription fills that did not overlap with the date of the CMR, or medications that were not considered to be used as long-term therapy for a chronic condition. Medications that were generally recognized to be dosed on a pro re nata (PRN), or “as needed” basis, were included in the list regardless of the days supply obtained or the date the prescription medication was filled. The rationale for including these PRN medications was the assumption that patients often keep PRN medications and have the potential to use them at any point throughout the year. Also, many PRN medications do not come with an end date alerting the patient when the treatment should be discontinued. Another reason for including the PRN medications was that the frequency of use for many of these medications may vary each month; therefore, the days supply may not correctly reflect how the medication was actually being used.

Diagnostic Billing Data
Diagnostic billing data in the form of ICD-9 codes were used to determine the chronic conditions each patient may have been diagnosed with, or received services for, prior to the interactive phone conversation. The ICD-9 codes that were provided for each patient dated back to January 1, 2009, and were current through the date of the patient’s CMR. Because of repetition in the codes and conditions that would not normally be classified as chronic conditions, the billing data were reorganized so as to be applicable and meaningful for the purposes of this study. In order to reorganize successfully and consistently within the construct of this study, chronic conditions were only counted once as an issue was encountered to account for any repetition of the ICD-9 codes.

Pre-CMR Identification of Problems
In order to evaluate potential MRPs and/or HRPs, the medication list coupled with the information regarding chronic comorbidities was evaluated by the pharmacist prior to the CMR. Potential problems identified were to be addressed with the patient during the CMR call. Categorization of the MRPs and HRPs was based on information found in the core elements model framework of providing MTM services2 and included the following:

Drug-drug interactions (level 1 [severe] and level 2 [major]). A drug-drug interaction occurs when a medication affects the activity of another medication if the medications are administered simultaneously. For consistency within providing MTM services, Level 1 and Level 2 interactions were the focus of the drug-drug interaction report. Level 1 (severe) interactions and level 2 (major) interactions were classified using the Elsevier/Gold Standard drug information software database Clinical Pharmacology.13 The drug-drug interaction report was completed prior to the CMR and then analyzed to identify potential problems. The significance of the potential problems was assessed during the consultation with the patient. The interaction report was also updated and assessed, during or immediately after the call, as new medication information was obtained from the patient.

Therapeutic duplications. For the study purposes, a therapeutic duplication included any medication that was being filled as 2 different strengths of the same medication, or the filling of 2 different medications, in the same class of medications, which would not normally be considered a conventional therapy regimen (i.e., multiple angiotensin-converting enzyme inhibitors).

Gaps in therapy. A gap in therapy was defined as any medication that was missing for a specified chronic condition. The medication list generated by the pharmacy claims data was compared with the patient’s chronic conditions to identify any potential gaps in therapy, and these gaps were then updated as information was obtained from the patient during the CMR interaction. The particular gaps that were considered during the study period were clearly defined and clinically accepted forms of therapy that have arisen from evidence-based medication, current therapy guidelines, and primary literature, and included applicable gaps in therapy as referenced in the START protocol (screening tool to alert doctors to the right treatment).14

Lack of therapy. A lack of therapy was defined as an indication in which there was not a corresponding medication being used for a particular indication or condition. Although there may be some overlap within the “gaps in therapy” section, the
lack of therapy section takes into account any chronic condition, regardless of guideline-based therapy.

**Preferred drug list alternatives.** Florida Medicaid employs a Preferred Drug List (PDL) formulary system. The PDL is a list of medications that will be covered by Medicaid. Prescribers are encouraged to prescribe medications listed on the PDL when ordering medications for their patients. The patient’s complete medication list was assessed for opportunities to use an equivalent medication as listed on the Florida Medicaid PDL.

**Combination products and/or alternate dosing.** A combination medication is a formulation of 2 or more active ingredients combined in a single dosage form. The patient’s complete medication list was examined for the possibility of using combination products when applicable. The medication list was also assessed to identify whether the patient was taking multiple tablets of a particular strength of a medication when a higher dose tablet of that same medication was available. Both of these opportunities were used to help reduce the patient’s daily pill burden and optimize current therapy.

**Tobacco use.** Using ICD-9 codes, patients with a history of smoking were identified prior to the CMR consultation. Actual tobacco use was then assessed during the CMR.

**Telephonic CMR Interaction**
The telephonic CMR interactions were completed by either licensed pharmacists or fourth-year student pharmacists on advanced clinical rotations under the direct supervision of a licensed pharmacist. During the CMR, each of the patient’s pre-CMR medications was systematically assigned as “confirmed” (the patient stated they were still taking the medication) or “eliminated” (the patient stated they were no longer taking the medication). During the CMR, the patient was also asked the indication for each medication. The indication questioning allowed for either the confirmation or elimination of previously identified chronic conditions. Following the discussion of the medications identified prior to the call, the patient was also asked about any other medication that was being taken, including all OTC products, vitamins, dietary supplements, herbal medications, samples, and/or products obtained from any other source. These newly identified medications and their respective chronic comorbidities (if not previously identified) were then considered a “new” medication or “new” chronic comorbidity for the purposes of this analysis.

Following the review of the medications and chronic comorbidities, each of the potential problems identified prior to the call was assessed with the patient to confirm or eliminate the problem. This assessment was also the time for the identification of any new problems that occurred based on information provided by the patient (Table 2).

When related to tobacco use, “confirmed” was noted if the ICD-9 code provided evidence of tobacco use, and the patient reported the current use of tobacco products. The notation “eliminated” was used if the ICD-9 code provided information of tobacco use, but the patient reported not currently using tobacco. Finally, the determination of “new” was used if no prior information about tobacco use was listed in the ICD-9 code history for the patient, and the patient reported during the CMR currently using tobacco products.

**Data Analysis**
A large variance was also observed with respect to medications, chronic comorbidities, and MRPs or HRPs that were listed as confirmed, eliminated or identified as new. A percent discrepancy for the variance in these items was then analyzed. The percent discrepancy was calculated as the sum of new and eliminated data elements divided by the total number of data elements for each category.

**Results**
For this study, 147 CMRs were completed out of 219 scheduled CMR appointments. Of patients asked to participate, 72 either refused the consultation or could not be reached after 3 attempts. Demographic data for the 147 patients that participated in the CMR are shown in Table 3. There was a wide variance in the amount of time spent on the phone with the patient during the CMR consultation. The minimum time for a telephonic encounter was 4 minutes and 10 seconds, and the maximum time for an encounter was 1 hour and 26 minutes. The average CMR consultation time was 33 minutes and 20 seconds.

There were a total of 4,441 data elements collected by the end of the study period. From these pieces of data, 2,469 were considered confirmed (56%), while 1,024 (23%) were considered eliminated. Of the total, 948 pieces of data (21%) were identified as new MRPs or HRPs that were discovered during the CMR.

The percent discrepancy calculated for the categories identified was as follows: medications, 42%; chronic comorbidities, 41%; level 1 drug-drug interactions, 77%; level 2 drug-drug

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**Table 2: Definitions of Confirmed, Eliminated, or New Problems**

<table>
<thead>
<tr>
<th>Problem Classification</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confirmed</td>
<td>Patient reports the problem exists, and/or it is deduced from the presence/absence of a medication that the problem does exist.</td>
</tr>
<tr>
<td>Eliminated</td>
<td>Patient reports the problem does not exist, and/or it is deduced from the presence/absence of a medication that the problem does not exist.</td>
</tr>
<tr>
<td>New</td>
<td>A problem that was not identified during precall identification of problems; however, following the review of the medication list and/or chronic conditions, it was determined that a problem now exists.</td>
</tr>
</tbody>
</table>
interactions, 93%; gaps in therapy, 35%; therapeutic duplications, 87%; lack of therapy, 26%; preferred drug list alternatives, 36%; combination products, 42%; and tobacco use, 54%. The percent discrepancy that was observed and calculated is shown in Table 4.

**Table 3: Study Participant Demographics**

<table>
<thead>
<tr>
<th>Age</th>
<th>%</th>
<th>n</th>
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<tr>
<td>10-19</td>
<td>0.70</td>
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</tr>
<tr>
<td>20-29</td>
<td>1.40</td>
<td>2</td>
</tr>
<tr>
<td>30-39</td>
<td>4.80</td>
<td>7</td>
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<tr>
<td>40-49</td>
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<td>30</td>
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<td>50-59</td>
<td>46.90</td>
<td>69</td>
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<tr>
<td>60-64</td>
<td>25.90</td>
<td>38</td>
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<table>
<thead>
<tr>
<th>Sex</th>
<th>%</th>
<th>n</th>
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</thead>
<tbody>
<tr>
<td>Male</td>
<td>44.00</td>
<td>64</td>
</tr>
<tr>
<td>Female</td>
<td>56.00</td>
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<table>
<thead>
<tr>
<th>Language</th>
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<tr>
<td>English</td>
<td>94.60</td>
<td>139</td>
</tr>
<tr>
<td>Spanish</td>
<td>5.40</td>
<td>8</td>
</tr>
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</table>

Discussion

Before discrepancies were actually analyzed, it was apparent that the data collected prior to a CMR encounter were vastly different from the data that were obtained from the patient during the interactive CMR consultation. Some of the newly identified discrepancies, such as drug-drug interactions and duplication of therapy, may have the potential to cause harm to the patient and may have been overlooked had the interactive consultation not been part of the actual medication review and assessment. Categorizing each data element in its proper data set provides better visualization of the impact of MTM services across the various categories captured in this study (Table 4).

Medications and Chronic Comorbidities

Data collected on medications alone had an overall discrepancy rate of 42%, which shows that almost half of the information obtained from pharmacy claims data was not representative of the medications the patient was actually taking. Some of the reasons for the discrepancy in the medication category include patients receiving OTC products not covered by Medicaid (some OTC products are covered but not others), paying cash out of pocket for medications that were not covered by Medicaid, obtaining medications from their pharmacies via free medication campaigns, getting medications from out of the country, and patients receiving samples from their physicians.

Chronic comorbidities resulted in a 41% discrepancy, yielding the same impression that almost half of the data was not accurate. Reasons for this discrepancy may include patients being recently diagnosed with a condition not represented in the current ICD-9 codes, receiving testing for a condition that was later ruled out but still appeared as a current condition, or patient indicating never having been diagnosed with the condition listed. Consequently, these 2 data sets in turn had a downstream effect on the other 8 data sets, since medications and chronic comorbidities help indicate treatment options, interactions, and alternative medications and/or combinations. In addition, since medication and chronic comorbidities data sets are to help guide resolution of MRPs or HRPs, we did not anticipate that these data sets would show this degree of discrepancy.

Drug-Drug Interactions

Problems related to drug-drug interactions had an overwhelming number of eliminated data elements, which further highlights the benefit of providing interactive MTM services. Though there are many opportunities for medications to produce interactions when the medications are administered simultaneously, this study shows that the actual occurrence of a clinically significant interaction was much lower than anticipated. For level 1 drug-drug interactions, 23% were confirmed, while 73% were actually eliminated. For level 2 drug-drug interactions, 7% were confirmed, while 77% were eliminated. By speaking with the patient and addressing interaction concerns, we discovered that about three-fourths of suspected interactions were negligible or not considered clinically significant, meaning the patient was not reporting any of the symptoms related to the interaction, the interaction may have already been addressed by the patient’s physician, or the patient was being followed more often by the physician through additional appointments or closer monitoring of laboratory values.

Gaps in Therapy and Lack of Therapy

Both the gaps in therapy and lack of therapy categories had different findings. Upon evaluating the data, results showed confirmed data at 65% and 74%; eliminated data at 18% and 19%; and new data at 16% and 7%, respectively. A high confirmatory rate indicates that the medication for a condition or indication that appeared to be missing was truly missing from the therapy regimen. By identifying the patients that truly lack therapy or actually have a gap in therapy, this information can be relayed to the patient’s primary health care providers so that the patients may benefit from the appropriate therapy that was previously lacking. Also, 16% of the gaps in therapy were identified after the consultation with the patient, which further highlights the validity of the idea that the review of claims data alone does not capture all the necessary information and supports the value of comprehensive interactive MTM services. These data also indicate that patients are going unrecognized
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### Table 4: Category Level Data for Study Parameters*

<table>
<thead>
<tr>
<th></th>
<th>Medications n (%)</th>
<th>Chronic Comorbidities n (%)</th>
<th>Level 1 Drug-Drug Interactions n (%)</th>
<th>Level 2 Drug-Drug Interactions n (%)</th>
<th>Gaps in Therapy n (%)</th>
<th>Therapy Duplications n (%)</th>
<th>Lack of Therapy n (%)</th>
<th>PDL Alternatives n (%)</th>
<th>Combination Products n (%)</th>
<th>Tobacco Use n (%)</th>
<th>Total n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confirmed</td>
<td>1,141 (58)</td>
<td>676 (59)</td>
<td>5 (23)</td>
<td>20 (7)</td>
<td>96 (65)</td>
<td>22 (13)</td>
<td>457 (74)</td>
<td>9 (64)</td>
<td>36 (46)</td>
<td>1,024 (23)</td>
<td>2,469 (56)</td>
</tr>
<tr>
<td>Eliminated</td>
<td>441 (22)</td>
<td>41 (4)</td>
<td>16 (73)</td>
<td>220 (77)</td>
<td>27 (18)</td>
<td>140 (85)</td>
<td>117 (19)</td>
<td>2 (14)</td>
<td>5 (42)</td>
<td>15 (10)</td>
<td>948 (21)</td>
</tr>
<tr>
<td>New</td>
<td>380 (19)</td>
<td>422 (37)</td>
<td>1 (5)</td>
<td>45 (16)</td>
<td>24 (16)</td>
<td>2 (1)</td>
<td>43 (7)</td>
<td>3 (21)</td>
<td>0 (0)</td>
<td>3 (19)</td>
<td>28 (35)</td>
</tr>
<tr>
<td>Total</td>
<td>1,962</td>
<td>1,139</td>
<td>22</td>
<td>285</td>
<td>147</td>
<td>164</td>
<td>617</td>
<td>14</td>
<td>12</td>
<td>79</td>
<td>4,441</td>
</tr>
</tbody>
</table>

*Medications, chronic comorbidities, and MRPs or HRP s confirmed, eliminated, or identified as new following a telephonic MTM interaction. HRP = health-related problem; MRP = medication-related problem; MTM = medication therapy management; PDL = Preferred Drug List.

in the health care system and may be lacking clearly defined and clinically accepted forms of therapy, proven and accepted in both the primary literature and consensus guidelines created using evidence-based medication.

**Therapeutic Duplications**

The therapeutic duplication category had mostly eliminated data at a rate of 85%. This high rate may have occurred from including all medications identified prior to the call versus making a clinical decision to not include medications that appeared to have been switched to a similar alternative. Though it may have been somewhat apparent based on the pharmacy claims data as to when one medication was switched to another, a concern always exists that the patient may continue to take both drugs simultaneously, which could potentially cause harm to the patient. This concern further promotes the use and value of providing MTM services, since there is potential for miscommunication and misunderstanding between the patient, the pharmacy, and the prescriber when the patient continues the use of medications that should have been discontinued.

**Preferred Drug List Alternatives and Combination Products**

While the category of PDL alternatives showed mostly confirmed data at a rate of 64%, there was still a relatively large amount of eliminated and new data elements at 14% and 21%, respectively. MTM services were beneficial in identifying opportunities for PDL alternatives and offer an opportunity for patients to accept to these alternatives. Similarly, the category of combination products had a high rate of confirmed data at 58% and also a high rate of eliminated data at 42%.

Similar to the PDL alternatives, a high confirmed data rate for combination products represents the potential for improved adherence to medications because of a reduction in the patients' daily pill burden. These patients also agreed that a combination alternative would be an acceptable change in their daily medication regimens.

**Tobacco Use**

The amount of tobacco users that were confirmed based on the interactive consultation was at a rate of 46%, while the amount eliminated was 19%. Most importantly, this study showed that out of the 147 patients that received MTM services, at least 35% of these patients were discovered to be new or current tobacco users that were not identified as such previously. The identification of new tobacco users created an excellent opportunity when providing MTM services. The interaction established a new group of patients that required smoking cessation counseling, which may not have received the counseling previously, or may have never been approached with the questions during previous medical visits, since billing codes were not identifying these patients as smokers. MTM services present the perfect opportunity to identify such patients while offering smoking cessation counseling during the interactive CMR consultation and then sending information to the patient regarding resources and tips to help the patient quit when the patient becomes ready. Also, with the incorporation of the core elements, including follow-up, these patients can be continuously monitored for successes, or relapses, in their efforts towards smoking cessation.

**Limitations**

While conducting this research study, a number of limitations were identified. First, the inclusion of PRN medications could have potentially caused the data to be skewed or presented more discrepancy within the data than necessary. For example, if the PRN medication was captured on the medication list prior to the call but the medication was indeed properly discontinued by the patient, it would have been added to the precall list of medications then later eliminated after the telephonic interaction, thereby possibly inflating the discrepancy percentages. Future analyses may want to set stricter guidelines on the inclusion or exclusion of PRN medications, or possibly create a separate category for PRN medications being used so that PRN medications may be assessed accordingly.
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Another limitation identified during the study was lack of a means to evaluate comorbidities that may have occurred greater than 2 years prior to the date of the consultation. Information may have been missing if that information was presented in the years prior to these 2 years. We anticipated that chronic comorbidities, such as diabetes or hypertension, would appear in the ICD-9 code billing data, since in accordance with standards of clinical care, these conditions should be re-evaluated on follow-up visits annually. However, health events such as a myocardial infarction or stroke that occurred prior to January 1, 2009, may not have been captured in more recent ICD-9 codes when reviewed prior to the CMR interaction. In retrospect, if each CMR interaction was designed to ask every patient about common comorbidities, other than those identified by ICD-9 codes or personally reported by the patient, there may have been a more complete picture of the patient and therefore a more thorough evaluation would have resulted.

The telephonic CMR interactions were conducted by either a pharmacist or a student pharmacist under the direct supervision of a pharmacist. This difference may also be considered a limitation as there may have been inconsistencies between the patient interactions performed by the pharmacist and the patient interaction performed by the student pharmacist under the supervision of a pharmacist. However, the majority of the CMR interactions were provided by the pharmacist, and the interview was structured and focused for both the pharmacist and student pharmacist, as previously described; therefore, inconsistencies or variances, if any, should be minimal. Additionally, the telephonic CMRs were conducted both for English-speaking and Spanish-speaking patients. The use of translators was necessary to conduct the telephonic CMR for this subset of patients; however, the translation was performed by a Spanish-speaking pharmacist in conjunction with the UF MTMCCC pharmacist or student pharmacist. Again, there is a concern regarding the consistency of information relayed back and forth during the consultation as well as how thorough the CMR is completed in such a setting with a language barrier and use of a pharmacist translator. Another concern during the call, and a limitation to the study, could be the occurrence of response bias, or the truthfulness or accurateness of the patient’s answers during the interaction. The patient intentionally answering the question incorrectly to please, or not disapproving, the pharmacist may occur and would affect the outcome of the data being evaluated.

Finally, the findings of our study may not be generalizable to other populations. The patients eligible to receive the MTM services were selected from the MEDS-AD Waiver Program. These patients were from a lower socioeconomic status in society. As the demographic data represent, all patients included in the study were also less than 65 years of age. Consequently this population may not be representative of the traditional MTM population that would receive MTM services as a part of their Medicare Part D plan benefits. Also, there were no inclusion criteria for the patients in the study, other than the requirements of having active Medicaid services and being in the MEDS-AD Waiver Program, to participate in the program and receive UF MTMCCC services. Traditional MTM programs, as provided by Medicare Part D health plans, have inclusion criteria defined as a specific number of chronic medications with a certain number of chronic health conditions and a specified annual amount of drug spending for their Part D medications. Therefore, the data found in this study may not be generalizable to the traditional MTM population receiving MTM services from Medicare Part D providers and may be more generalizable to other Medicaid MTM programs.

Conclusions

MTM is defined as “a distinct service, or group of services, that optimize therapeutic outcomes for individual patients.” Since it is a relatively new concept that is still evolving, we felt it was important to examine how effective the current methods for providing MTM services have been, as well as considering the benefit of the interactive patient consultation. This assessment has proven slightly challenging in the past and has given rise to many diverse programs and ways of carrying out MTM services. The UF College of Pharmacy established an MTM program that closely follows the definition and framework of the core elements for providing MTM services, while conducting telephonic interactive consultations with patients. This study set out to determine the degree of discrepancy between diagnostic billing codes (chronic conditions/comorbidities) and pharmacy claims data (medications) that was available prior to the patient interaction, as compared with patient-reported health conditions and medication use obtained from the patient when providing MTM services through telephonic interactive consultations.

