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Printmaking is often referred to as intaglio, an Italian word meaning “to carve.” It is a process used to produce multiple pieces of artwork. Artists who choose the medium of printmaking must be able to visualize the end result as they etch or cut into the printing surface, which is most commonly metal, wood, or linoleum.

Andrew Totman created his print, Learn to Be Still, using the process of etching, which, along with engraving, drypoint, mezzotint, and aquatint, is part of the intaglio family. Etching was first used in the early 16th century when it was found that acid could be used to dissolve exposed parts of a metal printing plate. An artist starts the process by coating the surface of a metal plate (usually copper) with a waxy material called a “ground,” which prevents the acid from etching the metal. Then the artist uses a sharp tool to draw an image in the ground. When the plate is put into an acid bath, the acid etches the metal where the artist has removed the ground. After the plate is taken out of the acid, the ground is removed with a solvent such as turpentine, and the entire plate is inked. The surface is wiped clean with a piece of stiff fabric known as “tarlatan” or newsprint paper, leaving ink only in the etched grooves of the plate. A damp piece of paper is placed over the plate, and it is run through the press to make a single-colored print. Multicolored prints are produced with multiple plates and inks.

Totman says that when beginning a project, “I start with an idea that is just for me, with a memory or event in mind, and I make a small drawing.” Learn to Be Still is a prime example of his personal style; a fascinating metaphorical work that depicts an ethereal figure paused in midflight. This half-human, half-spirit being wears a flowing cape that resembles a pair of wings. A golden, feather-like shape caresses the underside of the cape, and two gracefully curved dark blue shapes complement the lower part of the body that looks somewhat like a fish’s tail. He only drew one hand and one foot to suggest the humanity of the form, while the abstracted parts of the body represent the spiritual element. A pair of arms seems to embrace the figure, yet they temporarily halt its progress—perhaps Totman is alluding to a parent-and-child relationship. He chose red hues for the arms, providing a wonderful contrast of warm color against the cool background. His use of red completes the print’s trio of primary colors.

Totman was born in 1961 in Sebastopol, California, and reared in Napa, California. Interested in art from an early age, he enrolled at the University of San Diego as a printmaking major, receiving his BA in 1983. Totman earned his MFA in 1986 from Wichita State University in Wichita, Kansas, with a major in printmaking and a minor in drawing/painting. He also worked as a printmaking instructor at Wichita State during his tenure at the university. Totman then went abroad to participate in the Consultant Artists-in-Residence program at the Centre d’Art Contemporain Château Beychevelle in Bordeaux, France. From there, his career took him back to the United States, first working as an assistant professor of art at the University of Alaska in Anchorage, and then as an assistant professor of art in the Artsreach program at the University of California, Los Angeles.

In 1997, Totman and his family moved to Sydney, Australia, where he has continued his highly successful art career. He is the manager of the Mary Street Studios in St. Peters, Australia, and a printmaking lecturer at the National Art School in East Sydney, Australia.

Totman has shown his work in numerous solo and group exhibitions throughout the world, and his prints, paintings, and drawings are in museums, corporate collections, and galleries around the globe. A partial list of galleries includes Print Arts Northwest in Portland, Oregon; Groundfloor Gallery in Sydney, Australia; Port Jackson Press in Melbourne, Australia; Atelier Skara in Gressvik, Norway; and the Centro Venezolano Americano del Zulia gallery in Maracaibo, Venezuela.

In 2003, Totman’s work was on exhibit at the Stanford Art Spaces gallery in the Center for Integrated Systems on the Stanford University campus in Palo Alto, California. The exhibit showcased his recurring motifs of figures—often with an emphasis on the hand—and houses, reflecting the things that he holds most dear: his family and home life. Totman’s remarkable art style is described in a brief biography found on the Center for Integrated Systems’ Web site: “His work holds the particularly elusive quality that identifies a work of art as timeless in scope and intent. Abstracted figures moving in fields of vibrant colors undoubtedly tie Andrew’s style to the New Figurative movement, and his images tell of his journey through German Expressionism and French Symbolism tinged by an undeniable West Coast Pop Art flair. The figures symbolize both the artist’s alter ego and the universal spirit shared by all, independent of race, gender, and creed. The scenes depicted lead the audience into a psychological place as palpable yet fleeting as a glimpse through a window.”

Sheila Macho
Cover Editor

COVER CREDIT
Andrew Totman, Learn to Be Still, etching. Sydney, New South Wales, Australia. Copyright © 1999.

SOURCES
Interview with the artist.
http://cis.stanford.edu/~marigros/show34.html#artist3.
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OBJECTIVE: Peripheral arterial disease (PAD) is associated with high rates of morbidity and mortality and serves as an important marker for advanced systemic atherosclerosis accompanied by symptomatic or asymptomatic ischemia of the coronary, cerebral, and visceral vasculature. There are little published data on the use of health care resources and costs attributable to PAD. The objectives of this study were to evaluate, from a societal perspective, PAD-related health care resource utilization and to determine the total annualized costs and cost components for patients with PAD, with particular attention to the key outcomes of myocardial infarction (MI), transient ischemic attacks (TIA), stroke, and amputations.

METHODS: This study examined medical, hospital, and outpatient, and pharmacy claims from a large managed care database with dates of service from January 1, 1999, through August 31, 2003. Patients with PAD were identified from claims using International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis codes (primary or secondary codes), ICD-9-CM procedure codes, current procedural terminology (CPT) codes, or by a pharmacy claim for cilostazol or pentoxifylline. The index date for each patient was the first occurrence of either a medical claim for PAD or a pharmacy claim for 1 of the 2 drugs. Patients were required to be a minimum of 18 years old with continuous plan eligibility. The prevalence of PAD in adults in a managed care setting was also determined, as were annual rates for the key outcomes of MI, TIA, stroke, and amputations. Health care resource utilization and costs were calculated for PAD patients after the index date for a period of at least 12 months per patient for medications, outpatient/physician office visits, laboratory/diagnostic procedures, emergency department visits, and hospitalization. Cost was defined as the allowed charge on each administrative claim, including the amount paid by the insurer plus the amount paid by the health plan members (copay, deductible, and coinsurance).

RESULTS: Prior to application of exclusion criteria for patients aged 18 years or older and the minimum period of continuous eligibility, the overall prevalence of PAD was 1.18% of the total managed care organization population's 6.67 million members. The PAD study cohort consisted of 30,561 patients with a mean age of 70.7 years at index. The most common comorbidities identified in the preindex period for these PAD patients included hypertension (67% of patients); metabolic disorders/hypercholesterolemia (57%); heart disease including cardiomyopathy, dysrhythmias, and heart failure (55%); and ischemic heart disease (47%). Over a mean postindex period of 25.2 months (median 23.4 months), the total mean annualized PAD-related cost was $5,955 per patient per year (PPPY). Hospitalizations accounted for the largest component cost category, averaging $4,442 PPPY or 75% of the total annualized PAD-related cost per patient. PAD-related noncoronary procedures averaged $729 PPPY (12.2% of total annual PAD-related costs), and PAD-related medications (including antihypertensives and lipid-lowering therapy) totaled $610 (10.2% of total annual costs), including $313 PPPY for antihypertensives and $207 for lipid-lowering therapy. For the subgroup of 24,075 newly identified PAD patients, 8,479 (35.2%) were hospitalized during an average 25.2 months of follow-up, with the mean time to first hospitalization of 8.9 months.

CONCLUSIONS: Approximately 75% of the total PAD-related patient cost in an average of 25 months of follow-up is contributed by hospital costs, and 35% of patients newly diagnosed with PAD experienced a hospitalization in a mean of 8.9 months after the index diagnosis. Based upon mean annual health and member costs of only $313 PPPY for antihypertensives and $207 for lipid-lowering therapy, drug therapy in PAD patients may be underutilized.

KEYWORDS: Peripheral arterial disease, Peripheral artery disease, Atherosclerosis, Managed care, Prevalence, Resource utilization, Costs

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Authors

JAY MARGOLIS, RPh, is a health outcomes research manager; JOHN J. BARRON, PharmD, is a health outcomes research director; and W. DANIEL GROCHULSKI, PhD, is a health outcomes analytics manager, HealthCore, Inc., Wilmington, Delaware.

AUTHOR CORRESPONDENCE AND REPRINT REQUESTS: Jay Margolis, RPh, Health Outcomes Research Manager, HealthCore, Inc., 800 Delaware Ave., Fifth Fl, Wilmington, DE 19801-1366. Tel: (302) 230-2158; Fax: (302) 230-2020; E-mail: jmargolis@healthcore.com

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Health Care Resources and Costs for Treating Peripheral Artery Disease in a Managed Care Population: Results From Analysis of Administrative Claims Data

lagged behind that of CAD due to (1) a less robust body of evidence on effective treatments, (2) lack of awareness of the increased cardiovascular risk, and (3) lack of cost justification for medical management.10

Medical management currently involves smoking-cessation interventions, lipid-lowering therapies, blood pressure control, antiplatelet therapy, and promoting regular exercise as well as appropriate diabetes/blood sugar control and/or weight loss. While recent surveys have uncovered the need to increase physician knowledge and change attitudes about medical management of PAD,11 there is growing support that medical management for the PAD patient can dramatically reduce the cardiovascular risk as well as improve the patient’s functional status.7,12

Economic evaluations of preventative therapies for CAD are relevant for patients with vascular disease since CAD and peripheral arterial occlusive disease commonly occur together and share risk factors, pathophysiology, and response to preventative therapy. Cost-effectiveness analysis has shown that modification of vascular risk factors like tobacco use, hypertension, and hypercholesterolemia improve clinical outcomes at cost-effectiveness ratios usually less than $20,000 per year of life saved, making medical management for reduction of cardiovascular risk factors generally cost effective.13 To our knowledge, this paper is the first to provide a view of the health care resources and costs attributable to PAD from a societal perspective using managed care resource utilization and costs. The results from the present study provide a basis for future comparisons of cost-effective disease management interventions.

The objectives of this study were to determine from a societal perspective the health care resource utilization and total annualized costs and cost components for patients with PAD, using managed care organization (MCO) costs and patient cost-share amounts. Health care resources included medications, outpatient/physician office visits, laboratory/diagnostic procedures, emergency department visits, and hospitalization. The prevalence of PAD in adults in a managed care setting was also determined, as were annual rates for the key outcomes of myocardial infarction (MI), transient ischemic attack (TIA), stroke, and amputations.

Methods

Data were collected from 2 health plans in the southeast and western United States. Both health plans were able to provide medical claims, pharmacy claims, and eligibility information for members during the entire study period, from January 1, 1999, through August 31, 2003. These plans contained 6.67 million MCO members for which complete data existed, including medical, hospital, pharmacy, and eligibility data.

Patients were identified with PAD by the following criteria: (1) an International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis code of 440.xx (any ICD-9 code beginning with 440, atherosclerosis) or 443.9 (peripheral vascular disease, not otherwise specified) on a medical claim (medical claims include all inpatient hospital, outpatient hospital, medical visit, and emergency room); (2) an ICD-9-CM procedure code of 38.08 (incision of vessel, embolectomy or thrombectomy, lower-limb arteries), 38.13 (endarterectomy, upper-limb vessels), 38.18 (endarterectomy, lower-limb arteries), 39.25 (aorta-iliac-femoral bypass), 39.26 (other intra-abdominal vascular shunt or bypass), 39.29 (other peripheral vascular shunt or bypass), 39.50 (angioplasty or atherectomy of other noncoronary vessel, incl. percutaneous transluminal angioplasty of noncoronary vessel), or 39.90 (insertion of non–drug-eluting peripheral vessel stent) on a medical claim; (3) a PAD-related surgical procedure (noncoronary thrombectomy, embolectomy, angioplasty, atherectomy, bypass graft, or stenting) on a medical claim; or (4) a pharmacy claim for cilostazol (Pletal14) or pentoxifylline (Trental15). (Cilostazol was approved by the U.S. Food and Drug Administration [FDA] on January 15, 1999, for the indication of reduction of symptoms of intermittent claudication as indicated by an increased walking distance,14 and pentoxifylline was approved by the FDA on August 30, 1984, for intermittent claudication on the basis of chronic occlusive arterial disease of the limbs.15) Pharmacy claims for other drugs used in PAD (aspirin, clopidogrel, dipyridamole, etc.) were not used to identify PAD patients due to their use in other disease states.

Patients with PAD were identified from medical, hospital, and pharmacy claims with dates of service from January 1, 2000, through August 31, 2002. The date of the first medical, hospital, or pharmacy claim using the criteria for PAD, listed above, was identified as that patient’s index date. Study patients were required to have continuous enrollment for at least 12 months prior to their index date and at least 12 months after their index date to permit comparison for equally continuous periods. They were not required to be newly diagnosed with PAD.

Resource utilization was determined for all patients who qualified for the study cohort by evaluating medical, hospital, and pharmacy claims for all study patients postindex through the earlier of the end of the patient’s insurance eligibility (minimum of 12 months postindex date required), or August 31, 2003. Medical and hospital claims were identified from both primary and secondary diagnoses and by the PAD-related procedure codes on the claims. Patients were deemed to be newly identified with PAD if they had no PAD-qualifying drugs or claims, as described above, prior to the index date back to the time of their enrollment (minimum 12 months prior to index).

Comorbidities were identified using the ICD-9-CM codes, at the 3-digit level (e.g., 401.xx–405.xx for hypertensive disease), found in medical claims. In addition to ICD-9-CM codes, pharmacy claims for antidiabetic medication were also used to identify patients with diabetes mellitus. Patients could have had
more than one comorbidity.

Hospitalizations were identified from the 3-digit ICD-9-CM codes (e.g., 410.xx for acute MI) found in medical claims for the hospitalization, including both primary and secondary diagnoses. Patients were included in more than one hospitalization category if the diagnoses on the hospitalization claim qualified them for more than one category; (e.g., 250.xx for diabetes and 401.xx-405.xx for hypertension).

Costs were derived from claims for office/outpatient visits, outpatient prescriptions, laboratory/diagnostic tests, medical procedures, emergency facility visits, and hospitalizations. Cost was defined as the allowed charge for hospital, medical, and pharmacy claims, comprising the amount paid by the insurance plan plus the patient's copay, deductible, and coinsurance amounts.

Statistical analyses were performed using SAS version 8.02 (SAS Institute Inc., Cary, NC). Means, standard errors, and medians were reported for interval and ratio scaled data. Frequencies and percentages were reported for nominal (categorical) and ordinal scaled variables. For all analyses, an a priori 2-tailed level of significance (alpha value) was set at the 0.05 level.

Since this observational study used de-identified data from retrospective claims without using protected health information, it did not involve patient intervention, and, therefore, Institutional Review Board approval was not necessary.

#### Results

A total of 30,561 patients met all inclusion criteria for PAD (Table 1). These patients were observed after their index date for an average of 25.2 months (SD ± 9.3 months, median 23.4 months). The majority of the study cohort of 24,075 patients (79%) was considered newly identified PAD, not having a PAD-distinguishing diagnosis, procedure, or PAD-related medication at any time prior to their index date (minimum 12 months, from the date of enrollment in one of the health plans).

The demographics of this PAD study cohort are shown in Table 2. The mean age at index was 70.7 years (SD ± 14.3 years, median 73 years), with 78% of the PAD patients older than 60 years and 59% of patients older than 70 years. While 54% of PAD patients were female, there was a greater number of female health plan members overall and, thus, the prevalence for females was lower than for males.

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>Patient Selection Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inclusion Criteria</td>
<td>No. of Patients Excluded (%)</td>
</tr>
<tr>
<td>Patients with only PAD-related diagnosis or procedure*</td>
<td>–</td>
</tr>
<tr>
<td>Patients with only pharmacy claim(s) for cilostazol or pentoxifylline</td>
<td>–</td>
</tr>
<tr>
<td>Patients with PAD-related diagnosis or procedure and pharmacy claim(s) for cilostazol or pentoxifylline</td>
<td>–</td>
</tr>
<tr>
<td>Total PAD patients identified</td>
<td>79,058 (100.0)</td>
</tr>
<tr>
<td>Patients aged 18 years and older</td>
<td>6,804 (8.6)</td>
</tr>
<tr>
<td>Patients with continuous enrollment for 12 months before and 12 months after index date</td>
<td>41,693 (52.7)</td>
</tr>
<tr>
<td>Patients without a PAD-related diagnosis or pharmacy claim for cilostazol or pentoxifylline in the preindex period (i.e., patients without prior PAD)</td>
<td>6,486 (8.2)</td>
</tr>
</tbody>
</table>

* Medical claims include inpatient hospital and outpatient hospital and medical visits. Patients were identified with PAD by the following criteria: (1) an ICD-9-CM diagnosis code of 440.xx (atherosclerosis) or 443.9 (peripheral vascular disease, unspecified) on a medical claim; (2) an ICD-9-CM procedure code of 38.08 (incision of vessel, embolectomy or thrombectomy, lower-limb arteries), 38.13 (endarterectomy, upper-limb vessels), 38.18 (endarterectomy, lower-limb arteries), 39.25 (aorta-femoral bypass), 39.26 (other intra-abdominal vascular shunt or bypass), 39.29 (other peripheral vascular shunt or bypass), 39.50 (angioplasty or atherectomy of other noncoronary vessel incl. percutaneous transluminal angioplasty of noncoronary vessel), or 39.90 (insertion of non-drug-eluting peripheral vessel stent) on a medical claim; (3) CPT codes for a PAD-related surgical procedure (noncoronary thrombectomy, embolectomy, angioplasty, atherectomy, bypass graft, or stenting) on a medical claim. (The 30 different CPT codes are available from the authors upon request.)

† 1.08% of the 6,665,787 enrollees in the available data as of August 31, 2002. CPT = current procedural terminology; ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification; PAD = peripheral arterial disease.

<table>
<thead>
<tr>
<th>TABLE 2</th>
<th>Demographics of the PAD Patient Study Cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>All PAD Patients N = 30,361</td>
</tr>
<tr>
<td>Patient age (years)</td>
<td>70.7 ± 14.3</td>
</tr>
<tr>
<td>Median</td>
<td>73</td>
</tr>
<tr>
<td>&lt;40</td>
<td>826 (2.7%)</td>
</tr>
<tr>
<td>40-49</td>
<td>1,927 (6.3%)</td>
</tr>
<tr>
<td>50-59</td>
<td>3,027 (12.9%)</td>
</tr>
<tr>
<td>60-69</td>
<td>5,986 (19.6%)</td>
</tr>
<tr>
<td>70+</td>
<td>17,885 (58.5%)</td>
</tr>
<tr>
<td>Patient gender</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>13,978 (45.7%)</td>
</tr>
<tr>
<td>Female</td>
<td>16,383 (54.3%)</td>
</tr>
</tbody>
</table>

* PAD patients were designated as "Newly Identified" if they did not have a PAD-related diagnosis, procedure, or medication of interest from the time of their enrollment (12 months minimum) until their index date. PAD = peripheral arterial disease.
The PAD prevalence rate is based on the number of patients per 1,000 members within the indicated population category. For example, there were 3,184,813 males, of which 36,068 qualified as PAD patients, to yield a prevalence rate of 11.325 PAD patients per 1,000 members.

PAD = peripheral arterial disease.

### TABLE 3
Prevalence of PAD in Patients Aged 18 Years or Older per 1,000 Members in a Managed Care Population (N = 6,665,787)

<table>
<thead>
<tr>
<th>Population</th>
<th>PAD Patient Count</th>
<th>PAD Prevalence*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>36,068</td>
<td>11.325</td>
</tr>
<tr>
<td>Female</td>
<td>36,186</td>
<td>10.395</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18-40</td>
<td>3,401</td>
<td>0.100</td>
</tr>
<tr>
<td>40-49</td>
<td>6,605</td>
<td>0.442</td>
</tr>
<tr>
<td>50-59</td>
<td>11,511</td>
<td>13.925</td>
</tr>
<tr>
<td>60-69</td>
<td>17,756</td>
<td>37.531</td>
</tr>
<tr>
<td>70+</td>
<td>32,981</td>
<td>92.718</td>
</tr>
<tr>
<td>Total</td>
<td>72,254</td>
<td>10.840</td>
</tr>
</tbody>
</table>

* The PAD prevalence rate is based on the number of patients per 1,000 members within the indicated population category. For example, there were 3,184,813 males, of which 36,068 qualified as PAD patients, to yield a prevalence rate of 11.325 PAD patients per 1,000 members. PAD = peripheral arterial disease.

### TABLE 4
Common Comorbid Conditions in PAD Patients in the 12-Month Period Prior to Index Date (N = 30,561)

<table>
<thead>
<tr>
<th>Comorbidity</th>
<th>ICD-9-CM Code</th>
<th>No. of Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms, signs, and ill-defined conditions</td>
<td>780-789</td>
<td>26,189 (85.7)</td>
</tr>
<tr>
<td>Hypertensive disease</td>
<td>401-405</td>
<td>20,560 (67.3)</td>
</tr>
<tr>
<td>Metabolic/immunity disorders</td>
<td>270-279</td>
<td>17,497 (57.3)</td>
</tr>
<tr>
<td>Other heart disease</td>
<td>420-429</td>
<td>16,769 (54.9)</td>
</tr>
<tr>
<td>Rheumatism (excluding the back)</td>
<td>725-729</td>
<td>15,709 (51.4)</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>410-414</td>
<td>14,359 (47.0)</td>
</tr>
<tr>
<td>Arthropathies and related disorders</td>
<td>710-719</td>
<td>15,759 (51.6)</td>
</tr>
<tr>
<td>Disorders of the eye and adnexa</td>
<td>360-379</td>
<td>15,875 (51.9)</td>
</tr>
<tr>
<td>Diseases of skin and subcutaneous tissue</td>
<td>700-709</td>
<td>4,695 (48.1)</td>
</tr>
<tr>
<td>Diabetes mellitus*</td>
<td>250.xx</td>
<td>8,605 (28.1)</td>
</tr>
</tbody>
</table>

* Diabetes mellitus identified by claims with ICD-9=250.xx or antidiabetic drug therapy.

ICD-9-CM = International Classification of Diseases, Ninth Revision; Clinical Modification; PAD = peripheral arterial disease.

30,561 PAD patients prior to the patients’ index date included hypertension (67% of patients); metabolic/immunity disorders and hypercholesterolemia (57%); heart disease/cardiomyopathy; dysrhythmias, and heart failure (55%); and ischemic heart disease (47%). Rheumatism and arthropathies were also prevalent in at least half of the patients, and diabetes mellitus was documented in 28.1% of the study patients.

All-cause hospitalization was examined for newly identified PAD patients after the patient’s index date to determine the frequency of hospitalization events and the length of time to a first event for key outcomes. Overall, 35% of these PAD patients were hospitalized during their observation period, with a mean time to the first hospitalization at approximately 9 months postindex (Tables 5 and 6). The 8,479 hospitalized PAD patients incurred 14,642 hospitalizations over the average 25-month observation period to yield an annualized rate of 321.7 hospitalizations per 1,000 PAD patients.

Hospitalizations were analyzed for the key events of MI, stroke, TIAs, and amputations. Stroke was the most common diagnosis (on hospital claims, in any diagnosis field), occurring for 8.0% of the newly identified PAD patients during their observation period, nearly double that of MI, which occurred in 4.1% of the newly identified PAD patients. The percentage of PAD patients hospitalized for limb amputation was the lowest, at 1.1%. Among those PAD patients who were hospitalized, again the most common reason was for stroke, occurring in 22.7% of those hospitalized, nearly double that of MI, which occurred in 11.5% of the hospitalized PAD patients.

As displayed in Figure 1, measuring the key PAD-related outcomes of stroke, MI, TIA, and amputation over time, stroke was the most commonly occurring event over time and amputation was the least common. Mean time to the first hospitalization for these events was lowest for amputation (8 months), followed by stroke (10 months), and TIA and MI (11 months).

The most common hospitalization diagnoses for PAD patients involved respiratory/chest symptoms (dyspnea, stridor, chest pain, abnormal chest sounds, or sputum), seen in 46.5% of hospitalized patients. Cardiovascular diseases were the next most common hospitalization diagnoses, led by essential hypertension in 34.6% of hospitalized patients and ischemic heart disease in 30.0% of hospitalized patients. Since the average patient’s observation period was approximately 25 months, event rates were annualized giving the following annual hospitalization event rates per 1,000 PAD patients: all cause—322 events, respiratory/chest symptoms—123 events, essential hypertension—82 events, ischemic heart disease—76 events, and stroke—52 events. The average time to first hospitalization was shortest for atherosclerosis-associated events (4.5 months), followed by ischemic heart disease (10 months), essential hypertension (10.6 months), and respiratory/chest symptoms (11 months).

The total average annualized cost of PAD-related patient care was $5,955 per PAD patient per year (PPPY), which includes the amount paid by the insurer plus the patient’s copayments, deductibles, and coinsurances. Of the individual components of care (Table 7), hospitalizations for the PAD-related outcomes of MI, stroke, TIA, and amputations were the highest single item, averaging $4,442 PPPY or 75% of the total PAD-related cost of care for this managed care study cohort. Hospitalizations for the PAD-related outcomes of MI, stroke, TIA, and amputations represented 49% of the average all-cause hospitalization total of $9,149. Costs for PAD-related procedures were confined to non-crownary procedures (bypasses, angioplasty, atherectomy, embolectomy, and stents), which, in aggregate, averaged $729 PPPY (12.2%). Of these procedures, arterial bypass had the highest average cost at $240 PPPY (4.0%). The total of PAD-
attributable emergency department visits, office visits, and laboratory/diagnostic testing resulted in an average of $173 PPPY (2.9%) in aggregate.

PAD-related medications were divided into the following drug classes: antiplatelet agents (aspirin, cilostazol, clopidogrel, dipyridamole, pentoxifylline, and ticlopidine), antihypertensives (ACE inhibitors, angiotensin receptor blockers, beta-blockers, calcium channel blockers, diuretics, and other antihypertensives), and lipid-lowering therapy. The average annualized expense for these classes of medication totaled $610, or 10.2% of the average annual PAD patient-related expenditures. Antihypertensives were used by 67% of the patients and comprised $313 of the annualized medication costs. Lipid-lowering therapy was used by 38.8% of patients, at an annualized cost of $207.

Antiplatelet medications were used in 26.9% of patients and comprised $90 of the annualized medication costs (not including over-the-counter aspirin). Of the antiplatelet medications (Table 8), clopidogrel was the most commonly prescribed, used by 12.9% of patients and accounting for 41% of antiplatelet prescription volume. Pentoxifylline was used by 12.2% of patients and accounted for 40% of antiplatelet prescription volume. The other antiplatelet medications were used by 7% of the patients.

Note that these costs capture actual usage patterns rather than optimal or guideline patterns. Costs for the injectable antiplatelet drugs were usually incorporated into the hospital charges.

**Discussion**

The total average annualized PAD-related cost of care for patients in this managed care study cohort of $5,955 reflects only the PAD-attributed drugs, procedures, diagnostics, and office visits and so may understate the overall total costs for these patients, which can be higher due to significant comorbidities. As expected, the costs for PAD-related hospitalizations were the highest single expense item, averaging 75% of the patient’s total cost of PAD-related care. The hospital costs as a percentage of the total bill were much higher for PAD patients than the typical rate of 36% reported by the Health Care Financing Administration (now the Centers for Medicare and Medicaid Services),16 which may be indicative of the higher comorbidity and cardiovascular risk profile of the PAD patients but may also be due, in part, to the use of PAD-attributable costs.

It is noteworthy that approximately 1 of 3 PAD patients in the study cohort ended up in the hospital within 2 years of their index date. Further, the 8,479 hospitalized PAD patients incurred 14,642 hospitalizations, which is nearly 2 hospitaliza-
Health Care Resources and Costs for Treating Peripheral Artery Disease in a Managed Care Population: Results From Analysis of Administrative Claims Data

Mean Time to Event and Annual Event Rate of Hospitalization for Any Cause in Newly Identified PAD Patients (N=24,075)

<table>
<thead>
<tr>
<th>Event</th>
<th>Mean Time to First Event (Months ± SD)</th>
<th>Annual Event Rate* per 1,000 PAD Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause hospitalizations</td>
<td>8.9 ± 9.2</td>
<td>321.7</td>
</tr>
<tr>
<td>MI</td>
<td>11.5 ± 9.4</td>
<td>25.3</td>
</tr>
<tr>
<td>Stroke</td>
<td>10.0 ± 8.8</td>
<td>52.0</td>
</tr>
<tr>
<td>TIA</td>
<td>11.1 ± 10.0</td>
<td>15.2</td>
</tr>
<tr>
<td>Amputation</td>
<td>8.0 ± 9.9</td>
<td>8.8</td>
</tr>
<tr>
<td>Respiratory/chest symptoms</td>
<td>11.2 ± 12.6</td>
<td>122.9</td>
</tr>
<tr>
<td>Essential hypertension</td>
<td>10.6 ± 10.8</td>
<td>82.1</td>
</tr>
<tr>
<td>Other chronic IHD</td>
<td>10.0 ± 10.1</td>
<td>76.1</td>
</tr>
<tr>
<td>Atherosclerosis</td>
<td>4.5 ± 8.4</td>
<td>46.7</td>
</tr>
<tr>
<td>Cardiac dysrhythmias</td>
<td>11.9 ± 9.6</td>
<td>67.4</td>
</tr>
<tr>
<td>General symptoms</td>
<td>12.5 ± 9.7</td>
<td>63.6</td>
</tr>
<tr>
<td>Heart failure</td>
<td>12.4 ± 8.8</td>
<td>64.7</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>9.5 ± 7.9</td>
<td>54.2</td>
</tr>
<tr>
<td>Other diseases of lung</td>
<td>12.2 ± 8.4</td>
<td>46.2</td>
</tr>
<tr>
<td>Abdomen/pelvis symptoms</td>
<td>11.7 ± 8.1</td>
<td>45.9</td>
</tr>
</tbody>
</table>

* Annual event rates are computed by summing all events over each patient’s observation period (12 months minimum). The total number of events is divided by the total number of months in the patient’s observation period and multiplied by 12.

ICD-9-CM=International Classification of Diseases, Ninth Revision Clinical Modification; IHD=ischemic heart disease; MI=myocardial infarction; PAD=peripheral arterial disease; TIA=transient ischemic attack.

Proportion of Patients Without an Event

Analysis Time (Months)

Note: The figure shows the Kaplan-Meier survival curve of patients remaining over time who were not hospitalized for stroke (CVA), myocardial infarction (MI), transient ischemic attack (TIA) or amputation; incident cases only displayed, N=24,075. Data was censored at the length of each patient’s postindex eligibility, with a maximum postindex period of 44 months (January 1, 2000, to August 31, 2003).

Atherosclerotic events, appearing frequently throughout the managed care population, with 49% of the hospitalization costs attributable to the outcomes of MI, stroke, TIA, or amputation. Thus, interventions resulting in reduced hospitalizations in this population can have significant PPPY cost impacts. Since PAD is an indicator of a disease process within the entire circulatory system, it is not surprising that leading reasons for hospitalization were respiratory-, cardiovascular-, or cerebrovascular-related.

The average time to first hospitalization was shortest for atherosclerotic events. However, that timing may be affected by those patients whose index event was a hospitalization with a PAD diagnosis. Limb amputation was uncommon (1.1%) in this cohort, resembling percentages seen in recent literature. Similarly, 39% of patients were receiving antihyperlipidemias, which assumes the remainder are able to meet their low-density lipoprotein cholesterol targets using diet alone. It seems reasonable to suggest that antplatelet, antihyperlipidemic, and antihypertensive medications can provide the possibility of decreasing hospitalizations by optimizing the number of patients taking appropriate pharmacotherapy. Future research may be directed at exploring relationships between appropriate pharmacotherapy and the frequency of hospitalization.