Whether considering each individual data set or looking at the picture as a whole, the objective of this study was clearly met. Our findings determined that there is a definite degree of discrepancy when comparing diagnostic conditions (chronic conditions/comorbidities) and pharmacy claims data (medications) with patient-reported data when providing MTM services through telephonic interactive consultations. With the discrepancy being so large, the value of MTM telephonic interactions can be realized. Therefore, it may be impossible to make an accurate recommendation when having incomplete data or data that contain such discrepancies. Through interactive consultations with patients and evaluation of the available data provided prior to, and as a result of, patient-reported information, health care providers can make more appropriate recommendations with the goal of improving patient outcomes.
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DISCLOSURES

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Study concept and design were from Patel and Roane, and data collection was done by Patel and Knoblich. All authors were involved in data interpretation and writing the manuscript.

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REFERENCES


Incremental Health Care Resource Utilization and Economic Burden of Venous Thromboembolism Recurrence from a U.S. Payer Perspective

J. Lin, PhD; R. Preblick, PharmD, MPH; M. Lingohr-Smith, PhD; and W.J. Kwong, PharmD, PhD

ABSTRACT
BACKGROUND: The third leading cause of cardiovascular-associated death, venous thromboembolism (VTE), represents a significant health care and economic burden. Although the burden of a one-time VTE event has been assessed, there are limited data regarding the burden of VTE recurrence.

OBJECTIVE: To assess the rate and predictors of VTE recurrence within 1 year in the United States and evaluate the incremental health care resource utilization and costs associated with such VTE recurrences.

METHODS: Patients (≥18 years) diagnosed with deep vein thrombosis and/or pulmonary embolism between January 1, 2008, and December 31, 2010, were identified from the Truven Health Analytics MarketScan Commercial and Medicare databases. The earliest VTE diagnosis was defined as the index VTE event. Patients were required to have 12 months of continuous insurance coverage before (baseline period) and after (follow-up period) the index event. Patients were further required to have initiated anticoagulant usage within 30 days of the index VTE event and have at least 30 days of treatment. The incidence of recurrent VTE, defined as a hospitalization or emergency room (ER) visit with a VTE diagnosis in the follow-up period, was determined for the commercially insured and Medicare populations separately. A proportional hazards model was used to assess the predictors of time to VTE recurrences. All cause and VTE-related health care resource utilization including hospitalizations, length of stay, outpatient medical service claims, and outpatient pharmacy claims were assessed along with the associated costs incurred during the 30-day and 12-month post-index event periods. Commercially insured and Medicare patients with and without recurrent VTE were evaluated and compared separately. Generalized linear models were used to further assess the incremental cost burden of recurrent VTE.

RESULTS: Among the commercially insured population, 29,275 patients were diagnosed with VTE and received anticoagulant therapy. A recurrence of VTE associated with a hospitalization or ER visit occurred within 12 months of the index VTE in 15.4% of patients with a mean time to recurrence of 74.1 days. Among the Medicare insured population (n = 14,509), 11.4% of patients experienced another VTE with a mean time to recurrence of 115.6 days. A consistent predictor of VTE recurrence across both populations was greater comorbidity as indicated by Charlson Comorbidity Index scores. Among commercially insured VTE patients, total payments for health care resource utilization for all causes, including inpatient, outpatient medical services, and outpatient pharmacy use were higher for patients with a recurrent VTE relative to those without a recurrent VTE ($82,110 [$106,918] vs. $36,918 [$54,852], P < 0.001). The primary driver for the higher health care payments was greater use of inpatient care. Total payments for VTE-related resource use was also greater for patients with a VTE recurrence ($38,591 [$51,479] vs. $15,123 [$22,186], P < 0.001) with the majority (62.9%) attributed to care that took place within 30 days of the index VTE. After adjustment for key patient characteristics, VTE recurrence was associated with 2.2-fold and 3.0-fold higher post-index health care payments for all causes and for VTE-related claims, respectively. Similar results were observed for the Medicare population.

CONCLUSIONS: VTE recurrence associated with a hospitalization or ER visit is associated with substantial health care resource utilization, which is primarily inpatient care undergone within the first 30 days following an initial VTE event. Thus, a sizeable portion of the economic burden of recurrent VTE is also incurred during this short period of time following an initial VTE event. Given that rates of VTE recurrence were high among patients identified as having received anticoagulant treatment, strategies to improve anticoagulation therapy among VTE patients in addition to other preventative measures are needed to lessen the health care and economic burdens of VTE.

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What is already known about this subject
• The third leading cause of cardiovascular-associated death, venous thromboembolism (VTE), represents a significant health care and economic burden.
• The annual average number of hospitalizations attributed to VTE is more than 500,000.
• Average total annual hospitalization costs (1998-2004) for VTE patients have been estimated to range between $7,594 and $27,909, depending on the type of event and whether it was a primary or secondary diagnosis.
• Among hospitalized VTE patients, direct medical costs for VTE per patient per year are substantial and result not only from the initial VTE hospitalization event, but also from a high rate of hospital readmission for a subsequent VTE (3.3%-14.3%).

What this study adds
• Even with anticoagulant treatment, the incidence of VTE recurrence associated with a hospitalization or emergency room visit ranged from 11.4% to 15.4%, with the majority of recurrences occurring within 30 days of the initial VTE.
• The likelihood of VTE recurrence appears to be most strongly related to comorbidities.
• Among both commercially and Medicare insured VTE patients, total payments for VTE-related health care resource utilization, including inpatient, outpatient medical services, and outpatient pharmacy use, are 3.0-fold and 3.4-fold higher, respectively, for patients with a recurrence of VTE relative to those without a recurrent VTE.
• The primary driver for the higher health care costs is a greater use of inpatient care.
• Reducing VTE recurrence is critical to lessen the health care and economic burdens of VTE.
Venous thromboembolism (VTE) is a coagulation disorder that predisposes individuals to clot formation in the venous system, primarily in the veins of legs, called deep vein thrombosis (DVT). When a clot breaks free, it can travel to the lungs causing pulmonary embolism (PE), a sequelae of VTE that is directly associated with 5% to 10% of all in-hospital deaths.1-3 The incidence of VTE increases with age with the Centers for Disease Control and Prevention reporting average annual rates of VTE ranging from 60 per 100,000 population for persons aged 18-39 years to 1,134 per 100,000 for persons aged ≥ 80 years.4 Mahan et al. (2012) estimated that, in 2011 U.S. dollars, the annual cost of VTE ranges between $13.5 and $27.2 billion.5 The substantial burden to the health care system and the high frequency of preventable cases have prompted the Surgeon General and the U.S. Department of Health and Human Services (Partnership for Patients) to elicit a call to action focused on reversing the projected trends of VTE.6,7

The treatment goals of VTE therapy are to stop clot propagation and to prevent thrombus recurrence and PE.8 The American College of Chest Physicians recommends initial treatment for DVT or PE with parenteral low-molecular-weight heparin (LMWH) or anticoagulation with rivaroxaban and anticoagulation therapy (such as a vitamin K antagonist, LMWH, rivaroxaban, or dabigatran) for 3 months or longer depending on bleeding risk and whether the event was provoked, unprovoked, or associated with active cancer.9

The health care and economic burdens of VTE are not only related to diagnosis and treatment of the initial event, but also to VTE recurrence.8,10-12 Spyropoulos and Lin (2007) reported that hospital readmission rates of hospitalized VTE patients were between 5.3% and 14.3% by 1 year.10 It is important to better understand the overall health care and economic burdens of recurrent VTE among both inpatient- and outpatient-treated VTE patients and to define populations at high risk for VTE recurrence in order to potentially improve the quality of care for VTE patients.5 To that end, this study’s purpose was to evaluate the rate and predictors of VTE recurrences among both inpatient- and outpatient-treated VTE patients and determine the incremental burden of health care resource utilization and costs among patients with VTE recurrence who have commercial or Medicare insurance coverage in the United States.

## Methods

### Data Source

Patient-level data were extracted from the Truven Health Analytics MarketScan Commercial and Medicare databases from January 1, 2007, to December 31, 2011. The MarketScan Commercial Claims and Encounters database and Medicare Supplemental database capture person-specific health care use, expenditures, and enrollment in inpatient, outpatient, and prescription drug services for millions of beneficiaries residing in multiple states across the United States. Data from individual patients are integrated from all providers of care, maintaining all health care utilization and cost connections at the patient level. The MarketScan Medicare Supplemental database contains the Medicare covered, employer-paid, and any out-of-pocket portions paid for the health care encounter. In compliance with the Health Insurance Portability and Accountability Act of 1996 (HIPAA), the databases consist of fully de-identified data sets, with synthetic identifiers applied to patient-level and provider-level data to protect the identities of both the patients and data contributors.

### Study Population

Patients who had at least 1 inpatient claim with a primary or secondary VTE diagnosis or 2 outpatient claims (including emergency room (ER) visit) on 2 separate dates for VTE diagnosis as identified by International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes for VTE between January 1, 2008, and December 31, 2010, were eligible for inclusion in the study. The following ICD-9-CM codes were used to identify patients who had DVT: 451.1, 451.2, 451.8, 451.9, 453.2, 453.4, 453.8, and 453.9. The ICD-9-CM code of 415.1 was used to identify patients who had a PE. The first VTE diagnosis to occur during the index VTE identification period was defined as the index VTE event, and the type of VTE (i.e., DVT, PE, or DVT/PE) was determined on the first day of the VTE diagnosis. Two outpatient claims were required to maximize the likelihood that a medical visit associated with VTE treatment did occur and minimize the risk of misidentifying an outpatient visit with a “rule-out” VTE diagnosis as an index event. To further increase the likelihood that the identified VTE diagnoses were for VTE events, all VTE patients were required to have evidence of VTE pharmacological treatment, defined as treatment with unfractionated heparin (UFH), LMWH, warfarin, or fondaparinux for a duration of ≥ 30 days and initiated within 30 days of the index VTE event. All patients within the study populations were required to be ≥ 18 years at the index VTE event and have 12 months of continuous medical and prescription benefit coverage prior to (baseline period) and after the index VTE event (follow-up period).

### VTE Recurrence Definition

During the follow-up period, recurrence of VTE was evaluated for the commercially and Medicare insured populations. A recurrence of VTE was defined as having a hospital admission or ER visit identified by medical claims associated with a primary or secondary diagnosis of DVT and/or PE that occurred more than 2 days after the index VTE event (ICD-9-CM codes as previously mentioned). The 2-day period was used to rule out hospital admissions related to treatment of the index
VTE event. For both the commercially and Medicare insured populations, patients were grouped into one of 2 cohorts; one composed of patients without a recurrent VTE during the 12-month follow-up period and the second composed of patients who experienced a VTE recurrence during the follow-up period. The time to first recurrent VTE for patients having been identified as having a recurrence was summarized.

Baseline Demographics and Clinical Characteristics
Patient demographics consisting of age, gender, and U.S. region of residence along with type of health plan were collected. Clinical characteristics consisting of index VTE type (i.e., DVT only, PE only, DVT/PE), setting of initial care (inpatient vs. outpatient), Deyo-Charlson Comorbidity Index (CCI), comorbidities, and Elixhauser Comorbidity Index (EI) were assessed based on data collected during the 12 months prior to the index event. History of hospitalization and/or surgery 30 days prior to the initial VTE were determined for all patients within the commercially and Medicare insured populations. The CCI is a widely used measurement that is predictive of the likelihood of 1-year and 10-year mortality based on the presence or absence of 19 comorbid conditions and their associated assigned weights. The more recently developed EI, a comorbidity index based on the presence or absence of 30 comorbid conditions, was also measured for each patient within the commercially and Medicare insured populations.

General Statistical Analyses
Descriptive statistics were used to summarize and compare the demographic and clinical characteristics of the study cohorts within the commercially and Medicare insured populations. Means, standard deviations (SD), and medians were reported for continuous data, and counts and percentages were reported for categorical data. For comparisons of health care utilization and associated costs between patients with and without recurrent VTE, t-tests and chi-square tests were used for continuous and categorical variables, respectively. A P value of 0.05 was used to determine statistical significance. All statistical analyses were carried out using SAS 9.2 (Cary, NC).

Patient Characteristics that Impact VTE Recurrence
A Cox proportional hazards model, in which the time to VTE recurrence was the dependent variable, was conducted. Predictor covariates included age, gender, VTE type, setting of VTE diagnosis (inpatient or outpatient), CCI score, and U.S. region of residence.

Comparison of Health Care Resource Utilization and Payments at the Unadjusted Level: Patients with VTE Recurrence Versus Patients Without VTE Recurrence
Hospitalizations, including total length of stay (LOS), claims for outpatient medical services (all outpatient medical services and just those for ER visits), and outpatient prescription claims were evaluated for each patient in the study populations during a 30-day period following the index VTE event and for the entire 12-month follow-up period. Inpatient, outpatient medical services, and outpatient pharmacy resource utilization categories were grouped into all-cause (i.e., health care use for any reason) and VTE-related, which included all claims associated with a diagnosis of VTE. VTE-related outpatient pharmacy use consisted of prescribed anticoagulant use. All cost values in the study represent the health care payment amount. The health care payments made by health plans and the overall total reimbursed payments from health plans, patients and/or other third-party payers to the hospital for covered services provided during an admission were measured and reported. Health care resource utilization and associated costs were then compared among the study cohorts of patients with and without VTE recurrence. Results were reported separately for the commercially and Medicare insured populations.

Comparison of Adjusted Total Health Care Payments: Patients with VTE Recurrence Versus Patients Without VTE Recurrence
Generalized linear models with log transformation for cost data and gamma distribution as the link function were used to evaluate the impact of VTE recurrence on total payments, while controlling for key patient characteristics. Payments included those for health care resource utilization for any reason and those that were VTE-related. Absolute cost differences and cost ratios of total payments within 30 days and 12 months post-index VTE event were reported. Covariates used in the regression models were age, gender, VTE type, setting of initial VTE diagnosis (inpatient or outpatient), CCI score, and U.S. region of residence. We additionally carried out a sensitivity multivariable regression analysis in which additional covariates were added. These additional covariates were health plan types and comorbidities including cancer, congestive heart failure, chronic obstructive pulmonary disease/pulmonary diseases, severe infectious diseases, stroke/transient ischemic attack, acute coronary syndrome, hypertension, and diabetes.

Results
Study Population
Among the commercially insured, 29,275 patients with an index VTE event were identified during the study selection period (Figure 1). Among this study population, the recurrent VTE cohort consisted of 4,498 (15.4%) patients. The mean time to VTE recurrence was 74.1 days in this cohort. Among the Medicare insured, 14,509 patients with an initial VTE event were identified during the study selection period (Figure 1). The recurrent VTE cohort within this Medicare population consisted of 1,655 (11.4%) patients. The mean time to VTE recurrence was 115.6 days in this cohort.
Baseline Demographics and Clinical Characteristics

Baseline demographics for the commercially and Medicare insured populations are presented in Table 1. For the commercially insured population, the mean age was slightly higher for patients without a recurrent VTE (48.5 vs. 49.9 years, P<0.001). The VTE recurrence cohort had a lower proportion of male patients than the cohort without VTE recurrence (48.1% vs. 51.5%, P<0.001). For the Medicare insured population, mean ages (77.0 vs. 76.8 years, P=0.307) and proportion of male patients were similar (45.1% vs. 46.2%, P=0.370) for patients with and without VTE recurrence.

Baseline clinical characteristics for the commercially and Medicare insured populations are presented in Table 2. Among the commercially insured population, DVT was the most common index VTE event type for patients with and without recurrent VTE (~59% for both cohorts), followed by PE only (~25%), and DVT/PE (15%-16%). The majority of index VTE events were treated in the inpatient setting (58% with recurrent VTE and 60% without recurrent VTE). Mean CCI (1.5 vs. 1.2, P<0.001) and Elixhauser (2.7 vs. 2.4, P<0.001) scores at baseline were greater for patients with VTE recurrence in comparison with patients without VTE recurrence. The proportion of patients with a hospitalization 30 days prior to the index VTE event was higher for patients with a VTE recurrence (14.5% vs. 11.8%, P<0.001). Among the commercially insured population with recurrent VTE, significantly more patients had comorbidities of severe infectious diseases (29.3% vs. 24.7%, P<0.001), cancer (17.5% vs. 13.3%, P<0.001), chronic obstructive pulmonary disease/pulmonary diseases (15.7% vs. 13.9%, P=0.001), and congestive heart failure (5.1% vs. 4.1%, P=0.003).

Clinical characteristics of the index VTE event among the Medicare insured population were similar to the commercially insured population. DVT was the most frequent index VTE event type with a greater proportion of patients with recurrent VTE having this event type than patients without recurrent VTE (63.0% vs. 56.3%, P<0.001). There were also fewer patients with an index PE event in the recurrent VTE cohort than the no recurrent VTE cohort (24.2% vs. 30.0%, P<0.001). A lower proportion of patients who had a VTE recurrence were treated in the inpatient setting for their index VTE event in comparison with patients who did not have a recurrent VTE (51.4% vs. 58.6%, P<0.001). Mean CCI (2.6 vs. 2.3, P<0.001) and Elixhauser (3.9 vs. 3.6, P<0.001) scores at baseline were greater for patients with VTE recurrence versus those without a recurrence. Among the Medicare insured population with recurrent VTE, significantly more patients had severe infectious diseases (36.4% vs. 31.3%, P<0.001), cancer (32.8% vs. 28.6%, P=0.001), and chronic obstructive pulmonary disease/pulmonary diseases (27.5% vs. 24.7%, P=0.013).

Outpatient Anticoagulant Use Among Study Populations

Inpatient use of anticoagulation therapy could not be evaluated because the data are not captured in the MarketScan databases. In the outpatient setting, the vast majority of commercially insured patients received warfarin for their index VTE events...
(96.2% of patients with VTE recurrence and 97.5% of patients without VTE recurrence). Most patients were also treated with an LMWH (70.5% of patients with VTE recurrence and 62.5% of patients without VTE recurrence). In the outpatient setting, the majority of Medicare insured patients were also treated with warfarin (97%-98%) for their index VTE events.

**Incidence of Specific VTE Events and Time to Recurrence**

Figure 2a presents the cumulative 12-month incidence of VTE recurrence among commercially insured patients by index event type. Among commercially insured patients who experienced a VTE recurrence, DVT was the most common recurrent event (experienced by 58.8% of patients, with a mean time to recurrence of 70.5 days) followed by PE (experienced by 24.8% of patients, with a mean time to recurrence of 76.4 days). A combined DVT/PE type of recurrence was identified in 16.4% of patients experiencing a recurrent event with a mean time to recurrence of 83.5 days. Among patients with VTE recurrences, the majority of recurrences occurred within the first month after the index VTE, with 58.3% of such recurrences occurring within the first month among VTE recurrence patients who had DVT as their index event, 57.2% of such recurrences occurring among VTE recurrence patients who had PE as their index event, and 51.4% of such recurrences occurring among VTE recurrence patients who had DVT/PE as their index event (see Figure 3a).

Figure 2b presents the cumulative 12-month incidence of VTE recurrence among Medicare insured patients within 1 year of the index VTE. Similar to results of commercially insured patients, the majority of Medicare insured patients experiencing a recurrence had a DVT (63.0%) with a mean time to recurrence of 110.3 days. PE (24.2%) was the second most frequent type of recurrence with a mean time to recurrence of 116.4 days. A combined DVT/PE (12.7%) recurrent event was the least frequent type of VTE with a mean time to recurrence of 140.2 days. The mean times to recurrence for
each specific type of VTE recurrent event were greater than 3 months. However, 27%-38% of patients who had a recurrent VTE event experienced it within the first month after their index event (DVT only: 37.1%, PE only: 38.2%, DVT/PE: 27.0%, Figure 3b). The proportions of patients who experienced each specific type of recurrent VTE were between 8% and 9% within 3 months, between 4% and 6% at 6 months, and between 3% and 5% within 12 months.