While PAD-attributable office visits, emergency department charges, and laboratory/diagnostic costs appeared low, PAD contribution to nonhospital health care resources may be reflected in utilization attributed to related cardiovascular morbidity and mortality. Similarly, 39% of patients were receiving antihyperlipidemias, which assumes the remainder are able to meet their low-density lipoprotein cholesterol targets using diet alone. It seems reasonable to suggest that antplatelet, antihyperlipidemic, and antihypertensive medications can provide the possibility of decreasing hospitalizations by optimizing the number of patients taking appropriate pharmacotherapy. Future research may be directed at exploring relationships between appropriate pharmacotherapy and the frequency of hospitalization.

The demographics of this managed care PAD cohort appeared reflective of prior studies, with 78% of sufferers older than 60 years, a mean age of 70 years, and a slightly higher prevalence in men (1.13% versus 1.04% in women). Prevalence may be understated in this study because of the use of diagnoses originating from claims and surrogate markers compared with other studies that base their epidemiology on...
The comorbidity profile of these patients, similar to data from other studies, indicates a high percentage of patients with cardiovascular and other comorbidities, particularly for hypertension and heart disease. The clinical picture represented by the coding of comorbid conditions is one of diffuse disease processes throughout the circulatory system. The high comorbidity with diseases like rheumatism and arthropathies, although typical of older patients, can result in impairing or discouraging physical activity and therefore may contribute to stasis-inspired worsening of cardiovascular symptoms.

**Limitations**

Foremost among the limitations of this study is the attribution of hospitalizations associated with primary or secondary diagnoses of MI, stroke, TIA, or amputation in the cost and event rate calculations for PAD. This method may have resulted in over-estimation of the costs and resource utilization attributed to PAD. However, this method was necessary for 2 reasons: (1) the principal diagnosis code (i.e., the reason for the hospitalization) is generally not going to be attributed to a PAD-related code such as 440.0 (atherosclerosis) or 443.9 (peripheral vascular disease) and (2) broad sequelae result from peripheral artery disease.
Second, PAD patients could have been included in this study on the basis of a single medical or hospital claim with a PAD primary or secondary diagnosis or a single pharmacy claim for either pentoxifylline or cilostazol. A more rigorous method to identify PAD patients would have required at least 2 medical claims with relevant diagnosis or procedure codes or at least 1 relevant medical claim and 1 relevant pharmacy claim (for pentoxifylline or cilostazol). On the other hand, prevalence rates may be underestimated since physicians do not consistently code claims specifically for PAD.

Despite the limitations of claims data to estimate resource utilization and costs related to PAD, our results compare favorably with the findings reported by Migliaccio-Walle et al. in their analysis of 16,440 Canadian patients with PAD compared with 15,590 reference patients with a diagnosis of MI. The average annualized postdiagnosis cost in the 5-year follow-up period was $CN 8,394 in 2002 currency (approximately $US 5,400 in 2002) compared with $CN 9,716 (approximately $US 6,300 in 2002) for the MI patients. The authors concluded that by the end of year 1, the health care resource burden for PAD is comparable with a diagnosis of MI.

**Conclusions**

The overall prevalence of PAD was 1.18% of the total MCO population of 6.67 million members. Over a mean postindex period of 25.2 months (median 23.4 months), the total mean annualized PAD-related cost was $5,955 PPPY in 2001-2003 dollars for 30,561 PAD patients. Hospitalizations accounted for the largest component of cost category, averaging $4,442 PPPY or 75% of the total annualized PAD-related cost per PAD patient. For a subgroup of 24,075 newly identified PAD patients, 8,479 (35.2%) were hospitalized during an average 25.2 months of follow-up with the mean time to first hospitalization of 8.9 months. Based upon mean annual health and member costs of only $313 PPPY for antihypertensives and $207 for lipid-lowering therapy, drug therapy in PAD patients may be underutilized.

**REFERENCES**


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**DISCLOSURES**

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Evaluation of Omalizumab From a Health Plan Perspective

PAUL P. BELLIVEAU, PharmD, and MONINA R. LAHOZ, PhD

ABSTRACT

OBJECTIVE: To review the pathophysiology of allergic asthma and information on the pharmacology, clinical efficacy, safety profile, and direct drug costs for omalizumab to provide a basis for a defined role of this agent in allergic asthma therapy in managed care organizations.

SUMMARY: Omalizumab is a monoclonal antibody targeting the high-affinity receptor binding site on human immunoglobulin E (IgE). When bound by omalizumab, IgE does not bind to basophils. As a result, degranulation is attenuated and allergic asthma symptoms are reduced. In asthma trials, omalizumab reduced inhaled corticosteroid and rescue medication requirements and improved asthma control and asthma quality of life in moderate-to-severe allergic asthmatics with disease poorly controlled by inhaled corticosteroids. Omalizumab has generally been well tolerated. However, injection site reactions occur in nearly 1 of every 2 patients, a problem that generally becomes less with continued dose administration. Severe injection site reactions are reported in 12% of patients. Other adverse events commonly reported in clinical trials include viral infections (23%), upper respiratory infections (20%), sinusitis (16%), headache (15%), and pharyngitis (11%). Because the acquisition cost of omalizumab is high (generally $15,000 to $44,000 per patient per year, before contractual discounts), its use is cost-prohibitive in all but the most severe, poorly controlled allergic asthmatic patients.

CONCLUSION: Although omalizumab has demonstrated efficacy and safety in adults and adolescents with uncontrolled moderate-to-severe allergic asthma, its use should be restricted to a narrowly defined population of allergic asthmatics who utilize large amounts of emergency health care resources to manage exacerbations. Experience with use of this drug beyond 52 weeks is lacking.

KEYWORDS: Omalizumab, RhuMab-E25, Anti-IgE, Allergic asthma

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Asthma is a condition that has a significant societal impact. It affects a substantial population of patients and imposes a burden in terms of treatment costs, productivity loss, and reduced quality of life. Although many medications are available for treatment of asthma, some focus only on symptom relief, others are nonspecific in their mechanism of action (and therefore produce substantial side effects), and none provides relief in all patients. Hence, there is a clear need for new interventions to improve the care of asthma patients.

Omalizumab (Xolair), a monoclonal anti-immunoglobulin E (IgE) antibody, provides clinicians with an additional option for treating allergy-induced asthma. This review will provide a cost analysis of omalizumab to assist health plans in their decisions regarding the utility of this drug in select patient populations. Additionally, to provide the reader with a better understanding of the potential role for this product, the pathophysiology of allergic asthma will be reviewed, and relevant information on the pharmacology, clinical efficacy, and safety profile for omalizumab will be presented.

Pathophysiology of Allergic Asthma

Although not all cases of asthma are clearly attributable to atopy (the genetic tendency to develop the allergic diseases), it is accepted that atopy can play an etiologic role in its pathophysiology. Researchers who have reviewed this literature to calculate the weighted mean-population-attributable risk suggest that approximately 40% of asthma cases can be attributed to atopy. Additionally, atopy is one of the strongest predisposing factors for the development of asthma.

Discussion of the pathophysiology of allergic asthma begins with exposure of an allergen to antigen-presenting cells (macrophages, dendritic cells) that engulf the allergen, process it, and display the peptide epitope of the allergen on its cell surface for presentation to T and B lymphocytes. This is followed by direct interactions between T and B lymphocytes, which initiate B lymphocyte activation and subsequent allergen-specific IgE production (Figure 1).

IgE binds to high-affinity receptors (FcεRI) on basophils and mast cells (basophil-like cells located in tissues). During subsequent antigen exposure, the antigen forms a link with multiple FcεRI-bound IgE molecules on basophils. This triggers degranulation of these cells, resulting in the release of preformed inflammatory mediators (histamine, tryptase) and the synthesis and release of newly generated mediators (prostaglandins, leukotrienes) and cytokines (tumor necrosis factor [TNF], interleukin [IL]-4, IL-5, IL-6). Released mediators initiate an early-phase response within minutes after allergen exposure. In the bronchial mucosa, this manifests as an asthma exacerbation.
Evaluation of Omalizumab From a Health Plan Perspective

Clinical Efficacy Trials
Omalizumab has been evaluated in randomized, placebo-controlled, double-blinded clinical trials involving adolescents and adults with moderate-to-severe persistent allergic asthma (Table 1).23-26 Two of these trials were identically structured. Omalizumab doses were administered subcutaneously and standardized so that patients received an approximate dose of at least 0.016 mg/kg per IU of IgE/mL every 4 weeks. Smaller doses of 150 mg or 300 mg were administered every 4 weeks; with larger monthly requirements, 225 mg, 300 mg, or 375 mg doses were administered every 2 weeks. Prior to enrollment, all inhaled steroid doses were converted to inhaled beclomethasone dipropionate (BDP) titrated to previous asthma control. In addition to the inclusion criteria listed in Table 1, patients needed to have residual asthma symptoms during the 2 weeks prior to randomization despite treatment with moderate-dose or high-dose inhaled corticosteroids (ICSs). Patients received 16 weeks of placebo or omalizumab in addition to their ICS therapy (steroid-stable phase). Therapies were then continued for another 12 weeks while ICS therapy was tapered (steroid-reduction phase).

These studies enrolled 1,071 patients; the average baseline forced-expiratory-volume-in-1-second (FEV1) measurement was approximately 70% of what was predicted.23,24 There was a significant reduction in exacerbation frequency among omalizumab recipients during the steroid-stable and steroid-reduction phases of both trials when compared with placebo recipients (Table 1). Among the secondary end points, statistically significant differences were observed in favor of omalizumab treatment with regard to asthma symptom scores, beta-agonist rescue therapy use at most weekly intervals, FEV1 measurements at most weekly intervals, and the number of patients experiencing an exacerbation. These differences were observed despite more successful ICS tapering among omalizumab recipients, with patients being maintained on lower ICS doses or without any ICS requirements. These differences persisted in a 24-week double-blind extension phase in which patients continued their study treatment and the lowest effective BDP dose.27,28

In 2 other trials, study inclusion criteria stipulated that only patients with baseline high-dose ICS requirements be enrolled, thus capturing a sample of patients considered to have severe persistent allergic asthma (based on the fact that they required high-dose ICS for symptom control).23,26 In a clinical trial structured similarly to those above (except that patients were converted to inhaled fluticasone at doses that provided disease control, the steroid-reduction phase was 16 weeks, and the primary end point was the percentage reduction in the fluticasone dose needed to maintain disease control), Holgate et al. enrolled 246 adult-adolescents with severe persistent allergic asthma (mean baseline FEV1 of 62.9% and 66% for omalizumab and placebo recipients, respectively).23 Although the number of exacerbation episodes per patient was similar in the omalizumab and placebo (mucosal edema, mucous production, bronchial smooth muscle spasm).6,12-14 Some mediators released during the acute-phase response act as chemoattractants and promote the infiltration of mucosal surfaces with eosinophils.13,15 With subsequent release of eosinophil and newly generated basophil products, a second wave of allergic symptoms can be observed over the 6 to 12 hours following the early-phase response.

Omalizumab Pharmacology
Omalizumab is a monoclonal antihuman IgE antibody. Omalizumab binds free human IgE with a binding affinity higher than that observed between IgE and FcεRI (Figure 1).16,17; it does not bind to basophils or to IgE that is already bound to FcεRI.9,17,18 These binding characteristics allow omalizumab to neutralize IgE-mediated responses without causing basophil degranulation that could occur if omalizumab bound to basophils or if omalizumab cross-linked with basophil-bound IgE.19 Omalizumab also promotes FcεRI down-regulation on basophils because of the close direct correlation between free serum IgE and the number of FcεRIs expressed on basophils.20,22 As a result of these actions, the amount of basophil-bound IgE is reduced.

Figure 1: Pathophysiology of Allergic Asthma and the Action of Omalizumab

Note: After allergen exposure, the antigen-presenting cells (APC) process the antigen for presentation to the T lymphocyte, prompting interactions between T lymphocytes and B lymphocytes that result in immunoglobulin E (IgE) production. IgE may bind for presentation to the T lymphocyte, prompting interactions between T lymphocytes and an allergic-asthma exacerbation. Omalizumab prevents the exacerbation by binding to IgE before it can bind to the basophil.
groups, there was a greater reduction in fluticasone requirements and rescue medication use for omalizumab recipients (Table 1). Asthma symptom scores among omalizumab recipients were either lower or no different than those of placebo recipients at each assessment point.

In the most recently published trial, Humbert et al. evaluated 419 patients with severe persistent allergic asthma (mean baseline FEV₁ 61% and 61.6% for omalizumab and placebo recipients, respectively), continuing asthma symptoms despite high-dose ICS, and a history of 2 exacerbations requiring systemic steroids or 1 exacerbation requiring hospitalization/emergency department (ED) care over the year prior to enrollment.²⁶ When added to the patient’s baseline asthma therapy (attempts to taper inhaled ICS were not driven by study protocol) for 28 weeks, the asthma exacerbation rate was significantly lower among omalizumab recipients (Table 1). Among secondary parameters evaluated, omalizumab recipients had statistically significant greater improvements (versus placebo) in their morning peak expiratory

### Table 1: Design and Primary Outcome Parameters for Omalizumab Clinical Studies

<table>
<thead>
<tr>
<th>Study Citation</th>
<th>Design</th>
<th>Inclusion</th>
<th>Patients*</th>
<th>Principal Outcomes†</th>
<th>Comment/Other Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soler et al.²³</td>
<td>R, P, DB 28 weeks</td>
<td>12-75 YOA IgE 30-700 IU/mL FEV₁ 40-80% + SPT (1 allergen)</td>
<td>274/272</td>
<td>Stable phase: 0.28 vs. 0.66 exacerbations per patient (P &lt;0.001); 58% reduction Reduction phase: 0.36 vs. 0.75 exacerbations per patient (P &lt;0.001); 52% reduction</td>
<td>Omalizumab: greater % reduction of ICS doses (P &lt;0.001); ICS discontinued in 43% (vs. 19% for placebo)</td>
</tr>
<tr>
<td>Buhl et al.²⁷</td>
<td>Extension of Soler et al. 24 weeks</td>
<td>As for Soler et al.</td>
<td>254/229</td>
<td>0.48 vs. 1.14 exacerbations per patient (P &lt;0.001); 58% reduction</td>
<td>Omalizumab: fewer patients with an exacerbation (24% vs. 40.6%, P &lt;0.001)</td>
</tr>
<tr>
<td>Busse et al.²⁴</td>
<td>R, P, DB 28 weeks</td>
<td>12-75 YOA IgE 30-700 IU/mL FEV₁ 40-80% + SPT (1 allergen)</td>
<td>268/257</td>
<td>Stable phase: 0.28 vs. 0.54 exacerbations per patient (P = 0.006); 48% reduction Reduction phase: 0.39 vs. 0.66 exacerbation per patient (P &lt;0.003); 41% reduction</td>
<td>Omalizumab: greater % reduction of ICS doses (75% vs. 50%, P &lt;0.001); ICS discontinued in 39.6% (vs. 19.1% for placebo, P &lt;0.001)</td>
</tr>
<tr>
<td>Lanier et al.²⁸</td>
<td>Extension of Busse et al. 24 weeks</td>
<td>As for Busse et al.</td>
<td>245/215</td>
<td>0.60 vs. 0.83 exacerbations per patient (P =0.023); 28% reduction</td>
<td>Omalizumab: fewer patients with an exacerbation (31.8% vs. 42.8%, P =0.015)</td>
</tr>
<tr>
<td>Holgate et al.²⁵</td>
<td>R, P, DB 32 weeks</td>
<td>12-75 YOA IgE 30-700 IU/mL + SPT (1 allergen)</td>
<td>126/120</td>
<td>57.2% vs. 43.3% lower ICS dose requirement at end of steroid-reduction phase (P =0.003)</td>
<td>Designed to demonstrate that omalizumab allows ICS dose reductions without loss of disease control</td>
</tr>
<tr>
<td>Humbert et al.²⁶</td>
<td>R, P, DB 28 weeks</td>
<td>12-75 YOA IgE 30-700 IU/mL + SPT (1 allergen)</td>
<td>209/210</td>
<td>0.68 vs. 0.91 exacerbations per patient (P = 0.042); 25% reduction</td>
<td>Omalizumab: fewer severe exacerbations, (0.24 vs. 0.48 per patient, P =0.002) and fewer acute care visits (24% vs. 43%, P =0.038)</td>
</tr>
<tr>
<td>Ayres et al.²⁹</td>
<td>R, O, PG 52 weeks</td>
<td>12-75 YOA IgE 30-700 IU/mL + SPT (2 allergens)</td>
<td>206/106</td>
<td>Omalizumab recipients experienced 4.84 fewer ADRIs/patient year; 49.6% (95% CI: 27.8-64.8%) reduction compared with BSC</td>
<td>Omalizumab: more patients ADRI-free (36.1% vs. 20.2%); fewer with multiple ADRIs (40.8% vs. 66.3%, P =0.001)</td>
</tr>
</tbody>
</table>

*Omalizumab recipients/placebo recipients.
†Results of omalizumab recipients versus results of placebo recipients (or best standard care for Ayres et al.); stable refers to steroid-stable phase, and reduction refers to the steroid-reduction phase of the trials.
ADRL=asthma-related deterioration incidents; BSC=best standard care; DB=double-blind; FEV₁=forced expiratory volume in 1 second; ICS=inhaled corticosteroid; O=open-label; P=placebo-controlled; PG=parallel group; R=randomized; SPT=skin-prick test; YOA=years of age.
flow (PEF) readings, FEV\textsubscript{1} measurements, and asthma symptom scores. Additionally, omalizumab recipients experienced a significantly lower rate of severe exacerbations (PEF <60% of personal best, requiring systemic corticosteroids) and total acute care visit requirements (doctor visits, ED care, hospitalization). Based on their findings, the investigators reported that 3 patients needed to be treated for 1 year with omalizumab to avoid 1 severe exacerbation.

To better evaluate omalizumab utility in real-life clinical practice, Ayres et al., in a multicenter, open-labeled study, randomized 312 poorly controlled (defined as at least 1 ED visit or hospitalization or at least 1 course of oral corticosteroids for asthma over the prior year) adult and adolescent patients with moderate-to-severe persistent allergic asthma, to best standard care (BSC) plus omalizumab or BSC only.\textsuperscript{29} The model for BSC was the guideline published by the National Heart, Lung, and Blood Institute.\textsuperscript{30} Over 12 months, omalizumab recipients experienced fewer asthma-deterioration-related incidents per patient day (ADRs), defined as 2 or more lost work/school days, the need for an unscheduled physician or hospitalization/ED visit, or the need for treatment with systemic corticosteroids or antibiotics due to asthma (Table 1). Additionally, more omalizumab recipients remained ADRI-free and fewer experienced multiple ADRs. There were also differences in types of ADRs, with a smaller percentage of omalizumab recipients requiring systemic corticosteroids (51.8% vs. 65.2%, \textit{P} = 0.037), an unscheduled physician visit (33.5% vs. 50.6%, \textit{P} = 0.007), or >2 days time off from work or school (43.5% vs. 57.3%, \textit{P} = 0.031). Statistically significant differences in favor of omalizumab were observed in the measurements of rescue medication use, morning FEV\textsubscript{1} measurements, asthma symptoms scores, and mean daily ICS requirements.

### Asthma-Related Quality of Life and Perceptions of Treatment Efficacy

Because conventional clinical measures of asthma are not complete descriptions of the functional impairments or improvements experienced in clinical trials,\textsuperscript{31} investigators also included measures of quality-of-life and treatment-efficacy perceptions. Quality of life was evaluated via a validated Asthma Quality of Life (AQoL) Questionnaire.\textsuperscript{32,33} Impressions of therapy effectiveness were evaluated by asking patients and investigators to rate treatment efficacy as excellent, good, moderate, poor, or worse.

In the trials reported by Soler et al. and Busse et al., overall AQoL scores among omalizumab recipients showed significantly greater improvement (relative to baseline) during all 3 treatment phases. Additionally, in each phase, a significantly greater proportion of patients experienced a clinically relevant change in their overall AQoL score; a significantly greater proportion also experienced a large improvement (quantitatively greater than a clinically relevant change).\textsuperscript{34,35} Similar improvements were reported in the trials evaluating patients with severe persistent allergic asthma.\textsuperscript{23,26}

Patients’ and investigators’ impressions of therapy effectiveness were consistent with AQoL evaluations, lending validity to this simple assessment method. With assessments performed at the end of the steroid-reduction phases, ratings by patients and investigators were more likely to be good or excellent for the omalizumab recipients. The percentage of patients indicating that response was good or excellent among omalizumab and placebo recipients, respectively, was: Soler et al., 70% versus 40%, \textit{P} <0.001; Busse et al., 60.6% versus 38.1%, \textit{P} <0.001\textsuperscript{24,35}; Humbert et al., 64.3% versus 43.3%, \textit{P} <0.001.\textsuperscript{28} Investigator responses were similar to those of patients.

### Secondary Analyses of Clinical Trial Data

Bousquet and colleagues pooled data from 7 adult/adolescent trials of allergic asthma (5 discussed in this text,\textsuperscript{23-29} 1 not included here because it enrolled patients with concomitant allergic asthma and perennial allergic rhinitis, and 1 currently unpublished) to assess the effect of omalizumab treatment on exacerbations in patients with severe persistent allergic asthma.\textsuperscript{36} Asthma severity was based on the Global Initiative for Asthma guidelines, which categorize severity based on clinical features and the intensity of the therapy required for symptom control.\textsuperscript{37} This pooled analysis of 4,308 patients showed a lower rate of exacerbations for omalizumab recipients (0.91 vs. 1.47 exacerbations per year, \textit{P} <0.001; 38% reduction). Additionally, omalizumab recipients had rates of hospitalization that were 52% lower (\textit{P} = 0.041), ED visits that were 61% lower (\textit{P} = 0.013), and unscheduled doctor visits that were 43% lower (\textit{P} <0.001). Although the number needed to treat is not reported by the investigators, there are sufficient data to calculate such values. Approximately 6 patients would have to be treated for 1 year to avoid 1 unscheduled doctor visit, 25 would have to be treated for 1 year to avoid 1 ED visit, and 32 would have to be treated for 1 year to avoid 1 hospital admission.

In another publication, Bousquet and colleagues pooled data from 2 of the adult/adolescent clinical trials of allergic asthma to identify the baseline patient characteristics that are predictive of response to omalizumab.\textsuperscript{38} Logistic regression analysis of the data from the steroid-stable phase of these trials revealed that the following characteristics were predictive of response: a history of emergency asthma treatment in the prior year, a baseline requirement for high doses (>800 mcg/d) of inhaled BDP, and a baseline FEV\textsubscript{1} of <65% of predicted (odds ratio for response with all 3 factors present was 4.20, 95% CI: 1.69-10.45). Baseline IgE concentrations were not predictive of response. Among patients showing a response to omalizumab at 16 weeks (the end of the steroid-stable phase), 61% had responded by 4 weeks, and 87% had responded by 12 weeks of therapy.

With the data from the steroid-stable phases of 3 adult-adolescent trials of allergic asthma,\textsuperscript{23-25} Holgate et al. performed
a meta-analysis to evaluate the impact of omalizumab on an annualized rate of all asthma exacerbation episodes (AEEs) and significant AEEs (sAEEs, an exacerbation requiring doubling of the ICS dose or use of systemic steroids) among patients who were at high risk of serious asthma-related morbidity and mortality. The investigators defined this population as those patients who had ever been intubated or who, within the year prior to enrollment, had visited an ED, required an overnight hospitalization, or needed intensive care unit admission for an asthma exacerbation. The rate of AEEs and sAEEs was lower with omalizumab treatment relative to placebo (rates were 53% and 55% lower, respectively; \( P < 0.001 \)). The absolute difference (in favor of omalizumab) in sAEE rates increased dramatically with baseline FEV\(_1\) severity. Differences in the risk of sAEEs translated into the need to treat 5 patients with omalizumab to maintain 1 patient free of sAEEs for the period of study (average of 41.7 weeks for the 3 studies).

### Safety and Tolerability

In the omalizumab package insert, the descriptions of reported adverse events and those considered to be drug related in allergic asthma trials indicate that such events have occurred with similar frequency in omalizumab and placebo (injection) recipients. Most reactions were mild to moderate in severity. The most commonly reported adverse events with omalizumab therapy were injection-site reactions (45%), viral infections (23%), upper respiratory infections (20%), sinusitis (16%), headache (15%), and pharyngitis (11%). Injection-site reactions of any severity occurred in 45% of omalizumab recipients and 43% of placebo recipients. Reactions included bruising, redness, warmth, burning, stinging, itching, hive formation, pain, induration, mass formation, and inflammation. Most of these reactions occurred within 1 hour of injection, resolved within 8 days, and generally decreased in frequency with subsequent dosing. Severe injection-site reactions were reported in 12% of omalizumab and 9% of placebo recipients. The package insert provides neither a description of “severe injection-site reaction” nor data on the percentage of patients who stopped therapy due to such reactions.

Although 1 group of investigators has reported a greater frequency of headache (17.5% vs. 5.7%), cough (7.8% vs. 1.9%), and nausea (6.8% vs. 0.9%) with omalizumab therapy,\(^{20}\) in the published reports of the adult-adolescent allergic asthma trials, there was typically little difference between omalizumab and placebo recipients with regard to adverse-event reporting. The types of events reported are consistent with the product package insert.\(^{23,24}\) Local injection-site reactions were associated with 8.6% to 20.4% of omalizumab injections and 6.5% to 10.3% of placebo injections.\(^{23,25,27}\) In the trial by Soler et al.,\(^{23}\) bruising was the most common reaction reported by both omalizumab and placebo recipients; redness, warmth, and itching were more common among omalizumab recipients.\(^{23}\)

In studies that include descriptions of laboratory monitoring with omalizumab treatment, clinically significant changes in such values have not been observed.\(^{23,26,27}\) Although early animal studies raised concerns about omalizumab-induced thrombocytopenia, the product manufacturer reports that clinical trials have not revealed cases of sustained thrombocytopenia in patients with normal baseline platelet counts (data on file, Genentech, Inc.). Additionally, in a recent report of an open-labeled safety trial of 864 patients with moderate-to-severe asthma, platelet counts of <100,000/mm\(^3\) occurred in 4.8% of omalizumab recipients and 5.7% of control patients (standard therapy group); a 50% drop was observed in 0.86% and 0.71%, respectively.\(^{26}\) None of the patients had platelet counts of <75,000/mm\(^3\), all reductions were isolated and transient, and there were no reports of bleeding. Despite the early concerns with thrombocytopenia, there are no warnings, black-box messages, or contraindications in the product package insert that suggest that baseline platelet counts must be evaluated prior to initiating therapy with omalizumab.

According to the product package insert, anaphylaxis was reported in 3 patients (incidence of <0.1%). These reactions occurred within 2 hours of a first or subsequent omalizumab dose. Symptoms included urticaria and throat and/or tongue edema. Respiratory failure was not observed, and all patients survived.\(^{40}\) Although urticaria is described in patients involved in the discussed clinical trials, it was not described as a common adverse event.\(^{23,24,26}\) These reactions were typically mild or moderate in severity and usually resolved quickly with therapy discontinuation or despite continued therapy; the incidence of urticaria has been similar in omalizumab and placebo recipients.

In clinical trials of omalizumab, several investigators included analysis of the development of antiomalizumab antibodies. Such antibodies were not detected in any of these trials.\(^{23,24,27,28}\) In the product package insert, it is reported that low titers of antiomalizumab antibodies have been detected in 1 of 1,723 treated patients.\(^{40}\) Although omalizumab administration results in immune complex formation, investigators have not observed evidence of reactions that would be considered manifestations of complex precipitation or complement activation.\(^{27,28}\)

Among the warnings in the product package insert is mention of malignant neoplasms.\(^{29}\) Malignancies were observed in 20 of 4,127 (0.5%) omalizumab recipients and 5 of 2,236 (0.2%) placebo recipients involved in clinical studies. In 18 of these patients, the events occurred within 12 months of therapy initiation; approximately 60% were within 6 months. Several patients had a history of cancers, premalignant conditions, or other risk factors for development of a malignancy. Although it is hypothesized that the immune systems of atopic persons may be better able to identify and reject clones of malignant cells, a link between IgE and cancer has not been established.\(^{43,44}\) Nevertheless, since the majority of patients in clinical trials have had no more than a year’s exposure to omalizumab, the risk for
malignancy with more prolonged treatment needs to be studied, particularly in individuals who may be at higher risk for malignancies.

Cost Analysis

Asthma Prevalence and Severity

In the 2003 National Health Interview Survey of persons aged 18 years or older, an estimated 9.7% (20.6 million) reported that they have been diagnosed with asthma during their lifetime and 6.4% (13.6 million) reported that they still have asthma. Among children younger than 18 years, an estimated 12.5% (9 million) have had asthma diagnosed at some time in their lives, with the percentage increasing as age increases. Almost 6% of those surveyed (4 million) reported having had an asthma attack in the 12 months preceding the survey. Among U.S. high school students (grades 9 to 12) who participated in the 2003 National Youth Risk Behavior Survey, 18.9% have been diagnosed with asthma at some time in their lives; 16.1% reported that they still had a diagnosis of asthma.

The 1998 Asthma in America Survey reported that the percentage of patients reporting symptoms consistent with mild, moderate, and severe persistent asthma was 39.8%, 22.1%, and 19.1%, respectively, and 19.1% reported symptoms consistent with mild intermittent disease. In a more recent survey of pediatric asthmatics, the percentage of parents reporting that their child had symptoms consistent with mild, moderate, and severe persistent asthma over the 4 weeks prior to the interview was 14% in each category. The remainder of the respondents (58%) said their child had mild intermittent asthma.

Costs of Asthma

Recent economic analyses indicate that direct medical costs, particularly hospitalizations and medications, currently account for the largest component of asthma-related costs in the United States. Using data from surveys conducted by the National Center for Health Statistics, Weiss and colleagues examined the changes in asthma costs during the 10-year period from 1985 through 1994. The total cost of asthma was $10.7 billion in 1994, a figure that was more than twice the estimated cost of asthma (nearly $4.5 billion) 10 years earlier in 1984. This represented a 54.1% increase after adjustment to 1994 dollars. Direct medical costs (including charges for hospital inpatient and outpatient services, ED services, physician services, and medications) amounted to $6.10 billion in 1994 (56.8% of the total costs), an increase of 22.6% during the 10-year period. In 1985, hospital inpatient care represented the largest direct medical component cost (44.6% of total direct costs). In 1994, the largest component cost of asthma was medications ($2.45 billion, 40.1% of total direct costs), followed by hospital inpatient care ($1.80 billion, 29.5% of total direct costs). The authors indicated that these observed trends were the result of a decrease in length of hospital stay (rather than a decrease in hospitalizations) and an increase in both the total number of prescribed medications and the average unit cost per medication. Indirect costs (including the value of time lost from school and work, and mortality as measured by lifetime earnings) of asthma in 1994 were estimated at $4.6 billion (43.2% of the total costs). The largest component of indirect cost in 1994 was loss of work, which was estimated at $2.07 billion (44.6% of indirect costs). Table 2 presents the distribution of asthma costs in 1985 and 1994.

Cisternas and colleagues conducted a comprehensive study of the direct and indirect costs of adult asthma using data derived from a group of community physicians treating 401 adult asthma sufferers in the northern California area. In this study, annual asthma costs averaged $4,912 per person. Direct medical and nonmedical costs accounted for 64.8% of these costs. Fifty percent of direct total costs were ascribed to pharmaceuticals and only 14.6% to hospitalizations. Indirect costs (including wage losses associated with work disability and other productivity losses attributed to asthma disability in persons who did not work outside of home) accounted for 35.2% of total costs. Almost all of the indirect costs were attributed to work/productivity losses.