**Predictors of VTE Recurrence**

The relationship between VTE recurrence and certain patient characteristics, treatment setting, and demographics are presented in Table 3. Among commercially insured VTE patients, younger age, female gender, and outpatient treatment of index VTE increased the risk of VTE recurrence (lower age in years vs. each incremental year hazard ratio (HR): 0.99, P < 0.001; female vs. male HR: 1.1, P = 0.007; inpatient vs. outpatient setting HR: 0.9, P < 0.001). Patients who had an index DVT/PE versus those who had an index DVT only had a greater HR for VTE recurrence (HR: 1.2, P = 0.001). A greater index CCI score was associated with a greater risk for VTE recurrence, such that versus a score of 0, a score of 1-2 had an HR of 1.2 (P < 0.001), a score of 3-4 had an HR of 1.5 (P < 0.001), and a score of ≥5 had an HR of 1.8 (P < 0.001). U.S. region of residence did not impact VTE recurrence.

Among Medicare insured patients with a VTE, age and gender did not affect the likelihood of VTE recurrence. Patients who had an index PE only versus those who had an index DVT only had a lower HR for VTE recurrence (HR: 0.8, P < 0.001). A greater CCI score (>2) was associated with a greater risk for VTE recurrence, such that versus a score of 0, a score of 1-2 had an HR of 1.2 (P < 0.001), a score of 3-4 had an HR of 1.5 (P < 0.001), and a score of ≥5 had an HR of 1.8 (P < 0.001). U.S. region of residence did not impact VTE recurrence.

**Comparison of Health Care Resource Utilization and Associated Payments: Patients with VTE Recurrence Versus Patients without VTE Recurrence**

During the 12-month follow-up period, commercially insured patients with a VTE recurrence associated with a hospitalization or ER visit had higher all-cause and VTE-related health...
care resource utilization across all evaluated categories than patients without VTE recurrence. This higher resource utilization was reflected in higher associated health care payments (Tables 4 and 5). The primary driver for the increased health care payments for patients with recurrent VTE was a greater use of inpatient care (mean [SD] number of all-cause hospitalizations: 2.1 [1.9] vs. 0.9 [0.9]; all-cause hospital total LOS: 11.9 [17.6] vs. 4.5 [7.2] days; mean number of VTE-related hospitalizations: 1.6 [0.9] vs. 0.7 [0.5]; VTE-related hospital total LOS: 8.4 [10.1] vs. 3.4 [4.3] days; P < 0.001 for all comparisons). Total payments for all-cause hospitalizations ($47,201 [$79,977] vs. $17,225 [$34,512], P < 0.001) and for VTE-related hospitalizations ($33,594 [$50,762] vs. $12,158 [$22,003], P < 0.001) were consequently greater for patients with recurrent VTE in comparison with patients without recurrent VTE.

The number of all-cause and VTE-related outpatient medical service claims, ER claims, and outpatient pharmacy claims were also significantly greater for patients with recurrent VTE. Mean total payments for all health care resource utilization, including inpatient, outpatient medical services, and outpatient pharmacy use were 2.2-fold higher for patients with recurrent VTE relative to patients without recurrent VTE ($82,110 [$106,918] vs. $36,918 [$54,852], P < 0.001). Additionally, total payments for VTE-related health care resource use were significantly higher for patients with recurrent VTE ($38,591 [$51,479] vs. $15,123 [$22,186], P < 0.001). These results, in terms of higher health care resource utilization and associated payments among VTE recurrent patients, were similar in all
TABLE 3 Factors Impacting VTE Time to Recurrence (Day)

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<tr>
<td>Region (vs. South)</td>
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CI = confidence interval, DVT = deep vein thrombosis, PE = pulmonary embolism, VTE = venous thromboembolism.

respects for the Medicare population, with the exception that differences in total payments for VTE-related outpatient medical services (30 days and 12 months) did not reach statistical significance (Tables 4 and 5).

Comparison of Adjusted Total Health Care Payments: Patients with VTE Recurrence Versus Patients Without VTE Recurrence

After adjustment for key patient characteristics among cohorts of the commercially insured population, VTE recurrence was associated with 2.2-fold ($P<0.001$) and 3.0-fold ($P<0.001$) higher health care payments for all causes and for VTE, respectively, during the 12-month follow-up period (Table 6). VTE recurrence was associated with 1.8-fold and 2.1-fold higher health care costs for all causes and for VTE-related claims, respectively, during the 30-day period following the index VTE event (Table 6). Absolute differences in health care payments for patients with VTE recurrence versus those without a VTE recurrence during the 12-month follow-up period were $56,580 (confidence interval [CI]: $53,272, 59,888, P<0.05$) and $28,067 (CI: $26,748, 29,386, P<0.05$) for all causes and for VTE-related claims, respectively, and during the 30-day follow-up period were $14,310 (CI: $13,287, 15,333, P<0.05$) and $13,045 (CI: $12,184, 13,906, P<0.05$) for all causes and for VTE-related claims, respectively. These results were similar in the sensitivity regression analysis in which absolute differences in health care payments for patients with VTE recurrence versus those without a VTE recurrence during the 12-month follow-up period were $69,885 (CI: $61,468, 78,302, P<0.05$) and $33,258 (CI: $30,051, 36,465, P<0.05$) for all causes and for VTE-related claims, respectively, and during the 30-day follow-up period were $17,711 (CI: $15,032, 20,390, P<0.05$) and $15,793 (CI: $13,609, 17,977, P<0.05$) for all causes and for VTE-related claims, respectively.

After adjustment for key patient characteristics among cohorts of the Medicare insured population, VTE recurrence was associated with 1.8-fold ($P<0.001$) and 3.4-fold ($P<0.001$) higher health care payments for all causes and for VTE, respectively, during the 12-month follow-up period (Table 6). VTE recurrence was associated with 1.6-fold and 1.8-fold higher health care costs for all causes and for VTE-related claims, respectively, during the 30-day period following the index VTE event (Table 6). Absolute differences in health care payments for patients with VTE recurrence versus those without a VTE recurrence during the 12-month follow-up period were $25,287 (CI: $22,167, 28,407, P<0.05$) and $19,788 (CI: $18,185, 21,390, P<0.05$) for all causes and for VTE-related claims, respectively, and during the 30-day follow-up period were $5,677 (CI: $4,755, 6,599, P<0.05$) and $6,114 (CI: $5,304, 6,925, P<0.05$) for all causes and for VTE-related claims, respectively. These results were similar in the sensitivity regression analysis in which absolute differences in health care payments for patients with VTE recurrence versus those without a VTE recurrence during the 12-month follow-up period were $59,888 (CI: $53,272, 59,888, P<0.05$) and $18,630 (CI: $13,326, 23,933, P<0.05$) for all causes and for VTE-related claims, respectively, and during the 30-day follow-up period were $5,129 (CI: $1,878, 8,380, P<0.05$) and $5,562 (CI: $2,779, 8,345, P<0.05$) for all causes and for VTE-related claims, respectively.

Discussion

This study shows that despite efforts to reverse the trends of VTE at a national level,6,7 recurrence rates are high, resulting in an extensive resource and economic burden to the health care system. Among commercially and Medicare insured patients who experienced an initial VTE event, the
Incremental Health Care Resource Utilization and Economic Burden of Venous Thromboembolism Recurrence from a U.S. Payer Perspective

**TABLE 4** All-Cause and VTE-Related Health Care Resource Utilization, 30 Days and 12 Months Post Initial VTE Event: Commercially and Medicare Insured Patients with VTE Recurrence Versus Patients Without VTE Recurrence

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<th>Medicare Study Population</th>
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<td>Yes (n = 1,635) Mean [SD]</td>
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**All-cause hospitalizations**

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**All-cause outpatient medical service claims**

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**VTE-related hospitalizations**

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**VTE-related outpatient medical service claims**

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**All-cause emergency room claims**

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**VTE-related emergency room claims**

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<td>2.7 [1.5]</td>
<td></td>
<td>2.7 [1.5]</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2.7 [1.5]</td>
<td></td>
<td>2.7 [1.5]</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.825</td>
<td></td>
<td>0.825</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**All-cause outpatient pharmacy claims**

<table>
<thead>
<tr>
<th></th>
<th>Within 30 days post initial VTE event</th>
<th></th>
<th>Within 30 days post initial VTE event</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>9.8 [5.3]</td>
<td></td>
<td>9.8 [5.3]</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>8.5 [4.9]</td>
<td></td>
<td>8.5 [4.9]</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.001</td>
<td></td>
<td>0.001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*P values were obtained by Student’s t-test.
SD = standard deviation, VTE = venous thromboembolism.
## TABLE 5
All-Cause and VTE-Related Health Care Costs, 30 Days and 12 Months Post Initial VTE Event: Commercially and Medicare Insured Patients with VTE Recurrence Versus Patients Without VTE Recurrence

<table>
<thead>
<tr>
<th></th>
<th>Commercial Study Population</th>
<th>Medicare Study Population</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Recurrent VTE</td>
<td>Recurrent VTE</td>
</tr>
<tr>
<td></td>
<td>Yes (n = 4,498)</td>
<td>Yes (n = 1,635)</td>
</tr>
<tr>
<td></td>
<td>No (n = 24,777)</td>
<td>No (n = 12,854)</td>
</tr>
<tr>
<td></td>
<td>P Value^a</td>
<td>P Value^a</td>
</tr>
<tr>
<td><strong>All-cause inpatient costs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total payment (30 days)</td>
<td>22,196 [34,447]</td>
<td>10,717 [18,538]</td>
</tr>
<tr>
<td>Health plan payment (30 days)</td>
<td>21,309 [34,178]</td>
<td>4,125 [12,347]</td>
</tr>
<tr>
<td>Total payment (12 mos.)</td>
<td>47,201 [79,977]</td>
<td>28,564 [57,990]</td>
</tr>
<tr>
<td>Health plan payment (12 mos.)</td>
<td>45,440 [80,196]</td>
<td>10,212 [44,577]</td>
</tr>
<tr>
<td><strong>VTE-related inpatient costs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total payment (30 days)</td>
<td>21,279 [33,537]</td>
<td>10,302 [17,998]</td>
</tr>
<tr>
<td>Health plan payment (30 days)</td>
<td>20,407 [33,202]</td>
<td>3,882 [11,881]</td>
</tr>
<tr>
<td>Total payment (12 mos.)</td>
<td>33,594 [50,702]</td>
<td>20,639 [37,077]</td>
</tr>
<tr>
<td>Health plan payment (12 mos.)</td>
<td>32,327 [51,418]</td>
<td>6,995 [28,310]</td>
</tr>
<tr>
<td><strong>All-cause outpatient medical costs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total payment (30 days)</td>
<td>4,512 [7,115]</td>
<td>3,059 [4,882]</td>
</tr>
<tr>
<td>Health plan payment (30 days)</td>
<td>4,134 [6,874]</td>
<td>1,038 [2,191]</td>
</tr>
<tr>
<td>Total payment (12 mos.)</td>
<td>27,764 [45,273]</td>
<td>21,048 [31,397]</td>
</tr>
<tr>
<td>Health plan payment (12 mos.)</td>
<td>25,740 [43,884]</td>
<td>7,194 [71,249]</td>
</tr>
<tr>
<td><strong>VTE-related outpatient medical costs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total payment (30 days)</td>
<td>1,058 [3,366]</td>
<td>1,088 [2,245]</td>
</tr>
<tr>
<td>Health plan payment (30 days)</td>
<td>1,476 [3,108]</td>
<td>377 [994]</td>
</tr>
<tr>
<td>Total payment (12 mos.)</td>
<td>3,053 [5,696]</td>
<td>2,602 [5,303]</td>
</tr>
<tr>
<td>Health plan payment (12 mos.)</td>
<td>3,258 [5,340]</td>
<td>968 [1,301]</td>
</tr>
<tr>
<td><strong>All-cause ER medical costs</strong></td>
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<td></td>
</tr>
<tr>
<td>Total payment (30 days)</td>
<td>454 [1,247]</td>
<td>187 [748]</td>
</tr>
<tr>
<td>Health plan payment (30 days)</td>
<td>410 [1,193]</td>
<td>59 [319]</td>
</tr>
<tr>
<td>Total payment (12 mos.)</td>
<td>1,361 [3,158]</td>
<td>639 [1,609]</td>
</tr>
<tr>
<td>Health plan payment (12 mos.)</td>
<td>1,227 [2,974]</td>
<td>220 [723]</td>
</tr>
<tr>
<td><strong>VTE-related ER medical costs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total payment (30 days)</td>
<td>277 [944]</td>
<td>117 [527]</td>
</tr>
<tr>
<td>Health plan payment (30 days)</td>
<td>249 [904]</td>
<td>36 [282]</td>
</tr>
<tr>
<td>Total payment (12 mos.)</td>
<td>411 [1,143]</td>
<td>193 [638]</td>
</tr>
<tr>
<td>Health plan payment (12 mos.)</td>
<td>367 [1,075]</td>
<td>59 [314]</td>
</tr>
<tr>
<td><strong>All-cause outpatient pharmacy costs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total payment (30 days)</td>
<td>1,345 [2,343]</td>
<td>897 [1,480]</td>
</tr>
<tr>
<td>Health plan payment (30 days)</td>
<td>1,234 [2,311]</td>
<td>784 [1,427]</td>
</tr>
<tr>
<td>Total payment (12 mos.)</td>
<td>7,145 [11,768]</td>
<td>6,370 [11,460]</td>
</tr>
<tr>
<td><strong>VTE-related outpatient pharmacy costs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total payment (30 days)</td>
<td>989 [1,572]</td>
<td>539 [1,133]</td>
</tr>
<tr>
<td>Health plan payment (30 days)</td>
<td>922 [1,541]</td>
<td>490 [1,094]</td>
</tr>
<tr>
<td>Total payment (12 mos.)</td>
<td>3,213 [7,181]</td>
<td>1,888 [5,360]</td>
</tr>
<tr>
<td>Health plan payment (12 mos.)</td>
<td>3,035 [7,067]</td>
<td>1,758 [5,282]</td>
</tr>
<tr>
<td><strong>All-cause total medical costs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total payment (30 days)</td>
<td>28,053 [35,668]</td>
<td>14,673 [19,328]</td>
</tr>
<tr>
<td>Total payment (12 mos.)</td>
<td>82,110 [106,918]</td>
<td>55,982 [73,383]</td>
</tr>
<tr>
<td><strong>VTE-related total medical costs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total payment (30 days)</td>
<td>24,282 [33,596]</td>
<td>12,288 [18,155]</td>
</tr>
<tr>
<td>Total payment (12 mos.)</td>
<td>38,591 [51,479]</td>
<td>24,137 [37,758]</td>
</tr>
</tbody>
</table>

^aP values were obtained by Student’s t-test.

^bIncludes total inpatient, outpatient, and outpatient pharmacy payments.

ER = emergency room, mos. = months, SD = standard deviation, VTE = venous thromboembolism.

**Incremental Health Care Resource Utilization and Economic Burden of Venous Thromboembolism Recurrence from a U.S. Payer Perspective**

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Multivariable Regression Results of Total Health Care Payment for All-Cause and VTE-Related Health Care Resource Use During 30-Day and 12-Month Follow-up Periods

<table>
<thead>
<tr>
<th></th>
<th>Cost Ratio</th>
<th>CI Lower</th>
<th>CI Upper</th>
<th>P Value</th>
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<tr>
<td><strong>Commercial population</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30 days</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All cause</td>
<td>1.8</td>
<td>1.8</td>
<td>1.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>VTE-related</td>
<td>2.1</td>
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<td>2.1</td>
<td>&lt;0.001</td>
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<tr>
<td>12 months</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All cause</td>
<td>2.2</td>
<td>2.2</td>
<td>2.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>VTE-related</td>
<td>3.0</td>
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<td>3.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Medicare population</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30 days</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>All cause</td>
<td>1.6</td>
<td>1.5</td>
<td>1.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>VTE-related</td>
<td>1.8</td>
<td>1.8</td>
<td>1.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>12 months</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All cause</td>
<td>1.8</td>
<td>1.7</td>
<td>1.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>VTE-related</td>
<td>3.4</td>
<td>3.3</td>
<td>3.6</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

CI=confidence interval; VTE=venous thromboembolism.

frequencies of VTE recurrence ranged from 11.4% to 15.4%. These rates of VTE recurrence are substantially higher than the 3.6% rate of hospital-documented recurrent VTE recently reported by Lefebvre et al. (2012). One explanation for the greater VTE recurrence rates among our study populations is that we included ER visits in our definition of an acute VTE event, which were not included in the Lefebvre et al. study. VTE recurrence rates in the commercial and Medicare populations were similar to the 14.3% rate of hospital readmission for VTE among patients with VTE as a secondary diagnosis reported by Spyropoulos and Lin. Other less recent studies have reported VTE recurrence rates to range between 7.0% and 14.0%. Even in patients who only experienced an initial event with no recurrence, VTE-related care and associated payments (commercial: $15,123 per patient per year; Medicare: $10,399 per patient per year) were substantial. These results are in line with that of Spyropoulos and Lin in which total VTE-related health care costs in 1 year following a single VTE event were between $7,594 and $27,909, depending on whether the VTE event was DVT, PE, or DVT/PE and whether it was for a primary or secondary diagnosis of VTE. Payments for overall health care resource use, including inpatient, outpatient, and outpatient pharmacy claims were markedly higher for patients with VTE recurrence (~2- to 3-fold) in comparison with patients without a VTE recurrence. The mean total health care payment for any reason for commercially insured patients with VTE recurrence was $82,110 annually with 47.0% attributed to VTE-related care. Medicare patients with a recurrent VTE event incurred less costs than those insured commercially, with a mean total payment of $55,982 annually with 43.0% attributed to VTE-related care. Multivariable regression analyses that were conducted to test the validity of the effect of VTE recurrence status on the 30-day and 12-month all-cause and VTE-related health care costs further confirmed that VTE recurrence is associated with a substantial incremental cost burden.

The 12-month incidence rate of VTE recurrence was higher for the commercially insured patients than Medicare insured patients. As the mean age for the commercially insured VTE patients was much younger than Medicare VTE patients, these results seem counterintuitive, as age is a known risk factor for VTE. However, previous studies have reported that VTE recurrence is unrelated to age. In fact, although we found age to be inversely related to the risk of VTE recurrence among commercially insured patients in our analysis, it was not a significant predictor for VTE recurrence in the Medicare study population. Medicare enrollees included in the MarketScan database have employer-sponsored supplemental insurance, and it is plausible that they may have access to better VTE treatment resulting in lower risk of VTE recurrence. Among the Medicare study population, VTE recurrence rate was affected by the U.S. region in which VTE care took place, which demonstrates that, among the Medicare insured population, VTE recurrence rate appears sensitive to variations in the standards of care. Medicare insured patients may also be more adherent to warfarin therapy than commercially insured patients, since they seek medical care more often due to their higher comorbidity burden than younger patients. It is possible that there was a higher prevalence of VTE recurrence cases associated with the use of oral contraceptives in the younger commercially insured female patients. On the other hand, Spencer et al. (2008) did find that older patients were less likely to have unprovoked VTE than younger patients, and unprovoked VTE represents a greater risk for VTE recurrence than provoked VTE. In the absence of further clinical information, we were unable to obtain a complete clinical profile of study patients or to confirm the causes of VTE recurrences. Further research is needed to confirm our study findings and understand the risk profiles for recurrent VTE events in these 2 study populations.

Based on the results of our study, patients initially treated in the inpatient setting had a lower VTE recurrence rate than those treated in the outpatient setting. This may indicate that patients might have received better treatment for VTE in the inpatient setting. This is of concern, since a focus of health care reform is to switch more to outpatient versus inpatient treatment/management. Therefore, it will be important in future studies to further assess the differences and similarities of the standards of care for VTE patients in the outpatient versus inpatient settings.

Limitations

As in all studies using retrospective database claims analyses, there is the potential for bias in this study. We attempted to alleviate some potential bias by comparing patient groups in
which both had experienced an initial VTE event. Additionally, we further used multivariable regression analyses that controlled for differences in many patient characteristics to confirm the burden of VTE recurrences. However, there may be other potential confounding variables that were not measured and controlled for in this study, such as bleeding risk. Due to constraints within the databases, we were unable to differentiate between an outpatient office visit for a VTE recurrence and an outpatient office visit for a follow-up to a VTE event; therefore, VTE recurrence was evaluated only in the inpatient or ER setting during the follow-up period. This may have led to an underestimation of VTE recurrence frequency, since VTE is often diagnosed in an outpatient setting (i.e., physician’s office). Additionally, to rule out patients who were followed up in the inpatient setting soon after the index VTE diagnosis, patients admitted to the hospital or ER settings within 2 days of the index VTE event were not included in the patient population with VTE recurrence. Also, since we did not evaluate all VTE-related complications, such as thrombocytopenia, pulmonary hypertension, and post-thrombotic syndrome. Therefore, health care resource utilization and associated payments categorized as VTE-related may have been underestimated, although they were captured in the incremental costs of all-cause health care utilization and payments. The MarketsScan databases consist of claims submitted by health care providers on behalf of individuals who are beneficiaries, and such claims are subject to possible coding errors, coding for the purpose of rule-out rather than actual disease, and undercoding, either by the health care provider or due to limitations imposed by the database. In addition, the presence of a diagnostic code does not always definitively indicate the presence of a condition, and coding of secondary conditions may be less reliable. Since patients with acute and chronic VTE disease, which may more likely have received a secondary diagnosis code, were not differentiated in this study, the results may or may not be generalized to these subsets of patients with VTE disease, and further study is warranted. Lastly, the MarketScan databases are based on a large convenience sample, and since the sample is not random, it may fail to generalize well to other populations with alternate health care coverage such as Medicaid.