Asthma Severity and Health Care Resource Utilization

In 2002, asthma accounted for 12.7 million doctor visits, 1.2 million hospital outpatient visits, 1.9 million ED visits, and 484,000 hospitalizations. Of these numbers, children aged 0 to 17 years had 5 million doctor visits, 727,000 ED visits, and 196,000 hospitalizations. A disproportionate amount of these health care resources is utilized by a relatively small cohort of patients with difficult-to-treat asthma. Some investigators have reported that as much as 80% of direct asthma costs are consumed by less than 20% of asthma patients (defined as

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**Table 2: Distribution of Asthma Costs**

<table>
<thead>
<tr>
<th>Cost Category</th>
<th>1985 ($)</th>
<th>1994 ($)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cost ($ billions)</td>
<td>~4.5</td>
<td>~10.7</td>
</tr>
<tr>
<td>Direct costs†</td>
<td>53.2%</td>
<td>56.8%</td>
</tr>
<tr>
<td>Medications‡</td>
<td>30%</td>
<td>40.1%</td>
</tr>
<tr>
<td>Hospital inpatient care‡</td>
<td>44.6%</td>
<td>29.9%</td>
</tr>
<tr>
<td>Physician services‡</td>
<td>11.6%</td>
<td>12.2%</td>
</tr>
<tr>
<td>Hospital outpatient care†</td>
<td>5.4%</td>
<td>10.4%</td>
</tr>
<tr>
<td>Emergency department care‡</td>
<td>8.4%</td>
<td>7.8%</td>
</tr>
<tr>
<td>Indirect costs†</td>
<td>46.8%</td>
<td>43.2%</td>
</tr>
<tr>
<td>Work lost§</td>
<td>33%</td>
<td>44.6%</td>
</tr>
</tbody>
</table>

* Expressed in 1985 dollars; the 1994 equivalent was estimated to be approximately $7 billion.
† Expressed as a percentage of total cost.
‡ Expressed as a percentage of direct costs.
§ Expressed as a percentage of indirect costs.
Evaluation of Omalizumab From a Health Plan Perspective

### TABLE 3  Annual Drug Cost for Omalizumab*†

<table>
<thead>
<tr>
<th>Dose Regimen</th>
<th>Vials per Dose</th>
<th>Injections per Dose†</th>
<th>Drug Cost ($)</th>
</tr>
</thead>
<tbody>
<tr>
<td>150 mg every 4 weeks</td>
<td>1</td>
<td>1</td>
<td>7,388</td>
</tr>
<tr>
<td>200 mg every 4 weeks</td>
<td>2</td>
<td>2</td>
<td>14,776</td>
</tr>
<tr>
<td>225 mg every 2 weeks</td>
<td>2</td>
<td>2</td>
<td>29,552</td>
</tr>
<tr>
<td>300 mg every 2 weeks</td>
<td>2</td>
<td>2</td>
<td>29,552</td>
</tr>
<tr>
<td>375 mg every 2 weeks</td>
<td>3</td>
<td>3</td>
<td>44,328</td>
</tr>
</tbody>
</table>

* Based on average wholesale price (2005) of $568.31 per 150 mg in a 1.2 mL vial (from reference 58). Also available in a 0.6 mL, 75 mg vial.
† Dose requirements for the majority of patients will likely be ≥150 mg every 4 weeks since this regimen is used only for patients who are ≤90 kg and have serum IgE levels at the lowest end of the range (30-100 IU/mL). In clinical trials of omalizumab, the mean serum IgE concentrations were 167-267 IU/mL.23-26 Therefore, an average omalizumab dose may be 300 mg every 4 weeks or 225 mg every 2 weeks, depending on the patient’s body weight. Administration is for single use only; any remaining unused product is discarded.

“high-cost patients”).55 The estimated annual cost per high-cost patient was $2,584 compared with $140 for other patients with asthma.55 As highlighted by the Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (TENOR) study, these high-cost patients require a greater number of ED visits, hospitalizations, medications, and office/clinic visits.56 Cisternas and colleagues found significant differences in total per-person direct annual costs among asthma patients with varying self-reported severities of disease. The direct annual average costs (adjusted to 1998 dollars) for patients whose disease was categorized as mild, moderate, or severe were $2,646, $4,530, and $12,813, respectively.57 Disease severity also had an impact on specific components of expenses. Hospital admissions comprised 4%, 5%, and 17% of total direct annual costs, and medication costs comprised 47%, 39%, and 19% of total direct annual costs for persons with mild, moderate, and severe asthma, respectively. In a more recent investigation utilizing an independent expert panel of physicians to assess asthma severity, Godard et al. also reported significant differences in direct treatment costs of asthmatic patients, with greater costs being observed in patients with more severe disease.58

Improvements in the management of the most severe asthmatics could have a substantial impact on asthma care costs. Cisternas and colleagues concluded that a 5% shift of patients from a severe to a moderate asthma classification would save approximately $1.4 billion annually.59 As suggested by the inverse relationship between the direct costs of hospitalizations and medications reported by Cisternas and colleagues, adequately managed asthma is likely to reduce hospitalizations.50-57 With improved medication management, medication costs will likely increase, but the cost associated with hospitalization will likely decrease.

### Resource Use and Costs for Omalizumab Treatment: A Health Plan’s Perspective

#### Drug Product Costs

According to package insert dosing guidelines, omalizumab is administered only by subcutaneous injection.60 Doses are standardized so that patients receive an approximate dose of at least 0.016 mg/kg per IU of IgE/mL every 4 weeks. Smaller doses of 150 mg or 300 mg are administered every 4 weeks; with larger dose requirements (225 mg, 300 mg, or 375 mg every 4 weeks), doses are divided and administered every 2 weeks. Because of the viscosity of the product, doses greater than 150 mg must be administered as separate injections. The 2005 average wholesale price for one 150-mg single-dose vial of omalizumab is $568.31.61 As shown in Table 3, the lowest dose regimen (one 150-mg vial every 4 weeks) will cost $7,388 per year ($616 per month), while the largest dose regimen (375 mg, or 3 vials, every 2 weeks) will cost $44,328 per year ($3,694 per month). Dose requirements for the majority of patients will be likely be ≥150 mg every 4 weeks since this regimen is used only for patients who are ≤90 kg and have serum IgE levels at the lowest end of the range (30-100 IU/mL). In clinical trials of omalizumab, the mean serum IgE concentrations were 167-267 IU/mL.23-26 Therefore, an average omalizumab dose may be 300 mg every 4 weeks or 225 mg every 2 weeks, depending on the patient’s body weight.

#### Drug Acquisition, Preparation, and Administration-related Costs

Omalizumab distribution is restricted through a group of 5 specialty pharmacies, which can assist health care providers and patients with assessing insurance coverage and pursuing appropriate reimbursement authorization (i.e., obtaining prior approval). In order for specialty pharmacies to seek prior authorization from payers, the following information is requested: patient weight; International Classification of Diseases, Ninth Revision, (ICD-9) codes; current asthma therapies; documentation of a positive skin or radioallergosorbent test to a perennial allergen; a statement of medical justification for omalizumab treatment; and a pretreatment IgE serum level (see http://www.xolair.com/hcp/hcp_home.jsp). Although the health care provider can obtain payer approval themselves, the drug would still need to be obtained through one of the specialty pharmacies. Under this circumstance, however, providers would need to forward prior authorization documentation to the specialty pharmacy or purchase the drug and bill the payer themselves. The drug may be shipped to the provider or directly to the patient. The time spent in this drug acquisition process is a factor to consider when the total cost of therapy is being evaluated.
TABLE 4  Ancillary Cost Considerations for Acquisition and Administration of Omalizumab

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Measuring a patient’s serum total IgE (IU/mL) before the start of treatment.</td>
</tr>
<tr>
<td>2.</td>
<td>Preparing paperwork necessary for drug acquisition.</td>
</tr>
</tbody>
</table>
| 3. | Reconstituting/preparing the lyophilized product (for each 150 mg vial):  
|   | • 15 to 20 minutes; the vial has to be shaken for 5 to 10 seconds approximately every 5 minutes to dissolve the solid particles; reconstituted product must be used within 4 to 8 hours, depending upon storage conditions. |
| 4. | Injecting the product subcutaneously (no more than 150 mg injected per site) . |
| 5. | Observing the patient after subcutaneous injection for 1 to 2 hours for possible severe hypersensitivity reactions including anaphylaxis:  
|   | • medications (e.g., diphenhydramine, hydroxyzine, epinephrine) for the treatment of severe hypersensitivity reactions. |
| 6. | Health care professional fees to perform the above tasks. |
| 7. | Patient and family costs associated with time and travel every 2 to 4 weeks. |
|   | * It’s likely that a majority of patients will require doses >150 mg since the regimen of 150 mg every 4 weeks is used only for patients who are ≤90 kg and have serum IgE levels at the lowest end of the range (30-100 IU/mL). |

Doses and dosing frequency of omalizumab are based on patient weight and baseline serum IgE levels. Measuring a serum total IgE level (IU/mL) before the start of treatment adds to the total costs of therapy. Since the single-use product vials contain no preservatives, the solution must be administered within 4 to 8 hours of reconstitution, depending on storage conditions. This requires additional planning on the part of the provider. As the lyophilized product takes approximately 15 to 20 minutes to dissolve, the patient must typically arrive at least 30 minutes before drug administration. Because of the product’s cost, the patient’s arrival is likely to be used as the trigger for the drug preparation and reconstitution process so as to prevent unnecessary waste. It is recommended that the patient also stay 1 to 2 hours after subcutaneous injection and be observed for possible severe hypersensitivity reactions, including anaphylaxis. Table 4 shows some of the ancillary cost considerations associated with omalizumab prescribing and administration.

Although providers may wish to coordinate injections for multiple patients to avoid drug waste, there is currently no literature describing such an effort. Additionally, this practice may be hampered by the intricate acquisition process, the short time window between reconstitution and injection, and the fact that many providers may not have a sufficient volume of patients receiving this product.

Cost-effectiveness of Omalizumab

Health care plans and pharmacy benefit managers will have to evaluate how and where omalizumab fits in drug formularies and policies regarding restricted access. Because of product cost, omalizumab will likely be placed in a “restricted use” category, where prior authorization is needed to dispense omalizumab to patients who meet specific criteria (Table 5).

With appropriate screening for those severe, high-cost asthma patients who are most likely to benefit, use of this product could result in a reduction in the cost of care for patients who utilize large amounts of resources, particularly those who require frequent hospitalizations, ED visits, and physician visits. To address this issue, a health plan would review the disease demographics of its enrollees. In particular, a health plan would need to know the number of asthmatics it serves and determine the distribution of disease severity of these enrollees. Additionally, it could review the amounts spent on the most severe, highest-cost allergic asthmatics who have incurred expenses perhaps because of poorly controlled disease. Expenditures for these patients would then be compared with what it would cost to pay for omalizumab in such patients. The plan could determine if the anticipated reduction in resource utilization (e.g., fewer hospital admissions, reductions in ED use and outpatient visits) of patients receiving omalizumab would sufficiently offset the costs associated with product acquisition, preparation, and administration, including the incurred costs from adverse events associated with drug administration.

Omalizumab was approved by the U.S. Food and Drug Administration in 2003, and from the outset there have been concerns regarding the cost-effectiveness of omalizumab because of its high acquisition cost. One economic analysis has shown that it may not be cost effective to administer omalizumab to any patient who is not a high-end asthma resource consumer. Oba and Salzman, utilizing a third-party-payer’s perspective, performed a retrospective economic analysis to evaluate the cost-effectiveness of omalizumab. These investigators used the 52-week data from 2 of the previously discussed randomized clinical trials in adults and adolescents with moderate-to-severe allergic asthma. Direct costs were considered (including unscheduled physician office visits, hospitalizations, ED visits, treatment costs for drug-related adverse events, and asthma medication treatment costs). All costs were reported in 2003 dollars; at the time of analysis, the wholesale acquisition cost for omalizumab was $433 for one 150 mg vial. The authors estimated that the average daily treatment cost for patients treated with omalizumab was $39.85 per patient compared with $2.08 for patients receiving placebo injections, with the significant difference between the 2 treatments due primarily to drug product cost. The average daily cost associated with utilization of other health care resources was $0.08 and $0.36 per patient for the omalizumab and placebo recipients, respectively. The cost of gaining 1 additional successfully controlled day with the use of omalizumab was $523. In the opinion of the authors, omalizumab use could result in cost savings only if used in the patient who is hospitalized at least 5 times or 20 days per year or requires at least
7 monthly ED visits for treatment of asthma-related events. Hence, these and other authors recommend that its use be restricted for moderate-to-severe allergic asthma in patients who are suboptimally controlled and require regular use of intensive health care resources for management of exacerbations.6,52,61-63 Although other authors have questioned the validity of the outcome measures utilized by Oba and Salzman, even such critics agree that omalizumab use is cost prohibitive in most patients. Miller and Reeves calculated an incremental cost-effectiveness ratio of $88,837 to prevent 1 unscheduled office visit for omalizumab versus placebo, $577,812 to prevent 1 hospitalization, or $755,600 to prevent 1 ED visit.64

### Conclusion

Omalizumab is a subcutaneously administered monoclonal anti-IgE antibody that reduces free IgE concentrations and promotes down-regulation of IgE receptors on basophils. In patients with allergic asthma poorly controlled with inhaled steroids, omalizumab improves asthma symptom control and allows patients to be managed with lower inhaled steroid doses. Omalizumab has been well tolerated in clinical trials that have extended as long as 52 weeks. Almost half of patients experience injection-site reactions with omalizumab, and while these tend to decrease in frequency with subsequent dose administration, severe injection-site reactions occur in approximately 1 in 8 patients. Because omalizumab is much more expensive than standard asthma therapies, its use needs to be restricted to the most severe, poorly controlled allergic asthmatics who require frequent use of emergency care for exacerbations.

### DISCLOSURES

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principal author of the study. Study concept and design, data collection, and analysis and interpretation of data were contributed primarily by Belliveau, with input from author Monina R. Lahoz. Drafting of the manuscript was primarily the work of Belliveau, and its critical revision was the work of both authors.

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Evaluation of Omalizumab From a Health Plan Perspective


Product-Line Extensions and Pricing Strategies of Brand-Name Drugs Facing Patent Expiration

SONG HEE HONG, PhD; MARVIN D. SHEPHERD, PhD; DAVID SCOONES, PhD; and THOMAS T.H. WAN, PhD

ABSTRACT

OBJECTIVE: This study proposed an alternative to brand loyalty as the explanation for the continued price rigidity of patent-expired brand-name prescription drugs despite the increase in market entry of generic drugs facilitated by the 1984 Drug Price Competition and Patent Term Restoration Act. Study hypotheses were to test (1) whether market entries of new-product extensions are associated with market success of original brand-name drugs before generic drug entry, and (2) whether original brand-name drugs exhibit price rigidity to generic entry only when they are extended.

METHODS: The design is a retrospective follow-up study for the prescription drug brands that lost their patents between 1987 and 1992. Drug brands were limited to nonantibiotics, orally administered drugs containing only 1 active pharmaceutical ingredient. Information on patent expiration, entry of a product extension, and market success were determined from the U.S. Food and Drug Administration's Orange Book, First DataBank, and American Druggist, respectively. Market success was defined as whether an original drug brand was listed in the top 100 prescriptions most frequently dispensed before facing generic entry. Product-line extension was defined as the appearance of another product that a company introduces within the same market after its existing product. Drug prices were average wholesale prices from the Drug Topics Red Book. The relationship between product-line extension and market success was examined using a logistic regression analysis. The price rigidity to entry was tested using a panel regression analysis.

RESULTS: A total of 27 drug brands lost their patents between 1987 and 1992. Drug brands that achieved market success were 16 times more likely to be extended than were those that did not (OR = 16.95%, confidence interval, 2.12-12.60). The price rigidity to entry existed in drug brands with extensions ($\beta = 2.65\%$, $P < 0.003$), but not in those brands without extensions ($\beta = -2.40\%$, $P < 0.001$).

CONCLUSION: This study provided some support for the alternative explanation to brand loyalty that a new product-line extension introduced for an original brand helps the original price to be rigid despite the entry of generic drugs facilitated by the 1984 Drug Price Competition and Patent Term Restoration Act.

Keywords: Brand-name prescription drugs, Generic drug competition, Price rigidity to entry, Line extension

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Authors

SONG HEE HONG, PhD, is an assistant professor, Division of Pharmaceutical Evaluation and Policy, University of Arkansas for Medical Sciences, Little Rock; MARVIN D. SHEPHERD, PhD, is a professor, Department of Pharmacy Administration, University of Texas at Austin; DAVID SCOONES, PhD, is an associate professor, Department of Economics, University of Victoria, British Columbia, Canada; THOMAS T.H. WAN, PhD, is a professor, College of Health and Public Affairs, University of Central Florida, Orlando.

AUTHOR CORRESPONDENCE: Song Hee Hong, Ph.D., Assistant Professor, Division of Pharmaceutical Evaluation and Policy, University of Arkansas for Medical Sciences, 4301 W. Markham St., Slot 422-4, Little Rock, AR 72205. Tel: (501) 686-6298; Fax: (501) 296-1168. E-mail: hongsonghe@uams.edu

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In recent years, expenditures on prescription drugs rose more rapidly than any other component of health care. In 2001, the cost of prescription drugs was 15.7% higher than in 2000. In addition, prescription drug costs now represent a larger percentage of the total health care costs. In 2002, national retail spending on prescription drugs comprised roughly 10.5% of total spending on health care, an 81% increase from 5.8% of total spending in 1993.

The Kaiser Family Foundation attributed 42% of the spending increase experienced from 1997 to 2002 to increased utilization, 34% to shifts in the mix of drugs used (from older, less-expensive drugs to newer, higher-cost drugs), and 25% to price inflation of existing drugs. Shifting customers to newer, higher-cost drugs is controversial because newer drugs are not always innovative. In fact, only 15% of the 1,035 new drugs approved by the U.S. Food and Drug Administration (FDA) from 1989 through 2000 were innovative drugs.

The pricing strategy of brand-name drugs going off patent is equally controversial. Historically, brand-name drugs have been able to maintain high prices even after patent expiration. Prior to 1984, the price rigidity of the patent-expired brand-name drugs was explained by barriers to entry. According to the 1962 Kefauver-Harris Drug Amendments, both pioneer drugs and their generic versions had to document proof of drug safety and efficacy; as a result, few generic drugs were able to enter the market.

In the wake of public outcry over high drug prices and rising drug expenditures, the 1984 Drug Price Competition and Patent Term Restoration Act was enacted to pave the way for easier market entry for generic drugs. The act created the vehicle of an Abbreviated New Drug Approval (ANDA) to reduce the burden of proof of drug safety and efficacy for generic drugs. An ANDA requires only that a generic drug demonstrate bioequivalence to a drug already approved.

Since generic drugs are very similar to formulations already approved, this reduction of regulatory barriers to entry should have promoted price rivalry with little threat to consumer safety. However, although the number of generic entries has increased, empirical studies report no evidence of such price rivalry; rather, price increases of brand-name drugs were maintained or, in some cases, went up upon expiration of their patent. For example, the average rate of price increases for the 18 products that faced generic competition from 1983 to 1987 was 8.4% per year before the generic drug entry; however, in the postentry period, only 2 of the 18 products experienced a statistically significant moderation in the rate of price increase. This price rigidity of patent-expired brand-name drugs is well recognized,
but the phenomenon has puzzled economists and policy makers who had expected price rivalry from the eased entry of generic competitors following the 1984 law.

Many studies trace price rigidity of patent-expired drugs to consumers’ price insensitivity toward brand-name drugs.\(^{3,9,10,11}\) When a market is segmented between the price-sensitive consumers who adopt the generic and the price-insensitive consumers who continue to use the brand-name drug, the brand-name drug firm can raise its price optimally to its captive or price-insensitive clients and simply ignore the price-sensitive business siphoned off by its generic competitors.\(^7\) In fact, prescription drug markets have many characteristics that would predict price insensitivity. For example, physicians make prescribing decisions on drug therapy for consumers. Few physicians can inform themselves fully about a range of available alternatives because of the complex array of drugs. Third-party payment reduces drug prices dramatically for consumers by requiring fixed-dollar copayments that may be a small fraction of the total price of the drug. The combination of these factors makes drug markets less price sensitive.\(^{12}\)

However, the brand-loyalty theory is losing ground as market conditions conducive to brand loyalty fade dramatically in the 20 years since the 1984 law. The number of generic entries for patent-expiring drugs has increased substantially. Cook reported that for 13 major drugs with patents expiring between 1990 and 1993, 11 experienced generic entry within 2 months of patent expiration.\(^{13}\) In contrast, only 2 of the 10 top drugs with patents expiring between 1976 and 1982 had generic entry within 1 year of patent expiration. Managed care organizations like health maintenance organizations and pharmacy benefit managers have implemented cost-containing measures, and, once a brand-name drug faces generic competition, generic versions are substituted for the brand-name drug 92% of the time.\(^{14}\) A question then arises as to how brand-name drugs are able to maintain high prices despite losing the majority of the market to generic versions.

This study aims to answer that question by examining the 10 years following the 1984 law because this time period is unique in that a cost-sensitive market environment began to form. During this transition, not only did more generic drugs erode market shares of their brand-name drug counterparts but also more product-line extensions began to enter the pharmaceutical market. Furthermore, although many studies have examined price rigidity in this transition period, they did not control for whether or not brand-name drugs were extended.\(^7,10\)

This study proposes an alternative explanation for the price rigidity theory. It begins with a presumption that a brand-name drug faces price competition from generic versions once its patent expires. It also recognizes that drug firms compete not only on price but also in new-drug development for maximum profits. The brand owner, aiming to keep its market success protected from price competition, extends the original drug with a new modification. The extension is closely related to the original product and has the market exclusivity that the original is about to lose. The brand owner then sustains the price of the original product, despite the entry of its generic versions, to help increase its new extension’s demand. Therefore, the original brand-name drug, when extended, shows the price rigidity to entry.

A line extension is a variation of an existing product.\(^{15}\) The variation can be a new formulation of an existing product or a new modification of an existing molecular entity. The general marketing literature documents many types of line extensions, such as novel versus older line extensions (first time vs. repeated introduction of a continuous-release dosage form), nonbranded versus branded (Tide bath soap vs. Tide Irish Spring bath soap), slot-filler versus new-attribute expansions (e.g., Tide + bath soap vs. Life Savers + cough liquid) and cobranded versus self-branded ingredient (e.g., Life Savers with Dayquil vs. Life Savers with ClearCold).\(^{16}\)

Line extensions, although few in number prior to the 1984 law, are now prevalent in the pharmaceutical drug industry. Following the 1984 law, generic drugs began to erode market shares of brand-name drugs. To continue the success of patent-expiring brand-name drugs, the firms had to introduce new extensions and then shift demand from original brands to their new extensions. Peny and Young reported in 1996 that a majority of drugs facing the loss of patent protection had already been extended one way or another.\(^{17}\) Grabowski and Vernon (1992) noted strong market positions held by new extensions and said that an important strategy is to shift consumers from the original formulation, subject to severe price competition, to a new formulation, insulated from price competition.\(^{18}\) The National Institute for Health Care Management reported that as many as 674 (65%) of 1,035 new drugs approved by the FDA from 1989 through 2000 were modified versions of existing drugs; only 361 (35%) were of new molecular entities.\(^{19}\)

Quite a few studies in the economic literature for industries other than pharmaceuticals have examined how a line extension affects rivalry. According to Schmalensee\(^{19}\) and Judd,\(^{20}\) a line extension may preempt the market entry of a rival. Kadiyali et al.\(^{21}\) reported that a line extension helps rival firms achieve price coordination. Kadiyali et al.\(^{15}\) later examined how a line extension (Yoplait Lite yogurt) changed the price rivalry between Dannon and Yoplait in the dairy market. After the introduction of Yoplait Lite, the price of Yoplait became less sensitive to changes in the price of its rival product (Dannon) than it was before the introduction of Yoplait Lite.

The present study seeks to provide empirical evidence for the alternative explanation, that the original brand-name drug, when extended, exhibits price rigidity to entry. The specific objectives are (H1) to test whether market entries of new extensions are associated with market successes of original brand-name drugs and (H2) to determine whether original brand-name drugs exhibit price rigidity to generic entry only
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when they are extended. The results of this study will help explain why modified versions of existing drugs have frequently entered the market following the 1984 law and why postentry prices of brand-name drugs increase at preentry rates despite large shares of the markets being lost to their generic competitors.

Methods

Drug Brand Selection and Study Design

We identified a set of brand-name prescription drugs that lost its patent protection between 1987 and 1992. This set of drug brands was followed for prices and line extensions for the period of 1985 through 1995. The “brand-name” drug brand was limited to orally administered, nonantibiotic, single-ingredient pharmaceuticals. Antibiotic drugs were excluded because they have not been shown to have price rigidity to entry that requires alternative explanations to brand loyalty.

For the first study objective, data were collected on whether brand-name drugs attained market success before generic entry as well as whether they were extended. For the second objective, annual time series of price data were collected for each drug brand selected. The time series spans the same period of 1985 through 1995 for all the drug brands selected. Using the time-series data, the price rigidity to entry was examined first for all drug brands combined and then for each category of drug brand, i.e., brands with new extensions and brands with no new extensions.

Data Sources

Orally administered, nonantibiotic, single-pharmaceutical-ingredient brand-name drugs were identified from First DataBank. The FDA Orange Book was used to identify the year in which each drug brand lost patent protection. The information on the loss of patent protection was double-checked using a series of annual publications of the Drug Topics Red Book. The Drug Topics Red Book lists all drug products sold in the market in a given year; the first appearance of a generic version in a specific (year) issue of Red Book indicates that a brand-name drug has lost its patent protection and thus faced generic competitors in that year.

A line extension was defined as another product that a company introduced within the same market after its existing product. The market definition was based on a therapeutic categorical system of 3-digit Hierarchical Ingredient Codes (HICs). The HICs classify drugs into distinct categories such as antihypertensive drugs and nonsteroidal antiinflammatory drugs. A line extension is defined in this study as either a new formulation or a new molecular entity within the same HIC drug category. If the new formulation was a tablet or a capsule of an existing product, it was not defined as a line extension.

Market success of original drug brands was identified from the top 200 prescription drugs most frequently dispensed through the U.S. community pharmacy. American Druggist publishes this information annually. A market success was defined as a drug-brand presence in the top 100 drug list 1 year prior to the entry of its generic competitors.

Drug price data were collected from the Drug Topics Red Book, which lists average wholesale prices (AWPs) for drug products every year. Although AWPs are list prices and not transaction prices, they are related to transaction prices. AWPs are important because they are the customary basis for reimbursing pharmacies for drug dispensing by third-party payers.

A brand-name drug has multiple National Drug Codes (NDCs) determined by package size, dosage form, and strength. A representative NDC was selected for each brand-name drug based on its continuous availability throughout the time period, and its annual series of AWPs were obtained from the 1985-1995 issues of the Drug Topics Red Book. The AWPs were deflated using gross domestic product (implicit price indices) for the same years.

Data Analysis

Two research hypotheses were tested by following an endogenous switching selection model (Maddala, 1983). In other words, different price equations were specified depending on whether brands were extended or not.

(1) dichotomous switching equation:

\[ I_i = \begin{cases} 1 & \text{if } I_i = \text{yes} \\ 0 & \text{if } I_i = \text{no} \end{cases} \]

(2) price equation:

\[ p_i = X_i' \beta + u_i \]

The dichotomous switching equation (1) was specified as follows: Prob(I_i = 1) = \phi (p_{i0} + \beta_{top100i}). The index variable, I, indicates whether or not a line extension has been introduced for original brand i. The variable, “top100i,” as a proxy for the market success of original brand i, indicates whether or not the original brand ranked in the top 100 prescriptions most frequently dispensed 1 year prior to entry. Regression parameters were estimated using SAS logistic regression, which yielded an odds ratio of extension in brands that had ranked in the top 100, compared with those that had not ranked. Wald chi-square test statistics were used for hypotheses testing at \( \alpha = 0.05 \).

Ordinary least square estimates of the price equations (2) are biased because of the endogenous switching; the errors (u) are not independent of whether brands are extended or not. To resolve the endogenous switching problem, the Heckman 2-step correction is typically used. However, when panel (time series and cross-sectional) data are available, the endogenous switching problem can be better resolved by separating brand-specific effects (\( \lambda_i \)) from the errors; i.e., the remaining errors are independent of whether brands are extended or not (Heckman and Holtz, 1989).
Based on a panel form of Grabowski and Vernon’s (1992)\(^0\) model, the price equations were specified as below:

\[
p_{it}^E = \alpha \cdot \text{Year}_{it} + \beta \cdot \text{YearSinceEntry}_{it} + \zeta_i + \nu_{it}
\]

In the panel specification, the errors (\(\nu_{it}\)) were decomposed into \(\zeta_i\) and \(\nu_{it}\). The component (\(\zeta_i\)) represents the effects that are specific to each individual brand such as market success, therapeutic class, and year of generic entry. The component (\(\nu_{it}\)) is independent of whether brands are extended or not. A fixed-effects model that estimates \(\zeta_i\) individually treating only \(\nu_{it}\) as the errors gives nonbiased estimates (Wooldridge, 2000).\(^1\)

The variable \(p_{it}\) is the log of a brand \(i\)’s price at year \(t\). The variable \(\text{Year}_{it}\) is the year when the brand \(i\)’s price is taken. The variable \(\text{YearSinceEntry}_{it}\) indicates the number of years elapsed at time \(t\) since brand \(i\) faced generic competition. The regression parameter of \(\alpha\) thus estimates the preentry trend of annual price growth for all brands included in each equation (Figure 1). This trend will be influenced by generic entry. As time goes by, more generic competitors enter the market. As a result, the trend of annual price growth will gradually slow down postentry beginning at the time of generic entry. The parameter of \(\beta\) thus measures how the postentry trend of annual price growth has changed compared with its preentry trend. If \(\beta < 0\), the trend of price growth has fallen \(\beta\)% per year postentry from its preentry trend; i.e., the price rigidity is rejected. If \(\beta \geq 0\), the trend of price growth has gone up \(\beta\)% per year postentry from its preentry trend; i.e., the price rigidity is not rejected. SAS panel regression analyses of fixed-effect models were performed to estimate the regression parameters. One-tailed \(t\) test statistics were used for the hypothesis testing (Ho: \(\beta \geq 0\)) at \(\alpha = 0.05\).

**Results**

A total of 27 brand-name drugs met the sample selection criteria. Of those, 9 brand-name drugs lost their patents in 1987, 5 in 1988, 3 in 1989, and 10 in the years 1990 to 1992 (Table 1). All the brand-name drugs are indicated for chronic diseases except for one, the antidiarrheal loperamide.

**Product Extension and Market Success**

The relationship between product extension and market success was examined from the set of 27 brand-name drugs selected for this study (\(n_1 = 27\)). Overall, product extension was observed in 8 of the 27 brand-name drugs (30%, Table 2). Brand-name drugs were extended more frequently when they were faced with generic entry later rather than earlier in the study period. Faced with entry of a generic competitor in 1990 or later, 7 of the 16 (44%) brand-name drugs were extended compared with only 1 of the 11 (9%) brand-name drugs extended in the period prior to 1990. Also, when line extensions were introduced, they came ahead of generic entry; i.e., approval dates of new extensions, except for one, were earlier than those of generic drugs. Notably, of 9 extensions, 4 had their formulation modified. All the formulation modifications involved extended-release or delayed-release dosage forms.