Conclusions

Even with anticoagulant treatment, VTE recurrence ranged from 11.4% to over 15% with the majority of recurrences occurring within 30 days of the initial VTE event. VTE recurrence is associated with substantial health care resource utilization, primarily inpatient care, resulting in high health care costs. Strategies to improve treatment of patients with VTE are needed to lessen the health care and economic burdens of recurrent VTE.

Authors

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DISCLOSURES

This research was funded by Daiichi Sankyo, Inc. Lin and Lingohr-Smith are employees of Novosys Health, which has received research funding from Daiichi Sankyo, Inc., in connection with conducting this study and development of this manuscript. Preblick and Kwong are employees of Daiichi Sankyo, Inc.

Concept and design were contributed by Preblick, Lingohr-Smith, Kwong, and Lin. Lin and Lingohr-Smith were primarily responsible for data collection, with assistance from Preblick and Kwong. Data interpretation was done by Preblick, Kwong, Lin, and Lingohr-Smith. Lingohr-Smith was primarily responsible for writing the manuscript, with assistance from Lin, Preblick, and Kwong. The manuscript was revised by Preblick, Kwong, Lin, and Lingohr-Smith.

REFERENCES


Analysis of Gastrointestinal Prophylaxis in Patients Receiving Dual Antiplatelet Therapy with Aspirin and Clopidogrel

Kathleen M. Morneau, PharmD, BCPS; Anne B. Reaves, PharmD, BCACP; Julie B. Martin, PharmD; and Carrie S. Oliphant, PharmD, BCPS (AQ Cardiology)

ABSTRACT

BACKGROUND: Dual antiplatelet therapy (DAPT) has been found to reduce the risk of cardiac death, myocardial infarction, stroke, and stent thrombosis following acute coronary syndrome and percutaneous coronary intervention. However, this therapy has also been shown to increase the risk of gastrointestinal (GI) bleeding as high as 2-fold, especially in patients with multiple risk factors. Proton pump inhibitor (PPI) therapy decreases this risk. The current consensus document on reducing GI risks associated with antiplatelet agents no longer recommends PPI therapy for all patients receiving aspirin (ASA) and clopidogrel. The consensus recommendation reserves PPI therapy for patients receiving DAPT with a history of upper GI bleeding or prespecified risk factors for GI bleeding.

OBJECTIVES: To (a) describe the use of GI prophylaxis in patients on DAPT with ASA and clopidogrel and (b) assess the incidence of adverse outcomes that occurred during readmissions within 6 months of the index hospitalization.

METHODS: A retrospective chart review of patients receiving DAPT between February 1, 2011, and October 15, 2011, was performed to assess the appropriateness of GI prophylaxis based on the current consensus document. Therapy was defined as appropriate if an indication for prophylaxis was present and PPI therapy was prescribed, or if no indication was present and no GI prophylaxis was given. Inappropriate prophylaxis was defined as no indication for GI prophylaxis yet therapy received, or prophylaxis indicated but incorrect prophylaxis prescribed. Incorrect prophylaxis included no prophylaxis, histamine H2 blocker therapy, antacid, or combination therapy. During subsequent hospitalizations in the 6-month period following discharge from the index admission, patients were assessed for the development of vascular-, GI-, and PPI-related adverse events.

RESULTS: 250 patients receiving DAPT during the study period were evaluated. Gastrointestinal prophylaxis was appropriate in 48% (119/250) of patients. Of the remaining patients, 56.4% (74/131) met guideline criteria for GI prophylaxis but did not receive a PPI at discharge, whereas 43.5% (57/131) of patients received GI prophylaxis when not indicated. Thirty-three adverse events were identified during readmissions, with the most common type being vascular followed by GI and PPI adverse events, respectively.

CONCLUSION: More than half of the patients did not receive GI prophylaxis appropriately. The most common reason for nonadherence to the consensus document was no prophylaxis when indicated. Vascular events could not be directly attributed to PPI use, and GI events occurred despite prophylaxis. Overall, there was a low incidence of adverse events related to the use of PPI therapy.

What is already known about this subject

- Dual antiplatelet therapy (DAPT) with aspirin and clopidogrel reduces the risk of cardiac death, myocardial infarction, stroke, and stent thrombosis. As a result, DAPT is recommended following acute coronary syndrome and percutaneous coronary intervention.
- DAPT has been associated with an increased risk of gastrointestinal (GI) bleeding, as high as 2-fold, especially in patients with multiple risk factors. Proton pump inhibitor (PPI) use has been shown to reduce GI bleeding and is recommended in a current consensus guideline for patients with a history of upper GI bleeding or risk factors for GI bleeding (history of any type of GI bleed, peptic ulcer disease, advanced age, concurrent anticoagulants, nonsteroidal anti-inflammatory agents, steroids, and Helicobacter pylori infection).
- Although PPI agents are commonly prescribed and considered to be generally safe, adverse outcomes have been reported, including an increase in the rate of Clostridium difficile infections, fractures, acute interstitial nephritis, hypomagnesemia, and pneumonia. In addition, a potential drug interaction between PPI therapy and clopidogrel affecting clopidogrel metabolism to its active metabolite could place patients at risk for vascular events.

What this study adds

- This study evaluates the use of GI prophylaxis in patients receiving DAPT to assess compliance with the current consensus document as well as any potential adverse event from PPI use.
- In a sample of 250 patients, the use of GI prophylaxis was appropriate in only 48% of patients. The most common reason for inappropriate GI prophylaxis was guideline criteria for GI prophylaxis met but did not receive a PPI at discharge (56.4%, 74/131).
- During the 6-month follow-up period, 102 of the 250 patients were rehospitalized, which accounted for a total of 234 readmissions. Vascular events occurred most commonly at a rate of 58%, followed by GI events (24%) and PPI-related adverse events (18%).
- The use of GI prophylaxis is important in this population to reduce the risk of GI bleeding events, but potential adverse events associated with PPI therapy must be balanced to ensure no additional harm to the patient.
Dual antiplatelet therapy (DAPT) with aspirin and clopidogrel is commonly used in patients with cardiovascular disease to reduce vascular events. In acute coronary syndrome (ACS), DAPT reduces the risk of cardiac death, myocardial infarction, and stroke.\(^1,2\) It is also indicated following percutaneous coronary intervention (PCI) to reduce the risk of stent thrombosis.\(^3\) However, DAPT has also been shown to increase the risk of gastrointestinal (GI) bleeding, especially in patients with multiple risk factors. In a recent controlled trial, patients on DAPT had a 2-fold higher risk of GI bleed than those on aspirin alone.\(^4\) Proton pump inhibitor (PPI) therapy has been shown to decrease this risk.\(^5\)

In 2008, the American College of Cardiology (ACC) and American Heart Association (AHA) partnered with the American College of Gastroenterology (ACG) to develop a consensus document to reduce the incidence of GI events in patients receiving antiplatelet therapy and nonsteroidal anti-inflammatory agents (NSAIDs).\(^6\) This consensus document recommended gastroprotection with a PPI for all patients receiving DAPT. However, PPI use has been associated with multiple adverse outcomes, including an increased incidence of Clostridium difficile infection (CDI),\(^7,8,9\) fractures,\(^10,11\) acute interstitial nephritis,\(^12\) hypomagnesemia,\(^13\) and pneumonia.\(^14\)

In addition to adverse effects from PPI therapy, there is the potential for a drug interaction with clopidogrel. Clopidogrel is a prodrug, which requires a 2-step conversion to its active form.\(^15\) The cytochrome P-450 CYP2C19 enzyme is involved in both steps and is inhibited by PPIs as a class.\(^16\) Reports of a possible drug-drug interaction between PPIs and clopidogrel began to emerge in 2008. The OCLA (Omeprazole CLopidogrel Aspirin) study found that the combination of omeprazole and clopidogrel resulted in decreased platelet inhibition.\(^17\) Conversely, a similarly designed study found no effect with esomeprazole or pantoprazole.\(^18\)

Population-based, retrospective trials have been published showing an increased cardiac event rate in ACS patients taking concomitant clopidogrel and PPIs.\(^19,20\) These trials found an increase in the rate of re-infarction and the composite of all-cause mortality or rehospitalization for ACS. There are also a number of retrospective studies showing no increase in cardiovascular risk from this combination.\(^21,22\) Interestingly, a large cohort study using Danish registry data found a similar risk of cardiovascular events in patients taking PPI therapy regardless of clopidogrel use.\(^23\)

Two prospective studies, COGENT and a subgroup analysis of the PRINCIPLE TIMI 44/TRITON-TIMI 38 studies, have been published refuting this drug interaction as clinically meaningful.\(^24,25\) Furthermore, a cohort study published in 2011 concluded that DAPT in combination with PPI after ACS was not associated with risk of ACS-related rehospitalization.\(^26\) In the drug interaction section of the current package labeling for clopidogrel, which was most recently updated in late 2011, both omeprazole and esomeprazole are listed as drug interactions.\(^27\) The labeling suggests using an alternative acid-reducing agent with less CYP2C19 activity, such as lansoprazole, dexlansoprazole, or pantoprazole.

In November 2010, the ACCF/ACG/AHA published an update to the 2008 document on reducing the incidence of GI risks with antiplatelet therapy.\(^28\) This document no longer recommends that PPI therapy be prescribed for all patients receiving aspirin and clopidogrel but reserves this therapy for patients with a history of upper GI bleeding or multiple risk factors for GI bleeding (history of any type of GI bleed, peptic ulcer disease, advanced age, concurrent anticoagulants, NSAIDs, steroids, and Helicobacter pylori infection; Table 1). Patients without high risk factors for GI bleeding should not receive a PPI or histamine H2 blocker, as there is no likely benefit from this therapy. Given all of the published literature surrounding a potential drug interaction between clopidogrel and PPIs, the consensus document acknowledges that although there is evidence that PPIs may impair the conversion of clopidogrel to its active form, there is no evidence that this translates into an effect on clinical outcomes. Clinicians are reminded to weigh the risks and benefits of GI prophylaxis before initiating therapy.

Although the update to the consensus document better defines the patient population that should receive a PPI, the conflicting evidence regarding the drug interaction between clopidogrel and PPIs has led to confusion with prescribers. In addition, some prescribers may not be aware that the consensus document was updated. The purpose of this study is to assess the use of GI prophylaxis in patients taking DAPT with aspirin and clopidogrel and any adverse events from the use of PPIs.

### Methods

A retrospective chart review of patients receiving DAPT with an index hospitalization between February 1, 2011, and October 15, 2011, was performed to assess the appropriateness of GI prophylaxis.
Analysis of Gastrointestinal Prophylaxis in Patients Receiving Dual Antiplatelet Therapy with Aspirin and Clopidogrel

**FIGURE 1** Patient Selection Flowchart for Identified DAPT Patients

- **414 patients screened**
- **Not meeting inclusion criteria:**
  - n=82
  - 28 on DAPT <24 hours
  - 54 not discharged on DAPT
- **Meeting exclusion criteria:**
  - 82 on PPI for GERD
- **250 patients included**

**TABLE 2** Risk Factors Meeting Criteria for GI Prophylaxis with a PPI

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>% (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advanced age</td>
<td>26.8  (67)</td>
</tr>
<tr>
<td>Concurrent anticoagulation</td>
<td>8.0   (20)</td>
</tr>
<tr>
<td>NSAID use</td>
<td>5.2   (13)</td>
</tr>
<tr>
<td>History of GI bleed</td>
<td>3.6   (9)</td>
</tr>
<tr>
<td>PUD/Helicobacter pylori</td>
<td>3.6   (9)</td>
</tr>
<tr>
<td>Chronic steroid use</td>
<td>2.4   (6)</td>
</tr>
</tbody>
</table>

GI = gastrointestinal; NSAID = nonsteroidal anti-inflammatory drug; PPI = proton pump inhibitor; PUD = peptic ulcer disease.

prophylaxis based on the 2010 consensus document update. The study was conducted at Methodist University Hospital, a 661-bed academic medical center in Memphis, Tennessee, and was approved by the University of Tennessee Institutional Review Board. Patients were identified through a computerized report of all patients receiving concomitant aspirin and clopidogrel during the study period. Patients were included if they received concomitant aspirin and clopidogrel (DAPT) for more than 24 hours and were discharged on this regimen. Exclusion criteria included patients less than 18 years old or PPI use for a U.S. Food and Drug Administration (FDA)-approved indication, such as gastroesophageal reflux disease (GERD) or Zollinger-Ellison syndrome.

Each patient was assessed for clinical characteristics that increase the risk of GI bleeding as outlined in the consensus document. Advanced age and chronic steroid therapy is not defined, so we defined advanced age as greater than or equal to 75 years and chronic steroid therapy as steroid use for greater than or equal to 14 days. For this study, appropriate prophylaxis was defined as the following: indicated for GI prophylaxis and received PPI monotherapy or no indication and did not receive GI prophylaxis. Inappropriate prophylaxis was defined as no indication yet received GI prophylaxis or indicated but received incorrect prophylaxis. Incorrect prophylaxis was defined as no prophylaxis, H2 blocker, antacid, or combination therapy.

During subsequent hospitalizations in the 6-month period following discharge from the index admission, patients were assessed for the development of vascular, GI, or PPI adverse events. Vascular events were defined as myocardial infarction (MI), in-stent thrombosis, revascularization, or stroke documented by a physician in a progress note. ACS, unstable angina, non-ST segment elevation MI, and ST segment elevation MI were all categorized as myocardial infarction. Gastrointestinal adverse events included GI bleed or newly diagnosed ulcer or perforation by upper endoscopy (EGD) or colonoscopy. PPI adverse outcomes were defined as hypomagnesemia (magnesium level less than or equal to 1.5 milligrams per deciliter [mg/dL]), CDI, new fracture, acute interstitial nephritis, or pneumonia. An additional analysis was performed to evaluate the rate of vascular and GI events with or without PPI use.

**Results**

Patients screened for enrollment totaled 414. Of these, 28 were on DAPT for less than 24 hours, and 54 were not discharged on DAPT, thus, not meeting criteria for inclusion. Eighty-two patients were receiving a PPI for GERD and were excluded. Patients included for evaluation totaled 250 (Figure 1). The average patient was aged 68 years (±12 years). Fifty percent of patients were male, and 67% were African American. The indications for GI prophylaxis based on patient risk factors are reported in Table 2. Fifty-nine percent (147/250) of patients had no risk factors, while 8% (21/250) of patients had 2 or more risk factors present. The most common risk factor was advanced age (26.8%), followed by concurrent anticoagulation (8%) and NSAID use (5.2%).

Gastrointestinal prophylaxis was considered appropriate in 48% (119/250) of patients (Table 3). Of the remaining patients who received inappropriate prophylaxis, 56.4% (74/131) of patients met guideline criteria for prophylaxis but did not receive a PPI at discharge, whereas 43.5% (57/131) of patients had no indication yet were prescribed GI prophylaxis at discharge. In the group who met criteria for prophylaxis and should have received a PPI, 68.9% (51/74) received no prophylaxis, and 25.7% (19/74) received an H2 blocker. The remaining patients were prescribed a PPI combination regimen (2.7%; 2/74), a combination regimen not including a PPI (1.4%; 1/74), or a scheduled antacid (1.4%; 1/74). For patients who did not have an indication for GI prophylaxis yet received prophylaxis, the most commonly used agent was a PPI (60%; 34/57), followed by an H2 blocker (35%; 20/57).

**TABLE 2** Risk Factors Meeting Criteria for GI Prophylaxis with a PPI

<table>
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<td>Chronic steroid use</td>
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</tr>
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GI = gastrointestinal; NSAID = nonsteroidal anti-inflammatory drug; PPI = proton pump inhibitor; PUD = peptic ulcer disease.
Of the 51 patients who did not receive prophylaxis when it was indicated, the most common risk factors were advanced age 68.6% (35/51), NSAID use 17.6% (9/51), and concurrent anticoagulation 13.8% (7/51). Peptic ulcer disease and history of GI bleed were uncommon, at 7.8% and 3.9%, respectively. Six of these patients had more than 1 risk factor yet did not receive appropriate prophylaxis. Advanced age was a common risk factor, seen in 5 of these 6 patients.

Forty-one percent of patients (102/250) were readmitted during the 6-month follow-up period for a total of 234 readmissions. During these readmissions, 33 adverse events occurred. Vascular events were the most common (58%; 19/33), followed by GI (24%; 8/33) and PPI related (18%; 6/33; Table 4).

When evaluating vascular events by PPI use versus no PPI use, a greater number of events occurred in the no PPI group (4 vs. 15 events). Four patients at risk for GI adverse outcomes experienced GI events despite appropriate prophylaxis with a PPI. Gastrointestinal events were numerically similar in patients who did not receive a PPI when indicated and patients who were on a PPI or other inappropriate GI prophylaxis when not indicated. Two patients inappropriately receiving a PPI, and 2 patients who were candidates to receive a PPI but did not, experienced GI adverse outcomes.

**Discussion**

It is apparent from this study that prescribing habits at our institution are inconsistent with the most recent consensus document recommendations. Given the increased risk of GI events associated with DAPT in high-risk patients, this deviation could lead to adverse patient outcomes. Alternatively, the inappropriate use of GI prophylaxis in patients without an indication could be subjecting patients to a potential increased risk of adverse PPI outcomes as noted in previous studies. Inappropriate PPI prescribing is also associated with an increased cost burden to the health care system. In patients who received no prophylaxis at discharge when therapy was indicated, advanced age appears to be the risk factor most commonly overlooked or disregarded.

The number of adverse events within the 6-month follow-up period was low. This could be because the period of evaluation was too short for adverse events to have occurred or may be because of lack of follow-up for adverse events in the patient population. Since our hospital is not a closed system, patients are able to seek care at any facility. It is possible that additional adverse events may have occurred outside of our hospital system.

Although retrospective studies have shown an association between PPI use and increased rate of vascular events, this was not evident in our study. Overall, 19 vascular events were observed, and there was no correlation with PPI use. This is consistent with the results of prospective trials. We were unable to accurately collect data regarding medication compliance or over-the-counter PPI use. Therefore, it is possible that additional vascular events may have occurred in cases where the medication history was not accurate. Home medication reconciliation was based on retrospective chart review, patient self-reporting, and practitioner documentation.

Observed GI adverse outcomes were low overall. Four patients who were indicated for and received PPI therapy experienced a GI event despite receiving appropriate therapy. This is likely due to the patients’ underlying risk for GI adverse outcomes, which was not negated by PPI use; all 4 of these patients had advanced age. One of these patients had advanced age and anticoagulation as risk factors; another had advanced age and anticoagulation plus a third indication of GI bleed. Contrary to expectation, patients receiving a PPI without an indication and those indicated for PPI yet not receiving one had similar GI outcomes. This is likely because of the low incidence of adverse events.

---

**TABLE 3**

<table>
<thead>
<tr>
<th>GI Prophylaxis: Appropriate and Inappropriate</th>
<th>% (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appropriate GI prophylaxis</td>
<td>47.6 (119)</td>
</tr>
<tr>
<td>PPI indicated: received PPI monotherapy</td>
<td>25.2 (30)</td>
</tr>
<tr>
<td>No indication: did not receive GI prophylaxis</td>
<td>74.8 (89)</td>
</tr>
<tr>
<td>Inappropriate GI prophylaxis</td>
<td>52.4 (131)</td>
</tr>
<tr>
<td>PPI indicated: received alternate or no GI prophylaxis</td>
<td>56.4 (74)</td>
</tr>
<tr>
<td>No GI prophylaxis</td>
<td>68.9 (51)</td>
</tr>
<tr>
<td>H2 blocker</td>
<td>25.7 (19)</td>
</tr>
<tr>
<td>Combination drug regimen with PPI</td>
<td>2.7 (2)</td>
</tr>
<tr>
<td>Combination drug regimen without PPI</td>
<td>1.7 (1)</td>
</tr>
<tr>
<td>Antacid</td>
<td>1.7 (1)</td>
</tr>
<tr>
<td>No GI prophylaxis indicated: received GI prophylaxis</td>
<td>43.5 (57)</td>
</tr>
</tbody>
</table>

**TABLE 4**

<table>
<thead>
<tr>
<th>Event</th>
<th>% (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular</td>
<td></td>
</tr>
<tr>
<td>Revascularization</td>
<td>21 (7)</td>
</tr>
<tr>
<td>MI &amp; revascularization</td>
<td>18 (6)</td>
</tr>
<tr>
<td>MI</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Stroke</td>
<td>15 (5)</td>
</tr>
<tr>
<td>GI</td>
<td></td>
</tr>
<tr>
<td>GI bleed</td>
<td>9 (3)</td>
</tr>
<tr>
<td>New ulcer</td>
<td>6 (2)</td>
</tr>
<tr>
<td>New ulcer &amp; GI bleed</td>
<td>9 (3)</td>
</tr>
<tr>
<td>PPI</td>
<td></td>
</tr>
<tr>
<td>Hypomagnesemia</td>
<td>6 (2)</td>
</tr>
<tr>
<td>CDI</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>3 (9)</td>
</tr>
</tbody>
</table>

CDI = Clostridium difficile infection; GI = gastrointestinal; MI = myocardial infarction; PPI = proton pump inhibitor.
of adverse outcomes overall and incomplete follow-up. In our study, the incidence of GI bleeding of 2.4% (6/250) is similar to rates found in other studies, which varied from 1.3%-3.5% in patients receiving DAPT.30,31

Despite new information linking PPI use to numerous adverse events, the rate of events in this study was low, which affirms the historic tolerability of these agents. The incidence of pneumonia in patients receiving PPI was similar to that reported for patients receiving acid suppressive therapy in the study by Lahej et al. (2004), with 2.4 versus 2.45 per 100 person-years.14 No PPI-related fractures were observed, which may be related to the short period of observation. Fractures from PPI use have been associated with long-term, high dose PPI therapy, and the strength of association increases with an increased duration of therapy.10 The incidence of CDI infection was similar in patients receiving and not receiving PPI. The national point prevalence of CDI in U.S. health care facilities in 2008 was reported as 13.1 per 1,000 inpatients.32 In this study, the rate was similar at 1.2% (3/250) of patients or 12.0 per 1,000 inpatients. However, we observed a higher incidence of CDI in patients not receiving PPI. This may be due to the overall larger number of patients not receiving PPI (168/250) or the overall incidence of inpatient CDI versus the incidence of community-acquired CDI associated with PPI use that has been reported in the literature.5-6,33 The incidence of PPI-induced interstitial nephritis was unreportable due to infrequency of diagnosis.

Hypomagnesemia occurred in 2 patients receiving PPI with magnesium levels of 0.7 and 0.9 mg/dl, respectively. No data were available on magnesium urinary excretion or other causative agents, so it is difficult to definitively associate the hypomagnesemia to PPI use versus other unknown etiologies. However, the incidence has been estimated at 1% or less by postmarketing surveillance, with 38 cases from the FDA Adverse Event Reporting system and 23 cases from the medical literature, although the actual incidence cannot be quantified due to underrecognition and underreporting.34 This estimate correlates with the 0.8% incidence observed in our study.

Given the results found in this study, there is an opportunity to improve compliance with the consensus document recommendations. Following completion of this study, the results were presented to the medical community at our facility in the Pharmacy and Therapeutics (P&T) Committee meeting. In addition, since many patients are started on DAPT following PCI, a revision to the PCI order set is planned to provide physicians with the clinical characteristics indicated as high risk so appropriate GI prophylaxis can be ordered. Due to the general overuse of PPI therapy in our hospital, a proposal will be taken to the P&T Committee to require prescribers to check an indication box when ordering PPI therapy. Another opportunity is prescriber education provided by clinical pharmacists during patient rounding. This approach has been proven to reduce inappropriate prescribing.35 These suggestions for improvement through education, changes to order sets, and prescribing restrictions can be done at any hospital facility.

Limitations

The limitations of this study are primarily due to its retrospective nature. These include difficulty establishing causal relationships and unavailable data. In addition, we designed a 6-month follow-up period to complete the study in a 1-year time frame. It is possible that there would have been additional adverse events identified if patients had been followed for a longer time period, since most patients on DAPT receive therapy for a minimum of 12 months. Another limitation previously stated is the single-center, open-system of the study site. Patients were not contacted via phone to determine if additional hospital admissions could have occurred outside of our facility. Although this would have allowed for a more complete analysis of readmissions during the 6-month time period, it is possible that patients would not have been able to correctly describe any adverse events that may have occurred.

Conclusion

Despite the consensus document recommendations for GI prophylaxis in high-risk patients on DAPT, more than half of the patients at our institution did not receive appropriate GI prophylaxis. The most common reason for nonadherence was no prophylaxis when indicated, which could predispose patients to adverse GI outcomes. Although there was a low occurrence of adverse events, the incidence was similar to those reported in larger studies.

Authors

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Analysis of Gastrointestinal Prophylaxis in Patients Receiving Dual Antiplatelet Therapy with Aspirin and Clopidogrel

DISCLOSURES
The authors have no financial or intellectual conflicts of interest to disclose. Concept and design were contributed by Morneau, Oliphant, Reaves, and Martin. Morneau was responsible for data collection, which was interpreted by Morneau, Oliphant, Reaves, and Martin. The manuscript was written by Morneau, Oliphant, Reaves, and Martin, and all authors contributed equally to the revision of the manuscript. At the time of writing, Morneau was a PGY-1 Resident, and Martin was a Clinical Pharmacist at Methodist University Hospital, Memphis, Tennessee.

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REFERENCES


Adherence to National Recommendations for Safe Methotrexate Dispensing in Community Pharmacies

Ellen S. Koster, PhD; Joelle C.D. Walgers, BSc; Mariska C.J. van Grinsven, PharmD; Nina A. Winters, PharmD; and Marcel L. Bouvy, PhD, PharmD

ABSTRACT

BACKGROUND: The number of patients using methotrexate (MTX) has increased during the last decade. Because of the narrow therapeutic range and potential risks of incorrect use, vigilance is required when dispensing MTX. In 2009, the Royal Dutch Pharmacists Society, in accordance with the Dutch Health Care Inspectorate, published safe MTX dispensing recommendations for community pharmacies.

OBJECTIVE: To examine adherence to recommendations aimed at safe MTX dispensing.

METHODS: This study was conducted within a convenience sample of 78 community pharmacies belonging to the Utrecht Pharmacy Practice Network for Education and Research (UPPER). Data were collected in May 2011.

RESULTS: 95 pharmacists and 337 pharmacy technicians were interviewed to assess self-reported adherence with dispensing recommendations. In addition, medication records for patients using MTX were extracted in 52 pharmacies in order to objectively assess adoption of recommendations. More than 75% of the pharmacists and pharmacy technicians reported to be adherent to 6 of the 11 recommendations. There are variations in reported adherence between team members working in 1 pharmacy; higher adherence rates (>75%) for the pharmacy team as a whole were only shown for 2 recommendations (recording of day of intake on the label and moment of authorization by the pharmacist). The medication records showed that adherence with working procedures significantly increased: The number of dispensed records with notification of the day of intake on the medication label increased from 9.9% of the records per pharmacy in 2008 to 77.1% in 2010 (P<0.001).

CONCLUSIONS: Dutch community pharmacies seem to be adherent to most safe dispensing recommendations. However, inconsistencies exist between team members that emphasize the importance of addressing this issue and discussing recommendations within the team, as there is still room for improvement to ensure safe dispensing.

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What this study adds

• In 2009, the Royal Dutch Pharmacists Society, in accordance with the Dutch Health Care Inspectorate, published safe MTX dispensing recommendations for community pharmacies.
• It is generally known that implementation of guidelines in health care can be difficult.

What is already known about this subject

• Methotrexate (MTX) was originally designed as a chemotherapeutic drug in high doses. In low doses, the drug is generally safe; however, serious side effects and toxicity can occur due to overdosing. Serious events, including fatal incidents with MTX, have been reported in several countries.
• Medication errors are a common cause of harm to patients. Medication errors related to MTX can occur during all phases of use, but these errors often result from confusion about dosing schedules.
• In 2009, the Royal Dutch Pharmacists Society, in accordance with the Dutch Health Care Inspectorate, published safe MTX dispensing recommendations for community pharmacies.
• It is generally known that implementation of guidelines in health care can be difficult.

Due to increased prescribing of methotrexate (MTX) for autoimmune disorders such as rheumatoid arthritis (RA) and psoriasis, the number of MTX users in many Western countries has increased during the past years.1-6 This increase is especially a result of changes in the treatment guidelines for management of RA, which now recommend MTX as the first-choice disease modifying antirheumatic drug (DMARD).7 MTX is an antagonist of folate-dependent enzymes involved in DNA and RNA synthesis and was originally designed as a chemotherapeutic drug in high doses. In low doses, MTX is generally safe; however, serious side effects and toxicity can occur due to overdosing, including hepatotoxicity and ulceration of gastrointestinal and mouth mucosa.8

In the Netherlands, MTX is registered for the indications RA, plaque psoriasis, and several carcinomas (e.g., trophoblastic tumours, non-Hodgkin's lymphoma, and head and neck tumours). The dosage schedules for treatment of these diseases...
Adherence to National Recommendations for Safe Methotrexate Dispensing in Community Pharmacies

differs from “once a day” for the treatment of carcinomas to “once a week” for RA and plaque psoriasis. These different dosing frequencies may lead to confusion, substitution, and misinterpretation of MTX dosage schedules by physicians, pharmacists, and patients. Because of the narrow therapeutic range and potential risks of incorrect use of MTX, vigilance is required when dispensing MTX. Serious events, including fatal incidents with MTX, have been reported in several countries. Improving patient safety is a priority health policy across the world. Previous research shows that medication errors are a common cause of harm to patients. There are many factors that contribute to the complexity of the medication use process in general, and medication errors can therefore occur during all phases of use and can be related to prescriber, dispenser, or patient. Moore et al. (2004) showed that medication errors related to MTX occurred during all phases of use, but these errors often resulted from confusion about dosing schedules.

After urgent requests from the Dutch Health Care Inspectorate, in 2009, the Royal Dutch Pharmaceutical Society (in collaboration with the Medicines Evaluation Board and associations of hospital pharmacists, rheumatologists, dermatologists, and general practitioners) formulated recommendations for community pharmacists to prevent future MTX-related medication errors. These recommendations included, for example, recording of the day of intake on the medication label and patient counseling about MTX use. These recommendations are shown in Table 1. The purpose of this study was to explore Dutch community pharmacies’ adherence to these national recommendations.

**Methods**

**Study Setting**

The study was conducted in Dutch community pharmacies belonging to the Utrecht Pharmacy Practice Network for Education and Research (UPPER). This network consists of community pharmacies that regularly participate in research and traineeships for pharmacy students. Approximately 900 community pharmacists in the UPPER network received an e-mail invitation to participate in this study and were asked to respond within 4 weeks. This study was conducted in compliance with the requirements of the UPPER Institutional Review Board of the Pharmacoepidemiology and Clinical Pharmacology division of Utrecht University.

**Data Collection**

The study consisted of 2 parts in order to gain more insight into community pharmacies’ adherence with and implementation of MTX dispensing recommendations. First, we conducted interviews with the pharmacy staff to assess self-reported adherence to the national MTX dispensing recommendations. Second, implementation of working procedures to ensure safe MTX dispensing based on pharmacy dispensing records was assessed. Data collection was performed in May 2011 by 20 fourth-year master of pharmacy students who were involved in the course “Pharmacy Practice Research” at Utrecht University. All students received instructions on the interview procedure from 1 of the researchers.

**Interviews in Pharmacies: Self-reported Adherence with MTX Dispensing Recommendations**

To guide the interviews, a structured interview questionnaire—based on the recommendations of the Royal Dutch Pharmaceutical Society—was designed containing mostly closed-ended questions in 4 categories (prescription processing, authorization of dispensing, patient counseling, and multidisciplinary consultations; Table 1). Pharmacy team members were asked questions about the adoption of guidelines, and the responses were mostly recorded as yes/no/unclear or on a Likert-scale (never/sometimes/often/most of the time/always). The interviews were pretested with students and researchers involved in the course “Pharmacy Practice Research” at Utrecht University to assess the clarity of questions and to ensure similar interpretation and notation of answers by the different students during the data collection phase. Interviews of pharmacists and pharmacy technicians were adapted to their specific tasks in the pharmacy and were therefore slightly different. In addition, in every pharmacy, a pharmacist was asked to fill out a short questionnaire with general pharmacy characteristics, such as team size and location. In the analysis, besides adherence of pharmacists and other team members, we also assessed adherence for the complete pharmacy team by using the individual answers from the interviewed team members at each pharmacy and calculating guideline adherence for the complete team. The pharmacy team could be completely adherent (all team members indicated adherence to a specific working procedure); the team could be nonadherent (none of the team members indicated following a specific procedure); or there could be variation within the team (some team members working in the same pharmacy indicated adherence in following a guideline, while others did not).

**Extraction of Pharmacy Records: Assessment of Adherence to Recommendations**

Most patients in the Netherlands are registered at a single community pharmacy; therefore, pharmacy records are virtually complete with regard to outpatient medication use. For this study, we extracted electronic dispensing records of all patients meeting the following inclusion criteria: age > 18 years on January 1, 2008, and filling of ≥1 MTX prescription (Anatomical Therapeutical Chemical (ATC) code L04AX03) between December 1, 2010, and May 10, 2011. For all patients meeting these criteria, anonymous dispensing records were extracted for the period from January 1, 2008, to May 10, 2011,
to assess the implementation of the national recommendations for safe MTX dispensing. Only patients with dispensings of MTX in both 2008 and 2010 were included for analysis. Data from a 1-year period before publication of the recommendations (January 1, 2008-December 31, 2008) were compared with records of a 1-year period after publication of the recommendations (February 1, 2010-January 31, 2011), with respect to 2 working procedures: (1) registration of the day of intake on the label and (2) maximum dispensing period of 3 months. The pharmacy records contained the following data: study identification number, date of birth, gender, ATC code, drug name, dispensed amount, (prescribed) daily drug use, date of dispensing, and (dosage) label. Based on the information in the pharmacy records, adherence to the working procedures was calculated (maximum dispensing period [based on dispensed amount and prescribed daily drug use] and registration of day of intake [based on drug label information]). The average proportion of records fulfilling the recommendations was calculated.

### Results

#### Response Rate

Ninety community pharmacies belonging to the UPPER network responded positively within the 4-week response period. Twelve pharmacies were excluded, as they could not participate during the 1-month data collection period (May 2011), resulting in 78 (9%) participating community pharmacies. In total, 95 pharmacists and 337 pharmacy technicians were interviewed in these 78 different community pharmacies (Figure 1). In 52 of these pharmacies, suitable pharmacy dispensing records were collected. General characteristics of participating pharmacies (Table 2) were compared with characteristics of Dutch community pharmacies in general\(^{20}\) and seemed to be similar with respect to the number of pharmacists employed, participation in a chain or franchise, and degree of urbanization. However, pharmacies included in our study had fewer pharmacy technicians employed (5.1 full-time equivalent [FTE] vs. 5.5 FTE; \(P=0.04\)) and more often had a quality certificate (87.2% vs. 40.6%; \(P<0.001\)) compared with Dutch pharmacies in general.

#### Self-reported Adherence to Recommendations

For 6 of the 11 items on the questionnaire, self-reported adherence to the recommendations was more than 75% for both pharmacists and pharmacy technicians (Table 3). Five recommendations showed lower adherence rates: inquiring about

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**TABLE 1** Overview of Safe Dispensing Recommendations

<table>
<thead>
<tr>
<th>Recommendations of Royal Dutch Pharmaceutical Society</th>
<th>Recommendations Examined in This Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prescription processing</td>
<td></td>
</tr>
<tr>
<td>Always contact physician about indication and dosage when MTX is prescribed once a day</td>
<td>Always contact physician about indication and dosage when MTX is prescribed once a day</td>
</tr>
<tr>
<td>Always inquire about indication when a (repeat) prescription is provided by a general practitioner or nursing home physician</td>
<td>Always inquire about indication when a (repeat) prescription is provided by a general practitioner or nursing home physician</td>
</tr>
<tr>
<td>Record all performed actions with MTX into patient records</td>
<td>Record all performed actions with MTX into patient records</td>
</tr>
<tr>
<td>Never accept prescriptions with “known use” or “use according to schedule” as dosage schedule. Contact physician about schedule. Do not dispense MTX to the patient if the physician does not provide the schedule.</td>
<td>Clearly note dosage and day of use on label</td>
</tr>
<tr>
<td>Patient counseling</td>
<td></td>
</tr>
<tr>
<td>Counsel patients sufficiently about use of MTX</td>
<td>Counsel patients sufficiently about use of MTX</td>
</tr>
<tr>
<td>Authorization</td>
<td></td>
</tr>
<tr>
<td>Only dispense MTX after authorization by a pharmacist</td>
<td></td>
</tr>
<tr>
<td>Multidisciplinary consultations</td>
<td></td>
</tr>
<tr>
<td>Discuss and record agreements about these recommendations with general practitioners in pharmacotherapeutic audit meetings</td>
<td>Discuss and record agreements about these recommendations with general practitioners in pharmacotherapeutic audit meetings</td>
</tr>
<tr>
<td>Not included in this study</td>
<td></td>
</tr>
<tr>
<td>Pay attention to possible errors in dosage in the regional transfer of prescription data</td>
<td></td>
</tr>
<tr>
<td>Contact software supplier if there are no possibilities for sufficient monitoring of dosage frequency and indication in the automated pharmacy dispensing record system</td>
<td></td>
</tr>
</tbody>
</table>

MTX = methotrexate

---

**Data Analysis**

Descriptive statistics were calculated. Chi-square testing was used to study differences in self-reported adherence between groups (e.g., pharmacists and pharmacy technicians). Working procedures based on medication records in 2008 and 2010 were compared with Wilcoxon signed ranks tests (skewed variables). All data were analysed using IBM SPSS for Windows, version 19.0 (SPSS, Inc., Chicago, IL).
Adherence to National Recommendations for Safe Methotrexate Dispensing in Community Pharmacies

![FIGURE 1](Selection of Study Participants)

- UPPER Network invited ≥900 community pharmacies by e-mail
- Willing to participate: 90 pharmacies
- Included in study: 78 pharmacies
- Excluded due to practical reasons: 12 pharmacies
- Interview study: 78 pharmacies
- Pharmacy records: 78 pharmacies
- Excluded due to extraction problems: 26 pharmacies
- Interviews staff members: n=337 technicians
  - n=95 pharmacists
- Pharmacy records included in study: 52 pharmacies

**TABLE 2** Characteristics of Participating Community Pharmacies

<table>
<thead>
<tr>
<th>Pharmacy Characteristics</th>
<th>N = 78</th>
</tr>
</thead>
<tbody>
<tr>
<td>Team size</td>
<td></td>
</tr>
<tr>
<td>FTE pharmacist, mean (SD)</td>
<td>1.4 (0.06)</td>
</tr>
<tr>
<td>FTE pharmacy technicians, mean (SD)</td>
<td>5.1 (0.19)</td>
</tr>
<tr>
<td>Other team members, % (n)</td>
<td></td>
</tr>
<tr>
<td>Pharmaceutical business administrator</td>
<td>16.7 (13)</td>
</tr>
<tr>
<td>Pharmaceutical advisor</td>
<td>15.4 (12)</td>
</tr>
<tr>
<td>Part of pharmacy chain or franchise, % (n)</td>
<td>57.7 (45)</td>
</tr>
<tr>
<td>Quality certificate, % (n)</td>
<td>87.2 (68)</td>
</tr>
<tr>
<td>Degree of urbanization, % (n)</td>
<td></td>
</tr>
<tr>
<td>Extreme/strong</td>
<td>59.0 (46)</td>
</tr>
<tr>
<td>Moderate</td>
<td>15.4 (12)</td>
</tr>
<tr>
<td>Hardly not</td>
<td>25.6 (20)</td>
</tr>
</tbody>
</table>

*Degree of urbanization based on the address density per kilometer squared: ≥2,500, 1,500-2,500, 1,000-1,500, 500-1,000, and <500.
FTE = full-time equivalent, SD = standard deviation.