Market entries of line extensions were associated with market successes of patent-expiring brand-name drugs (Table 3). Brand-name drugs that had ranked in the top 100 drugs by volume 1 year prior to the entry of generic competition had odds of extension 16 times higher than those that had not ranked in the top 100 (odds ratio = 16, \(P = 0.02\)). Of 9 brand-name drugs that had ranked in the top 100 drugs dispensed by volume, 6 (67%) were extended. Of 18 brand-name drugs that had not ranked in the top 100, only 2 (11%) were extended.

**Product Extension and Price Rigidity**

The relationship between product extension and price rigidity was examined from a panel of drug price data; i.e., the price series for each of the 27 brand-name drugs spans 11 years (\(n_2 = 297\)). On average, prices of brand-name drugs selected for this study almost doubled during the period 1985 through 1995, from $43.50 to $82.45 (90%), after controlling for inflation during the period. Each year, average prices rose between 2.37% and 10.83%. Price growth was much higher in the earlier than in the later part of the period, i.e., 7.21% to 10.83% each year between 1985 and 1992 versus about 3% each year between 1993 and 1995.

Each brand-name drug was assigned to 1 of 2 categories: brands with new extensions and those with no new extensions. Preentry and postentry annual trends of price growth were computed individually for each brand-name drug (Table 4). Brands with no new extensions were more likely to experience a substantial postentry decline in price growth than those with extensions. Of 19 drugs with no extensions, 8 (42%) showed a
Product-Line Extensions and Pricing Strategies of Brand-Name Drugs Facing Patent Expiration

Table 1: Description of Brand-Name Drugs Selected for This Study

<table>
<thead>
<tr>
<th>Original Brands</th>
<th>Presentation*</th>
<th>Therapeutic Category</th>
<th>Generic Versions</th>
<th>Approval†</th>
<th>Entry‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serax</td>
<td>15 mg 25 C.</td>
<td>Anxiolytics</td>
<td>Oxazepam</td>
<td>Jan. 1987</td>
<td>1988</td>
</tr>
<tr>
<td>Lonten</td>
<td>10 mg 100 T</td>
<td>Antihypertension</td>
<td>Minoxidil</td>
<td>Mar. 1987</td>
<td>1988</td>
</tr>
<tr>
<td>Tranxene</td>
<td>7.5 mg 100 T</td>
<td>Anxiolytics</td>
<td>Clorazepate</td>
<td>Jun. 1987</td>
<td>1988</td>
</tr>
<tr>
<td>Norpramin</td>
<td>25 mg 100 T</td>
<td>Antidepressants</td>
<td>Desipramine</td>
<td>Jun. 1987</td>
<td>1988</td>
</tr>
<tr>
<td>Navane</td>
<td>1 mg 100 C</td>
<td>Tranquilizers</td>
<td>Thiorthixene</td>
<td>Jun. 1987</td>
<td>1988</td>
</tr>
<tr>
<td>Trilafon</td>
<td>8 mg 100 T</td>
<td>Tranquilizers</td>
<td>Perphenazine</td>
<td>Sep. 1987</td>
<td>1988</td>
</tr>
<tr>
<td>Centrax</td>
<td>10 mg 100 C</td>
<td>Anxiolytics</td>
<td>Prazepam§</td>
<td>Nov. 1987</td>
<td>1988</td>
</tr>
<tr>
<td>Ludomil</td>
<td>25 mg 100 T</td>
<td>Antidepressants</td>
<td>Maprotiline</td>
<td>Dec. 1987</td>
<td>1989</td>
</tr>
<tr>
<td>Surmontil</td>
<td>25 mg 100 C</td>
<td>Antidepressants</td>
<td>Trimipramine</td>
<td>Dec. 1987</td>
<td>1988</td>
</tr>
<tr>
<td>Lioresal</td>
<td>10 mg 100 T</td>
<td>Muscle relaxants</td>
<td>Baclofen</td>
<td>May 1988</td>
<td>1990</td>
</tr>
<tr>
<td>Nalfon</td>
<td>300 mg 100 C</td>
<td>NSAID</td>
<td>Fenoprofen</td>
<td>May 1988</td>
<td>1989</td>
</tr>
<tr>
<td>Loxitane</td>
<td>10 mg 100 C</td>
<td>Tranquilizers</td>
<td>Loxapine</td>
<td>Jun. 1988</td>
<td>1989</td>
</tr>
<tr>
<td>Tenormin</td>
<td>50 mg 100 T</td>
<td>Antihypertension</td>
<td>Atenolol</td>
<td>Jul. 1988</td>
<td>1992</td>
</tr>
<tr>
<td>Minipress</td>
<td>1 mg 250 C</td>
<td>Antihypertension</td>
<td>Prazosin</td>
<td>Sep. 1988</td>
<td>1990</td>
</tr>
<tr>
<td>Blocadren</td>
<td>10 mg 100 T</td>
<td>Antihypertension</td>
<td>Timolol</td>
<td>Apr. 1989</td>
<td>1990</td>
</tr>
<tr>
<td>Asendin</td>
<td>50 mg 100 T</td>
<td>Antidepressants</td>
<td>Amoxapine</td>
<td>May 1989</td>
<td>1990</td>
</tr>
<tr>
<td>Flexeril</td>
<td>10 mg 100 T</td>
<td>Muscle relaxants</td>
<td>Cyclobenzaprine</td>
<td>May 1989</td>
<td>1990</td>
</tr>
<tr>
<td>Procardia</td>
<td>10 mg 100 C</td>
<td>Antihypertension</td>
<td>Nifedipine</td>
<td>Jul. 1990</td>
<td>1991</td>
</tr>
<tr>
<td>Imodium</td>
<td>2 mg 100 C</td>
<td>Antidiarrhea</td>
<td>Loperamide</td>
<td>Aug. 1991</td>
<td>1992</td>
</tr>
<tr>
<td>Tolectin</td>
<td>400 mg 100 C</td>
<td>NSAID</td>
<td>Tolmetin</td>
<td>Nov. 1991</td>
<td>1992</td>
</tr>
<tr>
<td>Tavist</td>
<td>2.68 mg 100 T</td>
<td>Antihistamine</td>
<td>Clemastine</td>
<td>Jan. 1992</td>
<td>1993</td>
</tr>
<tr>
<td>Cardizem</td>
<td>30 mg 100 T</td>
<td>Antihypertension</td>
<td>Diltiazem</td>
<td>Mar. 1992</td>
<td>1993</td>
</tr>
<tr>
<td>Pamelor</td>
<td>25 mg 100 C</td>
<td>Antidepressants</td>
<td>Nortriptyline</td>
<td>Mar. 1992</td>
<td>1993</td>
</tr>
<tr>
<td>Feldene</td>
<td>20 mg 100 C</td>
<td>NSAID</td>
<td>Piroxicam</td>
<td>May 1992</td>
<td>1993</td>
</tr>
<tr>
<td>Dolobid</td>
<td>250 mg 60 T</td>
<td>NSAID</td>
<td>Diflunisal</td>
<td>Jul. 1992</td>
<td>1993</td>
</tr>
<tr>
<td>Visken</td>
<td>5 mg 100 T</td>
<td>Antihypertension</td>
<td>Pindolol</td>
<td>Sep. 1992</td>
<td>1993</td>
</tr>
<tr>
<td>Naprosyn</td>
<td>250 mg 100 T</td>
<td>NSAID</td>
<td>Naproxen</td>
<td>Oct. 1992</td>
<td>1994</td>
</tr>
</tbody>
</table>

* C=capsule; T=tablet.
† Approval dates are listed in the FDA Orange Book.
‡ Entry indicates the year in which annual publications of Drug Topics Red Book first lists a generic version.
§ The drug product was discontinued by the manufacturer in 1996.
NSAID=nonsteroidal anti-inflammatory drug.

The decline of more than 6% per year postentry. In contrast, of the 8 brands with extensions, only 1 (13%) experienced a price decline of as much. When annual trends of price growth were averaged over each category of brand-name drugs, those without extensions fell as much as 3.78% per year postentry. However, those with extensions fell less than 1% per year postentry. Notably, those with formulation extensions did not fall but, instead, gained 0.78% per year postentry.

Fixed-effects panel regressions were performed first for all brand-name drugs combined and then separately for each category of brands, i.e., those with no line extensions and those with line extensions (Table 5). On average, all brand-name drugs combined had a price increase of 7.49% per year during the preentry period (P <0.001) (Table 5). Postentry, the trend continued with little change; though a small decline occurred, it was not statistically significant (β = -0.86%, P = 0.21). In other words, the hypothesis of price rigidity was not rejected in all brand-name drugs combined. However, when examined separately for each category of brands, the price rigidity was rejected in brands with no extensions (β = -2.40%, P <0.001) but not in those with extensions (β = 2.65%, P <0.033).
Price rigidity existed in the set of 27 drug brands selected for this study. This finding coincides with previous studies. However, further analyses added more understanding of the price rigidity. When the price rigidity was separately examined for the 2 categories of brand-name drugs, price rigidity existed in drugs with extensions but not in drugs with no extensions. In other words, it was line extensions that helped the original brands remain price insensitive to generic entry. This finding is consistent with the findings of Kadiyali et al., that a line extension makes its original product less elastic to changes in its rival product’s price.

Traditionally, brand loyalty is the only explanation for the price rigidity of patent-expired brand-name drugs to generic drug entry. According to the brand-loyalty explanation, patent-expired brand-name drugs have price rigidity because a sufficient number of price-insensitive customers continue to buy brand-name drugs despite the availability of affordable generic versions. However, the price rivalry between brand-name drugs and their generic versions has increased substantially since the passage of the 1984 law. The penetration of generic drugs in the total pharmaceutical market has steadily increased since the drug legislation, from 19% to 42% of all prescriptions dispensed with generic drugs. When prescriptions written for single-source brand-name drugs that do not have generic versions are excluded, more than 92% of the prescriptions are dispensed with a generic drug. In other words, the number of price-sensitive consumers has increased over the years, which challenges the brand-loyalty explanation.

The findings of this study suggest that price rigidity can arise even when a prescription drug market consists primarily of price-sensitive consumers. An original brand is closely related to its generic version as well as to its extension, and thus the demand for the generic as well as for the extension will be elastic to changes in the prices of the original in a price-sensitive market. Since the extension has the market exclusivity the original brand has just lost, and its demand is elastic to changes in the

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Original Brands Class</th>
<th>Generic Approval</th>
<th>Type</th>
<th>New Extensions Difference</th>
<th>Approval Date</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Formulation</td>
<td>Delayed release</td>
<td>Oct. 1994</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Formulation</td>
<td>Once-a-day dosage</td>
<td>Dec. 1991</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Molecule</td>
<td>ACE inhibitor</td>
<td>Jan. 1991</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Molecule</td>
<td>Calcium channel blocker</td>
<td>Jul. 1992</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Molecule</td>
<td>ACE inhibitor</td>
<td>Dec. 1987</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Formulation†</td>
<td>Extended release</td>
<td>Jan. 1992</td>
</tr>
</tbody>
</table>

* The approval date is for the tablet form; the injectable form was approved in November 1989.† Approved but never marketed in the U.S. as Minipress XL.
ACE= angiotensin-converting enzyme, COX = cyclooxygenase.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Estimate</th>
<th>SE</th>
<th>Pr&gt; χ²</th>
<th>Odds Ratio 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>-2.08</td>
<td>0.75</td>
<td>0.006</td>
<td>16.00 2.12-120.65</td>
</tr>
<tr>
<td>Top 100†</td>
<td>2.77</td>
<td>1.03</td>
<td>0.007</td>
<td>16.00 2.12-120.65</td>
</tr>
</tbody>
</table>

* Number of brand-name drugs is 27.† Indicates whether the brand is in the top 100 drugs most frequently dispensed. CI= confidence interval.
original's price, the brand owner would change the original's price to support the demand for the extension. Thus, the original's price would become rigid with the entry of generic versions but would be sensitive to the entry of extensions. The present study has not examined the relationship between the original brand's price and the demand for the line extension. However, it does show that the price of the original brand is rigid to the entry of generic versions when extended, but not when not extended.

Two types of extensions were identified in this study, one due to a change in formulation (such as from immediate release to extended release) and the other due to a change in the molecule (such as from prazosin to doxazosin). A formulation extension is more closely related to its original brand than an extension created by a change in the molecule; thus its demand would be more elastic to changes in the prices of the original. As a result, the price of the original would be less likely to change with generic entry when the extension is a formulation type compared with a molecule type. According to the study results, price trends of original brands, on average, went up 0.78% per year postentry with formulation modification, while they went down 0.97% per year with all types of extensions (Table 4).

Product-line extensions propel examination of public policy issues amid concerns about rising prescription drug expenditures. Cardizem CD (diltiazem) made more than $735 million in retail sales during the 12 months ending May 31, 1999. Procardia XL (nifedipine) had sales of $299.7 million during the 12 months ending October 31, 2000. For these line extensions of calcium channel blockers, drug spending was greater than $1 billion per year despite the fact that generic versions of the original form had been available since 1992 for Cardizem and since 1990 for Procardia.

Wellbutrin (bupropion) is a more recent example. The XL (once-daily) form of the drug was ranked 35th ($949 million) in sales in community pharmacy in 2004, and the SR (twice-daily) form was ranked 63rd ($529 million); the combined sales of these extended-release versions ($1.5 billion) ranked this drug in the top 20 drugs by sales dollars in 2004 despite the availability of generic versions of the original form (3 times daily) since late in 1999.

The results of this study may motivate researchers to examine factors that help extensions fend off the otherwise competitive price rivalry from generic drugs. Some supply-side characteristics, for example, may hinder generic drug firms from introducing their own versions of extensions. In fact, generic drug firms have faced barriers to developing the continuous-release dosage form, a popular form of product-line extension. In the past, only a few generic drug firms had the resources necessary to develop continuous-release dosage forms.

Some demand-side factors may also encourage brand-name companies to use their extension products to fend off generic competition. Dispensing a generic version for a prescription

### Table 4

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Annual Price Increases (%)</th>
<th>Difference (±)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Brands with no extensions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fenoprofen 300 mg</td>
<td>10.58</td>
<td>0.53</td>
</tr>
<tr>
<td>Cyclobenzaprine 10 mg</td>
<td>11.29</td>
<td>1.56</td>
</tr>
<tr>
<td>Diflunisal 250 mg</td>
<td>4.64</td>
<td>2.00</td>
</tr>
<tr>
<td>Minoxidil 10 mg</td>
<td>7.44</td>
<td>3.15</td>
</tr>
<tr>
<td>Baclofen 10 mg</td>
<td>2.23</td>
<td>3.36</td>
</tr>
<tr>
<td>Maprotiline 25 mg</td>
<td>9.98</td>
<td>3.52</td>
</tr>
<tr>
<td>Piroxicam 20 mg</td>
<td>5.94</td>
<td>4.70</td>
</tr>
<tr>
<td>Loperamide 2 mg</td>
<td>5.28</td>
<td>4.71</td>
</tr>
<tr>
<td>Tolmetin 400 mg</td>
<td>8.07</td>
<td>5.42</td>
</tr>
<tr>
<td>Thiothixene 1 mg</td>
<td>7.23</td>
<td>6.84</td>
</tr>
<tr>
<td>Clemastine 2.68 mg</td>
<td>14.07</td>
<td>7.26</td>
</tr>
<tr>
<td>Pindolol 5 mg</td>
<td>16.86</td>
<td>7.26</td>
</tr>
<tr>
<td>Clorazepate 7.5 mg</td>
<td>19.28</td>
<td>13.34</td>
</tr>
<tr>
<td><strong>Subtotal</strong></td>
<td>9.88</td>
<td>6.10</td>
</tr>
<tr>
<td><strong>Brands with extensions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Naproxen 250 mg*</td>
<td>2.84</td>
<td>2.29</td>
</tr>
<tr>
<td>Timolol 10 mg</td>
<td>7.71</td>
<td>2.45</td>
</tr>
<tr>
<td>Diltiazem 30 mg*</td>
<td>4.01</td>
<td>4.42</td>
</tr>
<tr>
<td>Atenolol 50 mg</td>
<td>6.35</td>
<td>4.77</td>
</tr>
<tr>
<td>Prazosin 1 mg*</td>
<td>8.02</td>
<td>6.39</td>
</tr>
<tr>
<td>Nifedipine 10 mg*</td>
<td>6.10</td>
<td>6.44</td>
</tr>
<tr>
<td>Propranolol 5 mg</td>
<td>16.86</td>
<td>6.60</td>
</tr>
<tr>
<td>Clorazepate 7.5 mg</td>
<td>19.28</td>
<td>13.34</td>
</tr>
<tr>
<td><strong>Subtotal</strong></td>
<td>7.65</td>
<td>6.68</td>
</tr>
</tbody>
</table>

*Brands that had their formulation changed. For these cases, the average post-entry price increase was 5.40% per year, up 0.78% per year from the preentry.
written for the original brand is called generic substitution; this practice is promoted by health plans and pharmacy benefit managers and is encouraged by state laws adopted in recent years. The Texas regulations are representative of the nationwide trend to encourage generic substitution and, effective June 1, 2002, required physicians to specifically block generic substitution using specific hand-written language, “brand necessary” or “brand medically necessary.”\(^*\) The Texas statute in 2002 and consequent regulations went further in making generic drugs more readily available to Texas residents by not requiring pharmacists to inform physicians that a “brand-necessary” prescription does not conform to the new rules and that a generic drug will be dispensed.