The indication with the patient, recording the indication in the pharmacy information system, authorization of MTX dispensing during absence of the pharmacist, patient counseling at second dispensing, and discussion and recording of agreements with general practitioners.

Table 4 shows self-reported adherence to the recommendations for the pharmacy team as a whole. Higher adherence rates (>75%) for the pharmacy team as a whole were shown only for 2 recommendations (recording of the day of intake on the label and the moment of authorization by the pharmacist). Nonadherence to the recommendations for the pharmacy team as a whole was low, but there was variation within the teams (e.g., pharmacist indicated adherence to a specific recommendation, whereas pharmacy technician indicated nonadherence).

**Implementation of MTX Dispensing Recommendations**

To assess the change in MTX working procedures between 2008 (n = 3,452 MTX dispensing records) and 2010 (n = 4,718 MTX dispensing records), 2 recommendations (recording of the day of intake on the medication label and maximum dispensing period of 3 months) were studied (Table 5). Adherence to these procedures increased significantly from 2008 to 2010; for example, the number of dispensed prescriptions with notification of the day of intake on the drug label increased sharply (from 9.9% in 2008 to 77.1% in 2010, P < 0.001).

**Discussion**

In 2009, the Royal Dutch Pharmaceutical Society formulated recommendations for safe dispensing of MTX. The purpose of this study was to investigate how closely these recommendations are followed by Dutch community pharmacists. This study shows that the recommendations regarding MTX dispensing are in general adopted by community pharmacies in the Netherlands. This is in line with results of a study performed in 33 Dutch hospital pharmacies, which showed a high degree of adherence to recommendations regarding MTX dispensing in Dutch hospitals.

For some of the recommendations, we showed lower (self-reported) adherence, which might indicate these are the more complex recommendations to implement and appear to be less feasible in daily practice. It is generally known that implementation of guidelines in health care can be difficult. A study of dermatologists’ adherence to the guidelines of the Dutch Society of Dermatology and Venereology with respect to MTX treatment for plaque psoriasis also showed discrepancies between guideline recommendations and daily clinical practice (e.g., recommendations regarding liver biopsy after high cumulative doses of MTX are not always followed, as this is a procedure associated with risks for the patient).

In the present study, interviewees often gave explanations why a recommendation was not adopted or was addressed in another way. Some pharmacists adapted or modified the recommendations in order to have more workable procedures, such as deriving the indication from the prescription or prescribing physician (e.g., rheumatologist) instead of asking the...
TABLE 3  Self-reported Adherence to MTX Recommendations

<table>
<thead>
<tr>
<th>Category</th>
<th>Recommendation</th>
<th>Pharmacist (N = 95) %</th>
<th>Pharmacy Technician (N = 337) %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prescription processing</td>
<td>Inquire about MTX indication with the patient</td>
<td>67.4 (64)</td>
<td>65.9 (222)</td>
</tr>
<tr>
<td></td>
<td>Record MTX indication in the pharmacy information system</td>
<td>60.0 (57)</td>
<td>48.1 (162)*</td>
</tr>
<tr>
<td></td>
<td>Record day of MTX intake on label</td>
<td>92.6 (88)</td>
<td>91.4 (308)</td>
</tr>
<tr>
<td></td>
<td>Contact prescriber if MTX is prescribed once a day</td>
<td>86.3 (69)</td>
<td>78.6 (242)</td>
</tr>
<tr>
<td></td>
<td>Maximum MTX dispensing period ≤ 3 months</td>
<td>88.4 (84)</td>
<td>89.6 (302)</td>
</tr>
<tr>
<td>Authorization</td>
<td>Only dispense MTX after authorization by a pharmacist</td>
<td>80.0 (76)</td>
<td>83.7 (282)</td>
</tr>
<tr>
<td></td>
<td>Moment of authorization: MTX authorization before dispensing^a</td>
<td>95.4 (83/87)</td>
<td>91.4 (287/314)</td>
</tr>
<tr>
<td></td>
<td>MTX authorization in case of absence of pharmacist^b</td>
<td>51.7 (45/87)</td>
<td>42.5 (134/315)</td>
</tr>
<tr>
<td>Patient counseling</td>
<td>At first dispensing</td>
<td>83.2 (79)</td>
<td>82.8 (279)</td>
</tr>
<tr>
<td></td>
<td>At second dispensing</td>
<td>38.9 (37)</td>
<td>51.6 (174)*</td>
</tr>
<tr>
<td>Multidisciplinary meetings</td>
<td>Discuss and record agreements about these recommendations with general practitioners</td>
<td>17.2 (16)</td>
<td>N/A</td>
</tr>
</tbody>
</table>

^aP < 0.05.
^bParticipants who indicated MTX prescriptions were never authorized by the pharmacist were excluded from analysis.
MTX = methotrexate; NA = not available.

TABLE 4  Self-reported Adherence to MTX Recommendations: Complete Pharmacy Team

<table>
<thead>
<tr>
<th>Category</th>
<th>Recommendation</th>
<th>Complete Team Adherence %</th>
<th>Complete Team Nonadherence %</th>
<th>Variation Within Team %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prescription processing</td>
<td>Inquire about MTX indication with the patient</td>
<td>23.1 (18)</td>
<td>5.1 (4)</td>
<td>71.8 (56)</td>
</tr>
<tr>
<td></td>
<td>Record MTX indication in the pharmacy information system</td>
<td>6.4 (5)</td>
<td>14.1 (11)</td>
<td>79.5 (62)</td>
</tr>
<tr>
<td></td>
<td>Record day of MTX intake on label</td>
<td>83.3 (65)</td>
<td>3.8 (3)</td>
<td>12.8 (10)</td>
</tr>
<tr>
<td></td>
<td>Contact prescriber if MTX is prescribed once a day</td>
<td>48.7 (38)</td>
<td>2.6 (2)</td>
<td>48.7 (38)</td>
</tr>
<tr>
<td></td>
<td>Maximum MTX dispensing period ≤ 3 months</td>
<td>71.8 (56)</td>
<td>2.6 (2)</td>
<td>25.6 (20)</td>
</tr>
<tr>
<td>Authorization</td>
<td>Only dispense MTX after authorization by a pharmacist</td>
<td>67.9 (53)</td>
<td>5.1 (4)</td>
<td>26.9 (21)</td>
</tr>
<tr>
<td></td>
<td>Moment of authorization: MTX authorization before dispensing^a</td>
<td>79.7 (59)</td>
<td>2.7 (2)</td>
<td>17.6 (13)</td>
</tr>
<tr>
<td></td>
<td>MTX authorization in case of pharmacist absence^a</td>
<td>20.3 (15)</td>
<td>28.4 (21)</td>
<td>51.4 (38)</td>
</tr>
<tr>
<td>Patient counseling</td>
<td>At first dispensing</td>
<td>56.4 (44)</td>
<td>0 (0)</td>
<td>43.6 (34)</td>
</tr>
<tr>
<td></td>
<td>At second dispensing</td>
<td>56.4 (44)</td>
<td>0 (0)</td>
<td>43.6 (34)</td>
</tr>
<tr>
<td>Multidisciplinary meetings</td>
<td>Discuss and record agreements about these recommendations with general practitioners</td>
<td>15.6 (12)</td>
<td>83.1 (64)</td>
<td>1.3 (1)</td>
</tr>
</tbody>
</table>

^aParticipants who indicated MTX prescriptions were never authorized by the pharmacist were excluded from analysis.
MTX = methotrexate.

patient about the indication. Another recommendation that is more difficult to implement was the authorization of prescrip-
tions in the absence of the pharmacist. Although the absence of a pharmacist in the community pharmacy (for a longer period of time) is rare, a more detailed description of individual working procedures might be helpful to ensure continued safe dispensing. Pharmacists should teach their technicians about the most important aspects of MTX authorization to ensure safe dispensing of MTX without preceding authorization of pharmacists before dispensing MTX to the patient in some exceptions (afterwards dispensed prescriptions should always be checked by the pharmacist). For example, a guideline describing an additional check of a second technician might help pharmacy technicians in performing these incidental safe dispensing authorizations. A survey conducted among medical practitioners showed that the majority of doctors claimed to be familiar with and followed clinical guidelines in general. Practical issues were often reasons for nonadherence with clinical guidelines.25

We showed high levels of adherence (>75%) with most of the recommendations for both pharmacists and pharmacy technicians. However, when studying the complete pharmacy team, adherence to the recommendations was much lower, indicating inconsistencies within the pharmacy team. To ensure medication safety and prevent patient harm, communication and teamwork are of utmost importance.26 Therefore, pharmacy team members should make every effort to adhere to all the recommendations and overcome inconsistencies in
Adherence to National Recommendations for Safe Methotrexate Dispensing in Community Pharmacies

### TABLE 5
Adherence to Recommendations in 2008 and 2010 Based on Pharmacy Prescription Records (Data from 52 Pharmacies)

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Year 2008 N = 3,452</th>
<th>Year 2010 N = 4,718</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of MTX prescription records per pharmacy, mean (SD)</td>
<td>68.9 (47.0)</td>
<td>129.0 (72.8)*</td>
</tr>
<tr>
<td>Mean proportion of prescriptions with notification of day of intake on label, %</td>
<td>9.9</td>
<td>77.1*</td>
</tr>
<tr>
<td>Mean proportion of prescriptions with a maximum period of dispensing ≤3 months</td>
<td>68.2</td>
<td>80.9*</td>
</tr>
</tbody>
</table>

*P<0.001.
MTX = methotrexate; SD = standard deviation.

practice within the team. Pharmacists and pharmacy technicians might sometimes have different perspectives on working procedures. Differences among pharmacy team members might be a result of unclear working procedures and instructions, recently appointed pharmacists and technicians, or less strict maintenance of the procedures. Although differences within teams cannot be completely prevented, a discussion of procedures could contribute to consistency in applying, and attentiveness to, dispensing guidelines.

In addition to assessing self-reported adherence to safe dispensing guidelines, we assessed the adoption of working procedures based on objective data from pharmacy records. Pharmacy staff tended to overestimate adherence to safe dispensing guidelines. Based on pharmacy records (objective measurement of working procedure adoption), in 2010 77% of the prescriptions contained a notification of the day of intake on the medication label, while more than 90% of the pharmacists and pharmacy technicians indicated adherence to this recommendation. Previous studies comparing observational data and self-reported data about adherence to clinical guidelines also showed that self-reported adherence significantly exceeded observed adherence.27 A recent study carried out in the Netherlands showed that the number of MTX incidents involving patients since publication of the national recommendations has not decreased; however, consequences of these errors for patients seem to be less serious.28

It is important to stimulate increased adherence to recommendations by community pharmacy staff members, and the use of appropriate support tools such as online databases and easy-to-use-software has been shown to be successful. In their study of nursing home residents, Zarowitz et al. (2012)29 showed improvement in MTX safety by implementing such interventions as software programming and mandatory staff training in nursing homes. Furthermore, the process of guideline implementation should not be overly time consuming.30,31

### Limitations
This study provided valuable information about the integration of national recommendations into community pharmacy health care. Guideline adherence depends on different staff members in the community pharmacy, and by focusing on both pharmacists and pharmacy technicians, we were able to gain insight into differences in adherence rates. We used structured interviews to collect the data, which were carried out by a large number of students. The advantage of these interviews was that the students could rephrase questions if the answers were incomplete or unclear. Although students had received clear instructions, there is a chance of bias because of the different levels of interview skills between students, and there might be differences in interpretation of answers. However, we assume this limitation had only minimal effect because the interview questionnaire was straightforward, and questions were derived directly from the recommendations.

Furthermore, selection bias may have affected our results, since participating pharmacies were self-selected (responding to an invitation e-mail). It is reasonable to assume that participating pharmacies were perhaps more motivated and committed to the MTX guideline implementation than those pharmacists who refused to participate. However, general characteristics of the participating pharmacies within the study were similar to community pharmacies in the Netherlands in general, except that the pharmacies participating in our study more often had a quality certificate. Finally, our study was based on Dutch recommendations for safe dispensing, which might hamper the generalizability of our findings to other countries. However, adoption of guidelines and implementation of clinical guidelines or recommendations in health care will be relevant to other countries as well.

### Conclusions
Overall, Dutch community pharmacies have been able to implement the national recommendations for MTX dispensing and are adherent to most of them. The more complex recommendations were more likely to result in poor adherence. We showed inconsistencies in adhering to the recommendations between pharmacy team members, which underlines the importance of addressing this issue and discussing recommendations with the team. Previous research has shown that increased adherence to dispensing guidelines seems to improve processes of care with respect to MTX. Further research is necessary to determine the outcome of the implementation of the guidelines in the community pharmacy setting.
Adherence to National Recommendations for Safe Methotrexate Dispensing in Community Pharmacies

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Study concept and design were contributed by Grinsven, Winters, Bouvy, and Walgers, with assistance from Koster. Walgers and Grinsven had primary responsibility for data collection, with assistance from Winters. Data interpretation was primarily the work of Walgers, Koster, and Bouvy, with assistance from Grinsven and Winters. The manuscript was written by Koster, Walgers, and Winters, with help from Bouvy, and was revised by all the authors.

ACKNOWLEDGMENTS
The authors would like to thank the community pharmacists and the pharmacy students who participated in the study.

REFERENCES
17. de Leeuw M. Uitgifte methotrexaat moet beter; inspectie dringt aan op verbetermaatregelen [Methotrexate dispensing needs to improve; Dutch health care inspectorate insists on actions for improvement]. Pharm Weekbl. 2009;14(30/33):6-7.
PCMHs, ACOs, and Medication Management: Lessons Learned from Early Research Partnerships

Evan S. Schnur, PharmD; Alex J. Adams, PharmD; Donald G. Klepser, PhD, MBA; William R. Doucette, PhD; and David M. Scott, MPH, PhD

The Patient Protection and Affordable Care Act has greatly accelerated the formation of team-based models of care delivery, primarily accountable care organizations (ACOs) and patient-centered medical homes (PCMHs). Many have written about the need to incorporate medication management services into these systems in order to improve care and reduce total health care costs. Two primary ways of doing so have emerged: (1) an embedded model, whereby pharmacists are employed directly by a physician practice, or (2) a “virtual care team” model, whereby a PCMH or ACO develops an arrangement with external pharmacists in community settings to provide coordinated services.

While many research projects are testing embedded models, few examples of virtual care team approaches have been reported to date. Virtual care teams leverage the accessibility of community pharmacies and the benefits of longitudinal face-to-face interventions but lead to unique challenges related to developing partnerships, sharing data, and coordinating care. The National Association of Chain Drug Stores (NACDS) Foundation is supporting 3 research projects that launched in early 2013 and are among the first virtual care team models to reach the implementation stage. The purpose of this commentary is to describe lessons learned from the research teams’ early experiences to inform future research and practice in this domain.

Overview of Research Teams
Virtual care team research is by its nature a collaborative process. Diverse partners are necessary to provide coordinated services, share information, and evaluate the success of the services provided. Table 1 summarizes the partners involved in the 3 virtual care team projects funded by the NACDS Foundation. Each project is led by an academic research institution and includes a partnership between a PCMH or ACO and community pharmacies. While this basic structure is common across all 3 projects, the designs differ significantly.

The North Dakota project involves a statewide PCMH network (MediQHome) supported by a regional pharmacy chain with 27 participating pharmacy locations providing medication management services (medication therapy management [MTM], medication synchronization, and adherence). MediQHome was developed by Blue Cross Blue Shield of North Dakota and focuses primarily on chronic disease states (e.g., diabetes or hypertension) by providing timely medical information to primary care providers using MDInsight, a technology network. The project goal is to integrate the community pharmacist services into the MediQHome and then to assess patient outcomes.

The Iowa project involves a Medicare Pioneer ACO and a consortium of more than 20 chain and independent pharmacies in the 8-county service region; these pharmacies, while diverse, are all providing common medication management services to the ACO patients.

Nebraska’s project involves an individual chain community pharmacy working closely with a PCMH in a small community in a model that will eventually be expanded to other communities throughout the state. Each of the projects will span 2 years and will track the clinical, economic, and humanistic outcomes observed from the incorporation of virtually provided medication management services into the PCMHs and ACOs.

Early Lessons Learned
We focused on a limited set of key issues that have arisen as the 3 studies have progressed through planning and moved into implementing the virtual medication management services (see Table 2 for overview of project designs). These issues were identified during site visits and regular calls of the Foundation staff with the research teams. The specific issues include partnerships, alignment of services, data sharing, provider engagement, and patient engagement.

Partnerships
Given the diverse nature of the partners needed to carry out these projects, the academic researcher often plays the role of convener in addition to evaluator. The presence of pre-existing relationships between partners (e.g., academic institutions, PCMH/ACO, health plans, community pharmacies) often facilitated the research proposal’s development. These relationships tended to be the result of training and educational activities such as residencies, experiential rotations, and shared faculty positions with the partners. Creating these precursor relationships was reported as a major enabler to bring the right partners to the table for virtual care team projects.

Significant effort is required by the academic researcher not only to develop, but also to maintain relationships with partners and ensure that planned milestones are met. The “real-world” nature of these 3 projects (which frequently precluded the use of traditional, randomized control trial
PCMHs, ACOs, and Medication Management: Lessons Learned from Early Research Partnerships

**TABLE 1** Sample Research Architecture

<table>
<thead>
<tr>
<th>Project 1: Iowa</th>
<th>Academic Institution</th>
<th>PCMH/ACO</th>
<th>Pharmacies</th>
<th>Health Plan</th>
<th>Technology Vendor/ Enabler</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>University of Iowa</td>
<td>Trinity Pioneer ACO</td>
<td>Consortium of 25 pharmacies in ACO service area</td>
<td>N/A</td>
<td>OutcomesMTM</td>
<td>N/A</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Project 2: Nebraska</th>
<th>Academic Institution</th>
<th>PCMH/ACO</th>
<th>Pharmacies</th>
<th>Health Plan</th>
<th>Technology Vendor/ Enabler</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>University of Nebraska Medical Center</td>
<td>Kearney Clinic</td>
<td>Walgreen Co.</td>
<td>Blue Cross Blue Shield of Nebraska</td>
<td>Nebraska Health Information Initiative</td>
<td>N/A</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Project 3: North Dakota</th>
<th>Academic Institution</th>
<th>PCMH/ACO</th>
<th>Pharmacies</th>
<th>Health Plan</th>
<th>Technology Vendor/ Enabler</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>North Dakota State University</td>
<td>MediQHome Network</td>
<td>Thrifty White Pharmacy</td>
<td>Blue Cross Blue Shield of North Dakota</td>
<td>OutcomesMTM</td>
<td>Prime Therapeutics</td>
<td></td>
</tr>
</tbody>
</table>

ACO = accountable care organization; NA = not applicable; PCMH = patient-centered medical home.

methodologies) demands flexibility and creativity. Establishing the project teams typically involved members of the research team at the academic institution, as well as key people at the other participating organizations. Leaders from the ACO or PCMH should include a top administrator as well as representatives from various stakeholder groups within the organization, such as pharmacy, medical staff, and IT/data personnel. Involvement by top administrators allowed for the relevant group to make decisions and receive adequate support in a timely manner. Involving an interprofessional group of health care providers in the project design was valuable to ensuring successful implementation. In addition, it was vital to include team members from the participating community pharmacy organizations in order to address the practical significance of the many issues that needed to be discussed and decided. In planning their studies, the research teams found it valuable to host weekly or bi-weekly conference calls with all partners leading up to the launch. Once the medication management program was operating, it was determined that team meetings could be held less frequently. However, because “natural experiments” of the types discussed here frequently generate unexpected consequences (whether barriers to data collection or evolution in patient care and quality assurance processes), it was important to ensure that meetings continue to occur on a regular (but less frequent) basis.

**Alignment of Services**

Active partner engagement from the outset has been a critical driver of project implementation. Research teams that engage the PCMH or ACO to identify their highest priority needs, and align the pharmacy services to meet those needs, have reported success. The needs of PCMHs and ACOs are diverse. The Nebraska PCMH reported their biggest needs as comprehensive medication reviews paired with adherence information reported back to the physicians. The Iowa ACO has interest in managing medications of high-risk patients being discharged from its primary medical center. This has made medication reconciliation a part of the medication management program, which may be a new service for community pharmacists. The North Dakota PCMH seeks to integrate medication management services, including comprehensive medication review, medication synchronization, and medication adherence. Understanding the unique challenges that ACOs and PCMHs have in managing their patient populations can help position pharmacies to provide valued services.

In addition, it is important to have an awareness and understanding of ongoing programs across all partners. For example, if partnering with a health system that has a pre-existing hospital discharge program, the medication management services should augment, not duplicate, what is already being done. To be integrated properly, services should not unnecessarily disrupt the workflow of the ACO/PCMH or pharmacy. Having an appreciation for how to coordinate processes leads to greater buy-in from partners and potential sustainability. For academic researchers, this also requires an understanding of partner motivations beyond improving patient outcomes for a given disease state. By design, ACOs and PCMHs accrue financial gains from achieving certain process and outcome targets. Projects that align those incentives with the financial incentives of the community pharmacy partner are most likely to be supported in both organizations. In the North Dakota project, for example, pharmacists are reimbursed using the established payment model OutcomesMTM for cognitive services, including comprehensive medication reviews and other interventions such as medication adherence. The community pharmacy partner also has developed an incentivized program for community pharmacies to participate in medication synchronization. The improved clinical outcomes associated with these interventions align with the goals of the PCMH, and the pharmacists are equally incentivized both clinically and financially. Similarly, pharmacists in the Iowa project will be paid the usual MTM payments used by OutcomesMTM. Concomitantly, corporate partners must recognize that academic researchers have a professional obligation to evaluate the project using rigorous scientific methods in an objective fashion and cannot guarantee specific outcomes before the research takes place.

**Data Sharing**

Pharmacists need access to patient medical records to match diagnostic information with prescribing activities. Pharmacists working in integrated health system settings are more likely to gain access to these records. Unfortunately, pharmacists working in community settings, who are the most accessible to patients, have access to virtually none of this information.
In addition, patients may have their prescriptions filled at several different pharmacies, which prevents pharmacists from helping patients complete their drug therapies as intended. More complete patient records can be created by incorporating claims data with clinical data in the PCMH or ACO and distributing this information to the appropriate providers, which includes community pharmacists.

Accordingly, this integrated process requires planning, commitment, and communication among partners to make these models work. Hence, another critical factor of success is having a clear plan to assimilate data across the spectrum of health care providers from the outset. The diverse partnerships involved in this type of research resulted in a number of disparate data sources with needed patient information. To facilitate service delivery (e.g., identifying qualified patients and sharing recommendations or requests) from all health care providers, as well as for the evaluation of outcomes, these data sources should be integrated. In some cases, 2 parties may have access to the same data (usually patient claims data), which necessitates a discussion about which party is in the best position to provide the data. In our experience, research teams that discussed strategies to share patient data early on in the project development process overcome these barriers more efficiently and effectively.

The specific data sharing challenges cited by participating research teams primarily centered on 2 fronts: (1) the need for pharmacists’ ability to view medical and pharmacy records and (2) an enhanced communication channel between the community pharmacists and the PCMH or ACO. Success on the former depends on the current capabilities of partners. In the Nebraska research project, the pharmacy was provided full access to the PCMH’s registry, and pharmacists are now able to view lab values and other critical pieces of information that can improve patient care. Pharmacists can act on this information and send a secure e-mail with recommendations to a dedicated clinical care coordinator within the PCMH. In other research projects, full integration could not be achieved from the outset, but steps in the right direction were possible. For example, the Iowa research team has a focus on improving handoffs to community pharmacies following a hospital discharge. While the goal is to enable the real-time pharmacist access to discharge summaries for the targeted patient population, this capability did not exist at project implementation. A solution was that discharge summaries were made available to community pharmacists by calling the pharmacy staff at the medical center. As pharmacists schedule appointments with targeted patients, requested discharge summaries are delivered via fax prior to patients’ appointments.

Another example of the challenges of data sharing was seen in the North Dakota project. Here, direct access to the PCMH records is not currently possible; however, the development of a medication suite with access for community pharmacists is a long-term goal. Accordingly, the partners, along with the physician advisory board, have made this a priority, and this is expected to be achieved during the time period of the project. In the interim, PCMH record access is achieved through access to claims information provided to the MTM vendor. The MTM vendor integrates the medical and pharmacy information into its system and sends out interventions to the community pharmacy for a patient with a chronic disease state based on claims analysis. Then, the community pharmacist assumes the responsibility to act on the intervention, provides the services, and bills accordingly for the services.

<table>
<thead>
<tr>
<th>Size of Study Population (Approximate Number of Patients)</th>
<th>Research Design</th>
<th>Disease Focus of the PCMH/ACO</th>
<th>Disease Focus of Study</th>
<th>Clinical Measures Evaluated</th>
<th>Economic Outcomes Measured</th>
<th>Humanistic Outcomes Measured</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iowa</td>
<td>10,000</td>
<td>Quasi-experimental nonequivalent groups</td>
<td>N/A</td>
<td>High risk based on medication use and hospital discharge</td>
<td>30-day readmission rate, all-cause hospitalization rate, and ER visits related to adverse drug events</td>
<td>Annual per capita cost of care</td>
</tr>
</tbody>
</table>

Nebraska                                                  | 800 Phase 1: 800 Phase 2: up to 5,000 | Prospective randomized control | N/A                   | Hypertension and diabetes | Blood pressure, blood glucose, hospitalization rate, and ER visits | Overall health care utilization and costs | Patient and provider satisfaction |

North Dakota                                              | up to 8,000     | Quasi-experimental design with a treatment group and control group | Chronic diseases including asthma, hypertension, and diabetes | Chronic diseases including hypertension and diabetes | Blood pressure, HbA1c, LDL, HDL, and PDC | Drug costs, medical costs, and total health costs | Patient satisfaction |

ACO = accountable care organization; ER = emergency room; HbA1c = hemoglobin A1c; HDL = high-density lipoprotein; LDL = low-density lipoprotein; NA = not applicable; PCMH = patient-centered medical home; PDC = proportion of days covered.
Provider Engagement
Researchers noted that the willingness of practicing pharmacists to take on new roles within PCMHs and ACOs has been very enthusiastic. To ensure consistency of the delivery of research interventions, education was provided to participating pharmacists, including refresher courses on clinical guidelines for targeted disease states, both in-person and via online modules. Researchers also provided information on the research project goals and objectives to increase buy-in and understanding. While virtual care teams are necessarily interprofessional, some research teams also enhanced intraprofessional collaboration, linking pharmacists in community and hospital settings to assist with handoffs following hospitalizations and improve continuity of care.

Education has also been provided to physicians at the participating PCMHs and ACOs to ensure that they are familiar with the goals of the project and to raise awareness of their ability to refer patients for medication management services, among other goals. Identifying physician champions and the use of physician advisory committees have been useful strategies for generating support and buy-in from the physician community. In addition, 1 project team included a clinic manager, who has been able to contribute useful insights about operational issues within the clinics (e.g., responding to faxes from community pharmacists in a timely manner).

The physician advisory committee issues exhibit both commonalities and differences across the 3 projects. In a general sense, having key physicians participate in the advisory board provides advocacy for the project. The board also helps to identify gaps that need to be addressed, and board members will participate in the publication process. The specific types of advocacy needed, and the specific gaps in the patient care and assessment processes will necessarily vary depending on the scope of the project. As an example, in the North Dakota project, the partners identified the current inability of pharmacists to gain access to medical information (including laboratory data) as well as other data concerning chronic diseases as an area for improvement. Since the primary aim of this grant was to integrate medication management into the medical home with other providers, this became a major concern for the partners. With input from physicians and pharmacists, the medication suite will provide a useful format for both groups of providers when it is implemented.

Patient Engagement
Medication management services focus on improving adherence and other patient medication issues. These issues are rooted in patient behavior change, and thus strategies to engage patients in their own medication management are critical. Patient demand for medication management services has been limited. Previous research has shown that a variety of issues can limit patients’ use of medication management services, such as lack of familiarity with the service, limited outcome expectations from the service, patients’ relationships with their pharmacists, and the support for medication management stated by the patients’ physicians.8-13 Some of these issues can be addressed by providing timely and understandable information to patients likely to receive medication management services. Also, the community pharmacists could be prepared to offer the services to interested patients.

Some of the research teams provided training to participating pharmacists on motivational interviewing to help support patient behavior change. Research teams also focused on enhancing patient engagement through a mix of physician referrals, “warm handoffs” to the community pharmacists, and direct outreach by the local pharmacists. In 1 case, a patient targeted to receive medication management will receive information about the program through a telephone call or a mailed letter. Further, this information is supplemented by information on the organization’s website.

Another intervention being used by the North Dakota research team focuses on reducing nonadherence. Community pharmacists are working with the PCMH to identify causes of nonadherence and to coordinate services to change the behavior and improve the patient outcomes. The Appointment-Based Model (ABM)—a process by which patients schedule a time to meet with their community pharmacists on a monthly basis to pick up all of their refills and have a mini-MTM session to improve medication management14—was established in this project to improve patient medication adherence by synchronizing

### TABLE 3 Summary Recommendations for Successful Research Collaboration

- Early, frequent, and thorough communication among research partners (or potential partners) appears to be the key to a successful long-term project.
- Data sharing is often one of the largest barriers to overcome, so thoroughly evaluate what data are needed and how they can be shared early on, involving key decision makers from all stakeholders to ensure successful execution.
- Involve front-line health care practitioners from multiple disciplines in the design of the project for optimal engagement. Do not overlook input from staff and managers.
- Leverage pharmacists’ accessibility, patient relationships, and drug expertise for meaningful interventions.
- Pursue innovative research that identifies new opportunity for improved medication management in integrated care delivery models.
- To fit within the dynamic environment facing partners, projects should be shorter term (e.g., no more than 2 years).
- Strategies to engage patients in their own medication management are critical.
all of a patient's chronic fill medications to come due on a single day of the month. By simplifying the refill process, the researchers hypothesized that patients will be more likely to take their medications as prescribed.

Conclusions

PCMHs and ACOs are expanding and evolving at a rapid pace; thus, there is significant opportunity for innovation, especially in chronic disease management. For most chronic conditions, the primary intervention is based on drug therapy. Many patients face barriers that limit access to primary care providers in the PCMH for help with their medication regimens. Pharmacist-led medication management holds great promise to improve care and control health care costs. More specifically, pharmacists in community settings are well positioned to provide complementary and synergistic services virtually to PCMHs and ACOs. Including pharmacists in the PCMH and empowering them to perform comprehensive medication reviews, resolve medication-related problems, optimize adherence interventions, and recommend cost-effective therapies will enhance patient care in a cost-effective manner. More research is needed in this area, and the early lessons summarized here may prove useful to future research teams as they embark on this critical path (Table 3).

Acknowledgments

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References

Pharmacists’ Role in the Care of Patients with Heart Failure: Review and Future Evolution

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Heart failure (HF) affects approximately 5 million Americans. Whether the problem is chronic HF or acute management of patients with episodes of acute decompensated heart failure (ADHF), HF has proven to be a huge economic burden, with annual direct and indirect health care costs currently exceeding $34.4 billion. Annual incidence rates are continuing to climb, with current statistics revealing 550,000 new cases every year, in addition to significant morbidity and mortality rates associated with multiple rehospitalization. HF patients, even if stable and compliant with their current HF medication regimen, can quickly transition to an acute decompensated state at any time. Prevention of readmissions has become a national priority, and there is a growing fiscal incentive for health care institutions to develop strategies to smooth the transition from hospital to home and to provide more effective ambulatory HF treatment to keep patients out of the hospital. A multidisciplinary approach to management of this patient population has clearly provided an improvement in clinical outcomes. Pharmacists are important members of this multidisciplinary team. This article reviews the current documented role of pharmacists in the care of HF patients and discusses the future evolution of pharmacists’ role as the nation continues to develop innovative strategies in managing HF patients.

Methods
Peer-reviewed intervention trials, descriptive studies, and review articles were identified in MEDLINE and Current Contents Connect database, from 1966 to April 2013, using the search terms “pharmacists,” “pharmaceutical care,” “clinical pharmacy services,” “heart failure,” and “cardiomyopathy.” Citations from available articles were also reviewed for additional references. Table 1 summarizes pertinent studies described below.

Evidence Documenting the Role of Pharmacists in HF Care
The role of pharmacists in the care of HF is diverse and well described in the literature. Pharmacists generally provided care either as a sole practitioner or, more commonly, as part of a multidisciplinary team. The specific responsibility described varied and likely depended on the specific patient population, setting, and role of other health care team members. The sections that follow describe the documented roles and responsibilities of pharmacists in the care of HF patients.

Medication Reconciliation and Education
Medication reconciliation and patient education are 2 major areas and responsibilities of pharmacists that are now established to positively impact clinical outcomes of patients with different disease states. The effect of a clinical pharmacist on reconciliation of discharge medication of a HF patient population was evaluated in a study by Eggink et al. (2010). The aim of this study was to evaluate the effect of a clinical pharmacist discharge service on medication discrepancies and prescription errors. This open-label, randomized intervention study compared an intervention group with a control group receiving regular care by doctors and nurses. The role of the clinical pharmacist discharge service included review of medications at discharge, communicating prescribing errors with the cardiologists, preparing written overviews of the discharge medications, and communication with community pharmacists and patients’ primary care physicians about their medications, in order to establish a continuum of care. All patients were scheduled to return for a clinic visit with the discharge clinicians, and at that time, medication discrepancies were measured. The primary study endpoint was the frequency of prescription errors in discharge medications and medication after discharge combined. The control group included 44 patients, with 41 in the intervention group. In the control group, 68% of patients had at least 1 discrepancy versus 39% in the intervention group (relative risk [RR] = 0.57; 95% confidence interval [CI] = 0.37-0.88). This study validates the significant value of a clinical pharmacist discharge service in patients with HF.

In the Pharmacist Intervention for Low Literacy in Cardiovascular Disease (PILL-CVD) study, the effects of pharmacist-based medication reconciliation for patients with acute coronary syndrome or ADHF were evaluated. In this randomized controlled trial, 2 academic health care centers enrolled eligible patients and randomized them to usual care or usual care plus pharmacist intervention. Pharmacist interventions included obtaining in-depth medication history on admission, performing detailed medication reconciliation on admission and discharge, and offering patient medication education on discharge. Various methods were used to assist in the process of medication reconciliation, including pillboxes, verbal and written instruction, and telephone follow-up. The primary outcome was the number of clinically important medication errors per patient during the first 30 days after hospital discharge. Among 851 participants, 432 (50.8%) had 1 or more clinically...
### TABLE 1  
Studies Evaluating Pharmacist Intervention in Heart Failure Patient Management

<table>
<thead>
<tr>
<th>References</th>
<th>Study Characteristics</th>
<th>Design</th>
<th>Intervention</th>
<th>Outcomes</th>
</tr>
</thead>
</table>
| Eggink et al.5 | Intervention prior to discharge | Randomized controlled study | • Medication education  
• Medication reconciliation, communication with community pharmacists and patients' primary care doctors  
• By pharmacists | Reduce medication discrepancies and errors |
| Kripalani et al.6 | Intervention prior to discharge with follow-up | Randomized controlled study | • Medication education  
• Medication reconciliation, communication with community pharmacists and patients' primary care doctors  
• By pharmacists | No difference between groups |
| Jain et al.11 | Outpatient clinic service | Before and after intervention comparison | • Dose titration of heart failure medications based on a protocol  
• By pharmacist or nurse | • Improvement in drug prescribing rate  
• Improvement in target dose achievement  
• Improvement in symptoms |
| Stewart et al.13,14 | Intervention prior to hospital discharge with follow-up | Randomized controlled study | • Single home visit within 1 week of discharge from hospital by nurse or pharmacist  
• Optimize medication management, identify early clinical determination, intensify necessary medical follow-up | Fewer unplanned readmissions and out-of-hospital deaths in the intervention group |
| Rainville18 | Interventions prior to hospital discharge with follow-up | Randomized controlled study | • By pharmacist and nurse  
• Identification of hospital readmission risk factors, recommendation of medication changes to physicians if necessary | Less heart failure readmission |
| Patel et al.20 | Intervention prior to discharge and follow-up | Controlled study | • By pharmacist  
• Drug therapy evaluation, counseling over the telephone, recommended drug therapy changes to the physicians | No difference in number of readmissions |
| Varma et al.16 | Outpatient clinic service | Randomized controlled study | • By pharmacist  
• Education on heart failure, prescribed drugs and symptom management, contacted physician if needed | Improved exercise capacity, better compliance with drug therapy, fewer hospital readmissions |
| Gattis et al.17 | Outpatient clinic service | Randomized controlled study | • By pharmacist  
• Extensive education and counseling on medications, discussed and optimized patients' drug regimens with physicians, necessary recommendations regarding heart failure therapy, discussed changes made in drug therapy with patients, telephone follow-up | Reduction of clinic events, hospitalization, and death rates |
| Whellan et al.19 | Outpatient clinic service | Nonrandomized | • By pharmacist  
• Reviewed medications with patients, provided medication appraisals for physicians | Increased beta blocker use, decreased hospitalization rate |
| Goodyer et al.15 | Home-based intervention | Randomized controlled study | • By pharmacist  
• Intensive counseling using a standard written protocol | Intervention group patients showed significantly higher compliance and improved medication knowledge |
| Lowrie et al.21 | Outpatient clinic service | Randomized controlled study | • By pharmacist  
• Medication initiation and dose titration | Improved prescribing of disease-modifying medications but did not improve patient clinical outcomes |
| Gwadry-Sridhar et al.22 | Outpatient clinic service | Randomized controlled study | • By pharmacists and nurse educators  
• Education on medication adherence, dietary, and lifestyle modification | Improved quality of life but did not improve patient clinical outcomes |
| López Cabezas et al.23 | Intervention prior to discharge and follow-up | Randomized controlled study | • By pharmacists  
• Education on disease, diet, and drug therapy | Reduction in hospitalization at 2, 6, and 12 months |
important medication errors; 22.9% of such errors were judged to be serious and 1.8% life-threatening. Adverse drug events (ADEs) occurred in 258 patients (30.3%) and potential ADEs in 253 patients (29.7%). The intervention did not significantly alter the per-patient number of clinically important medication errors (unadjusted incidence rate ratio [IRR] = 0.92; 95% CI = 0.77-1.10) or ADEs (unadjusted IRR = 1.09; 95% CI = 0.86-1.39). Patients in the intervention group tended to have fewer potential ADEs (unadjusted IRR = 0.80; 95% CI = 0.61-1.04). This study revealed greater benefit from medication reconciliation in low-literacy patients, with nonsignificant benefit attained in high-literacy patients. In a follow-up substudy evaluating perspectives of 11 pharmacists (from the PILL-CVD study) on the value of the intervention, the pharmacists viewed medication reconciliation as the greatest and most important portion of the intervention in improving patient care transitions. The pharmacists also identified groups of patients who may be in greater need of medication reconciliation, particularly patients on multiple medications. Adherence aids such as pillboxes were more effective for patients with low health literacy as opposed to patients with adequate health literacy. Pharmacists' recommendations acknowledged a need for clear communications among team members, protected time for discharge counseling, and provision of tailored patient counseling for improved transitions of patient care.

Medication Initiation, Dosage Titration, Adjustment, and Monitoring

Although clinical evidence and treatment guidelines clearly mandate the use of evidence-based therapies such as angiotensin converting enzyme inhibitors (ACEI) and beta blockers in HF patients, these therapies are well known to be suboptimal when prescribed in actual clinical settings. The Acute Decompensated Heart Failure National Registry (ADHERE) collected HF case data from more than 275 hospitals in the United States and captured data on more than 40,000 patients hospitalized for HF. Data from the third quarter of 2004 revealed that clinicians had prescribed ACEI for 54% of patients at discharge, and use of ACEI or angiotensin receptor blocker (ARB) was approximately 68%. In addition, clinicians prescribed beta blockers for 72% of discharged patients. These data were encouraging compared with data previously reported and reflected better use of evidence-based therapies. Although prescribing does appear to be gradually improving, the use of ACEI and beta blockers for those at highest risk was still less than optimal. From the Enhanced Feedback for Effective Cardiac Treatment trial, a population-based cohort of patients with HF who were hospitalized in Ontario, Canada, from 1999 through 2001 (9,942 patients), patients with left ventricular ejection fraction of less than 40% and those younger than 79 years (1,418 patients) were assessed. HF drug use at time of discharge and 90 days after discharge was determined, and patients were categorized as being at low, average, or high risk for death. In these 3 risk groups, ACEI prescribing was 81%, 73%, and 60% at discharge and 83%, 76%, and 61% within 90 days after discharge, respectively. For ACEIs or angiotensin II receptor blockers (ARB), prescribing was 86%, 80%, and 65% at discharge and 89%, 83%, and 67% within 90 days after discharge, respectively. In addition, prescribing rate was 40%, 33%, and 24% at discharge for beta blockers and 43%, 36%, and 28% within 90 days after discharge, respectively. Compared with high-risk patients, low-risk patients were more likely to receive drug therapy with ACEI or ARB (adjusted hazard ratio [HR] = 1.61; 95% CI = 1.49-1.74) and beta blockers (adjusted HR = 1.80; 95% CI = 1.60-2.01).

Jain et al. (2005) evaluated the effectiveness of a protocol-driven HF clinic staffed by nurses and pharmacists for improving symptoms and optimizing treatment with therapeutic agents that have been demonstrated to improve mortality, without adversely affecting renal function. Of the 234 patients with at least 1 follow-up visit, 127 (57%) were receiving none or only 1 key therapeutic agent when first seen, a number that was reduced to 25 patients (11%) at most recent follow-up. The improvement in prescription rates was accompanied by significant up titration of dose, with the proportion of patients on “medium” or “high” doses rising from 43 (18%) to 134 (57%) for beta blockers and from 129 (59%) to 201 (86%) for ACEI/ARB. Clinical improvement was reflected in reductions in patients with New York Heart Association (NYHA) functional classes III and IV (93 [40%] to 53 [23%]) and in patients with moderate or severe symptoms. Uptitration of treatment was associated with reductions in heart rate and systolic blood pressure. Incidence of hyperkalemia and worsening of renal function was low. This study, however, did not differentiate the specific impact made by a nurse versus a pharmacist.

Other studies have also examined having a pharmacist on a multidisciplinary team to provide medication dosing recommendations (although not specifically targeted on just dose titration), which also improved patient outcome. Those studies are described in more detail in the next 2 sections.

Development of Disease Management Pathway

Disease management pathways have been demonstrated to efficiently improve care, especially in high-cost, high-volume, and high-risk diagnoses. HF is considered a high-cost, high-volume, high-risk diagnosis. Therefore, although there are no specific clinical studies of pharmacists developing and using disease management pathways to improve HF patient care, we anticipate that these pathways will improve the efficiency of care of such patients. Pharmacists play an important role on a team evaluating the pathway that requires appropriate drug use. Selection of a standard set of drugs to be used in the pathway should be based on the health system’s formulary, with a process in which new information on disease management,
including available drug therapies, can be incorporated. By incorporating evidence-based, rational, cost-effective therapy into critical pathways, pharmacists can ensure that interventions are consistent with local pharmacy department policies and procedures and with other hospital committee policies. Pharmacists can also prospectively design drug use evaluation in such a way that areas of the critical pathway involving safety, adherence, variation, and efficacy, including specifically designated outcomes, can be assessed.

**Posthospital Discharge Follow-Up, Clinic, and Home Visit**

Perhaps the pharmacist role most extensively researched and documented in HF patient management is the evaluation of such service in an “outpatient” or “postdischarge” setting, such as in clinics or in the community.

Stewart et al. (1998) evaluated the impact of a home-based intervention among 97 patients with HF, who were discharged from an acute-care hospital. The intervention was delivered by a nurse and a pharmacist and involved a single home visit within 1 week postdischarge to optimize medication management, identify early clinical deterioration, and identify whether medical follow-up was necessary. The effects of these home-based interventions were compared with standard postdischarge care. The predischARGE counseling was done by the nurse, whereas the home visit involved both a nurse and a pharmacist. The pharmacist’s role during the home visit included performing an assessment of the patient’s knowledge of prescribed medications and compliance. Patients who had poor medication knowledge and/or demonstrated nonadherence to a medication regimen received the following supports: verbal medication counseling, daily reminder to take medications, a dosage administration aid (such as a pillbox) to enable predistribution of medications, provision of a medication information and reminder card, increased monitoring by caregivers, and referral to a community pharmacist for regular medication review. The main outcome measures were the frequency of unplanned readmissions and out-of-hospital deaths in 6 months. Patients in the intervention group had fewer unplanned readmissions (36 vs. 63, P=0.03) and fewer out-of-hospital deaths (1 vs. 5, P=0.11). Patients in the control group who received usual care had more days of hospitalization (261 vs. 452; P=0.05). This study, however, did not specifically measure the impact on patient outcome made by the pharmacist.

In 1999, the same group of investigators carried out an extended 12-month follow-up study of all surviving patients from the previous 1998 study. This follow-up demonstrated fewer unplanned readmissions, out-of-hospital deaths, and days of hospitalization for the home-based intervention patients. There was also a significant lowering in hospital-based costs.

Goodyer et al. (1995) conducted a study to determine whether pharmacists providing intensive counseling to elderly patients with chronic HF can influence subjective and objective measures of HF. The randomized patients received either a 3-month counseling program or no counseling at all. Patients in the intervention group were counseled on their medications using a “standard written protocol,” the details of which were not provided. Compliance was measured by a tablet count, whereas medication knowledge was assessed using a questionnaire. Mean compliance scores by tablet count were calculated, the mean indicating the percentage of the maximum number of tablets that should have been consumed. At the beginning of the study, mean compliance was 49% in the control group as compared with 61% for the intervention group, which was not statistically significant (P=0.98). After the counseling program, compliance was significantly higher in the intervention group (93% vs. 51%, P<0.001). Medication knowledge also improved significantly (P<0.001). However, precise details of this improvement were not provided. A 6-minute exercise test that was carried out at the beginning and end of the study demonstrated worse results for the control group at the end of the study period. In the intervention group, these test results improved, suggesting that counseling improved the patient’s medication compliance, which in turn led to improved exercise capacity. Patients who received medication counseling also demonstrated improved signs of edema, which was attributed to improved medication compliance.

Varma et al. (1999) evaluated a structured pharmaceutical care program for patients with HF aged more than 65 years. The intervention group of patients (group A) received education from a pharmacist on the disease state and on the medications and management of HF symptoms, as well as an information booklet containing the discussed information. Patients were also encouraged to monitor their symptoms and comply with their medications. Patients were asked to self-monitor using diary cards to be shown to their physicians and community pharmacists and later mailed to the researchers. Group A also recorded their weight on a daily basis and adjusted their diuretic doses accordingly, based on a specific increase in weight or on a worsening of symptoms, such as increased shortness of breath or ankle swelling. The pharmacist-researcher contacted the community pharmacists and physicians via telephone to discuss the project and the self-monitoring program. Patients in the control group (group B) received standard management. All patients were assessed at baseline and at 3, 6, 9, and 12 months for the following: 2-minute walk test, blood pressure, body weight, pulse, quality of life, knowledge of symptoms and drugs, compliance with therapy, and use of health care facilities. From these assessments, patients in group A demonstrated better compliance with drug therapy, which led to improved exercise capacity compared with patients in group B. Over the 12 months of this study, group A patients also exhibited considerable enhanced knowledge of their drug therapy and had fewer hospital admissions.
compared with group B patients. Quality of life, as an outcome, was not shown to have statistically significant changes following pharmacy interventions when compared with usual care.

Gattis et al. (1999) conducted the Pharmacist in Heart Failure Assessment Recommendation and Monitoring Study, to examine the benefits of the addition of a clinical pharmacist to the HF management team on outcomes in outpatients with HF. In the intervention group, patients attended an outpatient clinic and received extensive medication education and counseling provided by a clinical pharmacist. The pharmacist discussed and optimized the patient’s drug regimen by collaborating with the patient’s physician, implemented changes to the patient’s HF drug therapy, and then discussed the changes with the patient. Follow-up was conducted via telephone at 2, 12, and 24 weeks after the initial clinic visit to identify any issues with drug therapy. The control group patients received usual care. Primary endpoint was the combination of all-cause mortality and nonfatal HF events (i.e., emergency department visits or hospitalizations for HF). There were 4 events in the intervention group as compared with 16 in the control group. The effect on all-cause mortality was not found to be statistically significant, but the effect on nonfatal HF events was significant. This difference may be because of the closer follow-up by the clinical pharmacist of the patients in the intervention group. This close follow-up may have led to the early recognition of signs and symptoms of fluid overload, which in turn allowed quicker reviews by the physician and dose adjustments of diuretics, preventing the deterioration of HF. In addition, patients in the intervention group were more likely to receive target ACE inhibitor doses. The follow-up by the pharmacist also allowed the re-evaluation of the patient’s medication regimen, recognition of potential drug interactions, the significance of medication compliance, and the reinforcement of dietary sodium intake.

In a study based in an acute care facility in the United States, Rainville (1999) evaluated the impact of pharmacist interventions on the functional health status of HF patients and their rate of readmissions. The patients, nurses, and physicians were blinded to the allocation to minimize the potential for bias. Control group patients received routine care, which involved written prescriptions, physician-discharged instructions, a nurse review of diet, treatment plan, medication, and drug information sheets. The intervention group received routine care plus education from a pharmacist and nurse specialist, and patient issues that could contribute to readmission were also identified and corrected if necessary. The pharmacist also reviewed the pharmacotherapy and pathology of HF with the patient or their caregiver, monitored the patient’s weight, and reviewed risk modifications. In addition, the pharmacist provided a patient information brochure, medication organizer, weight log booklet, and video tape, and the pharmacist recommended medication changes to the physician when necessary.

Both patient groups received a follow-up telephone call after 30 days, 90 days, and 12 months of postdischarge. Patients in the intervention group also received a telephone follow-up 3 and 7 days postdischarge. There was a significant improvement in hospital readmissions for HF in the intervention group as compared with the control group (24% vs. 59%) over the 12-month period. In addition, there was a significantly longer time to readmission for the patients in the intervention group. The author concluded that the pharmacist intervention in this study “led to significantly fewer readmissions for HF,” noting that the validity of this study would need to be evaluated in a larger study.

Whellan et al. (2001) undertook a study to evaluate the potential benefit of implementing an HF disease management program, the Duke Heart Failure Program (DHFP). This study assessed the benefits of beta blocker use and the cost to the health care system. The outcomes were assessed based on the rates of pre-enrollment versus postenrollment into the program. Although this study involved a myriad of health professionals, the role of the pharmacist was clearly stated as reviewing medications with the patient and providing a medication appraisal for the physician. The pharmacist, with the help of the nurse, emphasized weight monitoring and when to contact a DHFP nurse in the event of experiencing worsening symptoms. The results showed that both beta blocker usage and doses increased significantly during the study, whereas hospitalization rates significantly decreased, and the number of clinic visits significantly increased. The doses of ACEIs used increased, although not significantly. This increase could reflect the increased prescribing rates of ACEIs and beta blockers that occurred over the course of the study.

The role of pharmacists as part of a pilot HF program to help prevent exacerbations and hospitalizations among HF patients was evaluated in a 2003 study by Patel et al. The intervention group received pharmacist interventions such as drug therapy evaluation, telephone counseling, and recommended drug therapy changes sent to the physician by telephone or fax. Patients received pharmacist interventions every 4 to 6 weeks for 6 months, and outcomes were evaluated after 3 and 6 months. There was no difference in the number of hospitalizations between the intervention and control groups. This study, however, was limited by a very small sample size (n = 18).

Lowrie et al. (2012) performed a randomized controlled study, where 1,090 HF patients from 87 primary care practices were randomized to pharmacist intervention or usual care. The intervention was delivered by non-specialist pharmacists working with family doctors to optimize medical treatment. The primary outcome was a composite of death or hospital admission for worsening HF. The median follow-up was 4.7 years. At baseline, 86% of patients in both groups were treated with an ACEI or an ARB. In patients not receiving one or other of these medications, or receiving less than the
recommended dose, treatment was started, or the dose increased, in 33.1% of patients in the intervention group and in 18.5% of the usual care group (odds ratio [OR] = 2.26; 95% CI = 1.64-3.10; P < 0.001). At baseline, 62% of each group was treated with a beta blocker and the proportions starting or having an increase in the dose were 17.9% in the intervention group and 11.1% in the usual care group (OR = 1.76; 95% CI = 1.31-2.35; P < 0.001). The primary outcome occurred in 35.8% of patients in the intervention group and 35.4% in the usual care group (HR = 0.97; 95% CI = 0.83-1.14; P = 0.72). The investigators concluded that a low-intensity, pharmacist-led collaborative intervention in primary care resulted in modest improvements in prescribing disease-modifying medications but did not improve clinical outcomes in a population that was relatively well treated at baseline.

Gwadry-Sridhar et al. (2005) performed a randomized controlled pilot study, in which 134 patients with left ventricular dysfunction were placed in the intervention group, where they received education on medication adherence, diet, and lifestyle modification provided by a pharmacist and nurse educator compared with standard of care. Although intervention did not improve mortality, hospital readmission, or emergency department visits, patients demonstrated significant improvement in quality of life measured by the Minnesota Living with Heart Failure Questionnaire. This study did not differentiate the specific impact on patient outcome between the pharmacists and the nurse educators.

Lopez-Cabezas et al. (2006) performed a randomized controlled trial enrolling 134 patients hospitalized for HF. Patients were randomized to standard of care or interventions including education on disease, diet, and drug therapy from a pharmacist at discharge, with monthly follow-up phone calls for 6 months and every 2 months after. The intervention group demonstrated significant reduction in hospital readmission at 2 months, 6 months, and 12 months (P < 0.05 at both time points).

**Impact on Patient Outcomes**

As discussed above, numerous studies have described the role of pharmacists in the care of HF patients. These studies demonstrated service performed with varied scope, in different settings, and with various outcome measures. Because some of these studies are small, and intervention may not be evaluated in a randomized fashion, meta-analysis and systematic reviews may be able to help us better determine the impact of these services to patient outcomes.

Holland et al. (2005) performed a systematic review of 30 randomized controlled trials conducted in both hospital and community settings, evaluating the impact of multidisciplinary team interventions on HF patient outcomes in terms of all-cause hospital admission, mortality, and HF hospital admission. Multidisciplinary interventions reduced all-cause admission (RR = 0.87; 95% CI = 0.79-0.95), although significant heterogeneity was found among studies (P = 0.002). All-cause mortality was also reduced (RR = 0.79; 95% CI = 0.69-0.92) as was HF admission (RR = 0.70; 95% CI = 0.61-0.81). These results varied little with sensitivity analyses.

Koshman et al. (2008) also performed a systematic review to specifically characterize the role of pharmacists in the care of patients with heart failure. They identified 12 randomized controlled studies. The extent of involvement of the pharmacist varied among studies, and each study intervention was categorized as pharmacist-directed care or pharmacist-collaborative care. Pharmacist care was associated with significant reductions in the rate of all-cause hospitalizations (11 studies [2,026 patients]; OR = 0.71; 95% CI = 0.54-0.94) and HF hospitalizations (11 studies [1,977 patients]; OR = 0.69; 95% CI = 0.51-0.94) and a nonsignificant reduction in mortality (12 studies [2,060 patients]; OR = 0.84; 95% CI = 0.61-1.15). Pharmacist-collaborative care led to greater reductions in the rate of HF hospitalizations (OR = 0.42; 95% CI = 0.24-0.74) than pharmacist-directed care (OR = 0.89; 95% CI = 0.68-1.17). The authors concluded that pharmacist care in the management of patients with HF greatly reduces the risk of all-cause and HF hospitalization.

**Potential Future Roles for HF Pharmacists**

**Management of Mechanical Circulatory Support**

Advances in mechanical circulatory support, such as the use of ventricular assist devices (VADs), and total artificial heart systems have become a means for prolonging survival in end-stage HF. VADs decrease the symptoms of HF and improve quality of life. They unload the ventricle to provide improved cardiac output and end-organ perfusion, resulting in improvement in cardiorenal syndromes and NYHA functional class rating. VADs are currently used as a bridge to heart transplantation, a bridge to recovery of cardiac function, or as destination therapy. Total artificial heart systems are currently used as a bridge to heart transplantation. Complications of VAD and total artificial heart systems may include bleeding and thrombosis, infections, arrhythmias, multiple organ failure, right ventricular failure, and neurological dysfunction. Patients with VAD and an artificial heart have unique pharmacotherapeutic requirements in terms of anticoagulation, appropriate antibiotic selection, and continuation of HF medications. Because evidence available in managing this patient population is still sparse compared with other areas of HF management, pharmacist expertise in pharmacology and therapeutics can really contribute to both acute care and community settings in optimizing patients’ medication care. Jennings et al. (2011) described establishing a clinical pharmacy service for patients with left VAD (LVAD). During the data collection period, the clinical pharmacist documented 400 interventions made in patients with LVADs (262 interventions on the cardiothoracic surgery service,
average 8.7 interventions per patient encounter; 138 interventions on the acute heart failure service, average 1.8 interventions per patient encounter). Overall, the most common type of pharmacist intervention was change in dose/route/frequency (33%), followed by initiating evidence-based HF therapy (31%), discontinuing therapy (18%), ordering a laboratory test (12%), and changing therapy (6%). The most common reasons for pharmacist intervention were treatment of a disease or condition that was not controlled on present therapy (36%), followed by dose correction (17%), improved monitoring of drug therapy (13%), and adverse drug reaction/drug-drug interaction (11%). Antimicrobial agents were the most frequent medication class involved in pharmacist intervention. The role of pharmacists in this area will continue to expand as the use of mechanical devices in end-stage heart failure patients continues to increase.

Outpatient HF Infusion Clinic
The rate of hospital readmissions for ADHF is a major benchmark statistic for third-party payers, including Medicare and private insurers. A small pilot study has demonstrated that planned intravenous diuretic therapy administered in an outpatient setting may reduce heart failure hospital admissions and 30-day readmissions.27 Many institutions across the United States have an interest in developing these clinics. Such settings provide another opportunity for pharmacists to work with other health care professionals not only to develop infusion protocols but also to optimize other medication therapy. In addition, such clinics allow pharmacists to work with patients directly through medication reconciliation, teaching, and improving medication adherence.

Patient-Centered Medical Home
Patient-centered medical home is a model of care where patients have a direct relationship with a provider who coordinates a cooperative team of health care professionals, including pharmacists, whether the patient is being seen at the doctor's office, becomes hospitalized, or is recuperating at home, through ongoing preventive care. Comprehensive medication management is an important part of care provided by the patient-centered medical home. Comprehensive medication management includes an individualized care plan that achieves the intended goals of therapy with appropriate follow-up to determine actual patient outcomes. Chronic HF is a disease state that is well suited to a patient-centered medical home model of coordinated care. The role of pharmacists in comprehensive medication management will be pivotal in improving overall patient outcomes.

Discussion
HF is a high prevalence medical condition. Many medical and therapeutic advances have been made with respect to HF and its management. Despite these advances, therapeutic challenges still exist. The pharmacist plays a pivotal role in the management of HF patients through medication reconciliation, patient education, and collaborative medication management efforts. A substantive body of data shows that pharmacists, when actively engaged in these efforts, may decrease length of stay and reduce the number of readmissions. Furthermore, patient wellness and overall perception of self may be improved through educational efforts and active involvement in self-monitoring of the symptoms of HF. The pharmacist’s involvement in medication reconciliation and concurrent therapeutic recommendations at time of prescribing also lead to fewer prescribing errors and greater awareness of patient-specific needs for dosage adjustments or other therapeutic interventions. The multidisciplinary team approach, with inclusion of a pharmacist, improves patient outcomes in a multitude of ways. The American College of Clinical Pharmacy and the Heart Failure Society of America have published an opinion paper recently in support of clinical pharmacists participating in HF patient care, describing the potential roles for clinical pharmacists in a multidisciplinary HF team, recommending minimum training for clinical pharmacists engaged in HF care, and suggesting financial strategies to support clinical pharmacy services within a multidisciplinary team.28 As the health care system continues to develop innovative approaches of care to minimize the burden of this disease, pharmacists will have an expanded role in the care of HF patients.

Conclusions
Pharmacists as active participants in the care of HF patients may effect significant positive change in the therapeutic outcomes, decrease hospitalizations and readmissions, and improve overall patient perception of self. Medication reconciliation, patient education, and collaborative medication management are 3 major areas best documented in the literature in which a pharmacist may positively impact patient outcomes. Novel pharmacist roles may include medication management of patients with mechanical circulatory support for end-stage HF; pharmacist-run intravenous diuretic outpatient clinics, combined with concomitant patient education sessions; and provision of comprehensive medication management in a patient-centered medical home. The role of the pharmacist as liaison between patients and other health care providers is essential for effective management of a patient's HF medication therapy. Pharmacists should also be encouraged to prospectively evaluate their role in the care of this patient population, document their interventions, record cost avoidance, and document the relation to patient outcomes.
Pharmacists’ Role in the Care of Patients with Heart Failure: Review and Future Evolution

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