However, dispensing a generic version of the original brand for a prescription written for the line extension of the original brand extension is called therapeutic substitution or therapeutic selection and is not yet widely facilitated by state law and regulation.\(^*\) In this market environment, the owner of the brand is able to shift demand from the original brand to the line extension by promotion of the line extension brand to physicians, including the use of product sampling to physicians.\(^*\)

**Limitations**

The present study used AWPs for empirical analyses. The AWPs are obtained through surveys of manufacturers, distributors, and other suppliers.\(^*\) AWPs differ from the actual prices that buyers pay at transaction because they do not account for rebates, charge-backs, and discounts that may occur and are, therefore, not the purchase prices paid by pharmacies or third-party payers. However, AWPs are relevant and important because pharmacy reimbursement is most commonly based on discounts from AWP for brand-name drugs, the principal economic focus of the present study.

Other strategic behaviors may influence pricing decisions for original brand-name drugs. For example, comarketing, the switch from prescription to over-the-counter status, and the phenomenon of brand-name pharmaceutical manufacturers increasingly engaging in ownership of generic drug production may have some bearing on the prices of brand-name drugs, including product-line extensions. Future studies need to sort out these influences.

Factors other than the market success of original brands before facing generic entry may influence the market entry of extensions. For some drugs, it is easier to produce a line extension. For others, it may not be feasible to develop an extension because of clinical, scientific, or economic factors. Future studies need to examine those factors that may influence the market entry of product-line extensions.

Also, from another perspective, the original brand-loyalty hypothesis is not inconsistent with these study findings. Products are only extended if they are successful in the market (e.g., in the top 100 drugs by sales revenue). Successful brand-name products command brand loyalty and can price-discriminate against loyal customers. Less-successful products (e.g., not in the top 100 by sales) are already known to have less market support and/or brand loyalty and thus have less brand value to support through price discrimination or price rigidity.

The present study used the number of prescriptions dispensed as a proxy for market success. Although prescription volume is one element of profit, market success is better measured by sales revenue or by profit (sales revenue minus production and other operating costs). Since production costs and other operating costs are difficult to estimate because of their confidential nature, the present study used prescription volume as a proxy for market success. We also did not investigate the effect on our results of using the top 100 drugs in community pharmacy ranked by sales revenue rather than by dispensing prescription volume.

**Conclusion**

This study provides an alternative explanation for the continued price rigidity of patent-expired brand-name drugs despite the increased market entries of generic competitors facilitated by the 1984 drug price and patent law. According to this alternative explanation, the price rigidity results from product-line extensions that brand-name drug firms introduce for their patent-expiring brand-name drugs. This study provided some support for this alternative explanation using a set of orally administered, single pharmaceutical ingredient, original brand-name drugs that had lost their patents between 1987 and 1992.

The marketing strategy of extending the original drug brands facing generic drug competition has important policy implications. Product-line extensions thwart generic competition and inherit the market success of the original brand, sometimes with little quality improvement over the original brand. With
prescription drug expenditures rising faster than the expenditures for other goods and services in the general as well as in the medical economy, the marketing strategy of using product-line extensions is of interest from a policy perspective and of interest in the cost-effective administration of pharmacy benefits.

DISCLOSURES
No outside funding supported this study. The authors disclose no potential bias or conflict of interest relating to this article. Author Song Hee Hong served as principal author of the study. Study concept and design were contributed primarily by Hong, with input from authors Marvin D. Shepherd and David Scones. Data collection was the work of Shepherd and Hong, with contributions from Scones and author Thomas H. Wan. Data interpretation was the work of all authors. Drafting of the manuscript and its critical revision was primarily the work of Hong and Wan, with input from the coauthors.

REFERENCES
Effect of a Clinical Pharmacy Education Program on Improvement in the Quantity and Quality of Venous Thromboembolism Prophylaxis for Medically Ill Patients

PAUL P. DOBESH, PharmD, FCCP, BCPS, and ZACHARY A. STACY, PharmD, BCPS

ABSTRACT

OBJECTIVE: The American College of Chest Physicians (ACCP) recommends unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH) for prevention of venous thromboembolism (VTE) in medically ill patients. Despite these recommendations, a previous analysis at our institution revealed a low utilization of VTE prophylaxis in medically ill patients. Our objective was to evaluate the effects of a pharmacy-driven education program on the quantity and quality of VTE prophylaxis in medically ill patients.

METHODS: An educational program focusing on the importance of VTE prophylaxis in medically ill patients was developed by clinical pharmacists and presented to nurses, pharmacists, and physicians in a 493-bed community teaching hospital. The educational program was conducted between June 2002 and June 2003 and consisted of in-service presentations, newsletters, and quality assurance presentations on VTE prophylaxis. The educational program focused on 4 main points: (1) hospitalized medically ill patients are at risk for developing VTE, (2) how to identify medically ill patients who require VTE prophylaxis, (3) the fact that VTE prophylaxis is currently underutilized in medically ill patients, and (4) appropriate VTE prophylaxis strategies for medically ill patients. A posteducation retrospective chart review was performed in medically ill patients with discharge dates between October 2003 and March 2004, and these posteducation medical chart data were compared with the results from a preeducation analysis of patients with discharge dates from January 2001 to March 2002. Data collection included patient demographics, VTE risk factors, and use and type of VTE prophylaxis.

RESULTS: The posteducation retrospective chart review was performed for 297 medically ill patients with discharge dates between October 2003 and March 2004 and for 344 preeducation patients discharged between January 2001 and March 2002. Patient demographics and primary diagnoses were similar between the preeducation and posteducation groups. The mean number of risk factors per patient in the preeducation group was 2.53 ± 0.96 versus 2.38 ± 0.88 in the posteducation group (P=0.626). Pharmacy education was associated with an increase in the utilization of any VTE prophylaxis (43% in the preperiod vs. 58% in the postperiod; P <0.001). Prophylaxis judged to be optimal (UFH 5,000 units twice daily, or UFH 5,000 units 3 times daily, or LMWH once daily), increased from 38% in the preeducation period to 49% in the posteducation period, P=0.006. Prophylaxis judged to be optimal (UFH 3 times daily or LMWH once daily) increased from 11% to 44% of patients, P <0.001.

CONCLUSIONS: A hospital-wide clinical pharmacy education program was associated with significant improvement in the quantity and quality of VTE prophylaxis in medically ill patients in a community teaching hospital.

KEYWORDS: Venous thromboembolism, Venous thromboembolism prophylaxis, Medically ill, Pharmacy education, Pharmacy intervention

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Venous thromboembolism (VTE), encompassing both deep vein thrombosis (DVT) and pulmonary embolism (PE), affects approximately 2 million Americans annually.1,2 Data indicate that only 280,000 to 300,000 of the 2 million patients (14% to 15%) who experience VTE are objectively diagnosed with VTE.3 VTE is often a silent disease. When symptoms do occur, they are often nonspecific and the first manifestation of the disease may be death.3 Due to the significant morbidity and mortality associated with VTE, prevention is critical.

Several groups of patients, such as those undergoing orthopedic surgery, general surgery, and experiencing acute myocardial infarction, are known to be at high risk for VTE.4 General medical patients, or the medically ill, are a much more heterogeneous group of patients whose VTE risk is often not assessed. Despite inadequate assessment in the clinical environment, medically ill patients have a moderate-to-high risk of developing VTE.5 In trials in which a placebo or no therapy was given, the incidence of VTE during hospitalization has been 10% to 26%.6

While some of these trials are decades old, the more recent MEDENOX (Prophylaxis in Medical Patients with Enoxaparin) Trial confirmed that, in current practice, medically ill patients are still at risk for VTE.6 Medically ill patients in MEDENOX were generally admitted with severe congestive heart failure (34%), acute respiratory failure that did not require ventilator support (53.5%), or acute infection without septic shock (53%). The 1,102 patients in this trial were randomized to either placebo or 1 of 2 doses of enoxaparin for VTE prophylaxis. The placebo group in MEDENOX revealed an in-hospital total VTE rate of 14.9% and a proximal DVT rate of 4.9%. Therefore, a thromboembolic event was documented in 1 of every 6 medically ill patients randomized to placebo.

Authors

PAUL P. DOBESH, PharmD, FCCP, BCPS, is an associate professor of pharmacy practice, College of Pharmacy, University of Nebraska Medical Center, Omaha; ZACHARY A. STACY, PharmD, BCPS, is an assistant professor of pharmacy practice, St. Louis College of Pharmacy, Missouri.

AUTHOR CORRESPONDENCE: Paul P. Dobesh, PharmD, FCCP, BCPS, Associate Professor of Pharmacy Practice, College of Pharmacy, University of Nebraska Medical Center, 986045 Nebraska Medical Center, Omaha, NE 68198-6045 Tel: (402) 559-3982, Fax: (402) 559-5673; E-mail: pdobesh@unmc.edu

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The American College of Chest Physicians (ACCP) currently recommends that every hospital develop specific strategies for assessing VTE risk and also plan for implementation of appropriate prophylaxis. ACCP currently recommends unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH) for prevention of VTE in medically ill patients. Despite these ACCP recommendations, the administration of prophylaxis in medically ill patients remains underutilized.

A previous analysis at our 493-bed community teaching hospital revealed a low utilization of VTE prophylaxis in medically ill patients. In the previous analysis, only 43% of medically ill patients received any type of VTE prophylaxis, and only 11% received optimal prophylaxis. The clinical pharmacy department developed a hospital-wide education program to address the underutilization of VTE prophylaxis in these patients. We hypothesized that this educational strategy would increase both the quantity and quality of VTE prophylaxis.

### Methods

Data on patients in the preeducation group were collected by a retrospective chart review for patients with discharge dates between January 2001 and March 2002 in this 493-bed community teaching hospital. Patients were included in this analysis if they met the MEDENOX criteria for defining medically ill: (a) had to be at least 40 years old, (b) had a hospital stay of at least 6 days in other than an intensive care unit (ICU), and (c) had a primary diagnosis of acute respiratory failure (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] codes 491.20, 491.21, and 518.81), heart failure (ICD-9-CM codes: all of 428), or bacterial pneumonia (ICD-9 code 482.9). Patients were excluded if they was a clear indication for receiving anti-coagulation, i.e., patients with a history of atrial fibrillation, mechanical heart valve, or stroke, or who were on warfarin at home and continued during the hospitalization. Patients with contraindications to anticoagulation (e.g., active bleeding or thrombocytopenia) were also excluded (Table 1). Data were also collected on patient demographics, presence of ACCP-recognized VTE risk factors (i.e., immobility, history of VTE, presence of cancer, obesity, heart failure, current central venous catheter, estrogen use, major surgery, irritable bowel syndrome, nephritic syndrome, documented thrombophilia, and documented varicose veins), and length of stay (Table 2).

After identifying patients meeting the MEDENOX criteria, patient records were reviewed for the use and type of VTE prophylaxis (Table 3). “Any” VTE prophylaxis was defined as any pharmacological prophylaxis, regardless of dose, as well as any type of mechanical prophylaxis implemented for VTE prevention. “Suitable” prophylaxis was defined as either subcutaneous (SC) UFH 5,000 units twice daily, SC UFH 5,000 units 3 times daily, or SC enoxaparin. We defined “Optimal” prophylaxis as either SC UFH 5,000 units 3 times daily or SC enoxaparin 40 mg once daily. These categorical definitions of type (quality) of drug prophylaxis of VTE were based on recommendations from the 6th ACCP Consensus Conference on Antithrombotic Therapy and the published medical literature.

**Table 1: Sample Selection**

<table>
<thead>
<tr>
<th></th>
<th>Total Number of Patients (% of Total): Preeducation</th>
<th>Total Number of Patients (% of Total): Posteducation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inclusion criteria</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary diagnosis of HF</td>
<td>159 (36.4)</td>
<td>163 (43.2)</td>
</tr>
<tr>
<td>Primary diagnosis of ARF</td>
<td>76 (17.4)</td>
<td>68 (18.1)</td>
</tr>
<tr>
<td>Primary diagnosis of pneumonia</td>
<td>202 (46.2)</td>
<td>146 (38.7)</td>
</tr>
<tr>
<td>Total before exclusion criteria</td>
<td>437 (100.0)</td>
<td>377 (100.0)</td>
</tr>
<tr>
<td>Exclusion criteria</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Admitted with anticoagulation for AF</td>
<td>79 (18.1)</td>
<td>70 (18.6)</td>
</tr>
<tr>
<td>Admitted with anticoagulation for stroke</td>
<td>8 (1.8)</td>
<td>6 (1.6)</td>
</tr>
<tr>
<td>Admitted with anticoagulation for MHV</td>
<td>6 (1.4)</td>
<td>4 (1.1)</td>
</tr>
<tr>
<td>Total patients selected</td>
<td>344 (78.7)</td>
<td>297 (78.8)</td>
</tr>
</tbody>
</table>

**Table 2: Patient Characteristics**

<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>77 ± 12</td>
<td>77 ± 13</td>
</tr>
<tr>
<td>Gender (% male)</td>
<td>36</td>
<td>38</td>
</tr>
<tr>
<td>Weight (kg)†</td>
<td>76.4 ± 26</td>
<td>74.1 ± 25</td>
</tr>
<tr>
<td>Height (inches)†</td>
<td>66 ± 4.6</td>
<td>66 ± 4.4</td>
</tr>
<tr>
<td>Mean LOS (days)‡</td>
<td>9.7 ± 4.7</td>
<td>9.5 ± 5.5</td>
</tr>
<tr>
<td>Primary diagnosis (%)</td>
<td>18</td>
<td>20</td>
</tr>
<tr>
<td>Acute respiratory failure</td>
<td>26</td>
<td>32</td>
</tr>
<tr>
<td>Heart failure</td>
<td>56</td>
<td>48</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>34</td>
<td>29</td>
</tr>
<tr>
<td>Previous VTE</td>
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</tr>
<tr>
<td>Cancer</td>
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<td>10</td>
</tr>
<tr>
<td>Obesity</td>
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<td>20</td>
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<tr>
<td>Heart failure</td>
<td>69</td>
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</tr>
<tr>
<td>Central venous catheter</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>Estrogen use</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>Other‡</td>
<td>4</td>
<td>4</td>
</tr>
</tbody>
</table>

* P >0.1 for all comparisons.
† Mean LOS, weight, and height were compared using the Mann-Whitney U test. All other variables were compared using the chi-square test.
‡ “Other” represents the category of major surgery, irritable bowel syndrome, nephritic syndrome, documented thrombophilia, and documented varicose veins as risk factors.
LOS=length of stay, VTE=venous thromboembolism.
posteducation period who received the same dose. There was also 1 patient in the posteducation period who received enoxaparin 60 mg once daily. Since these 4 patients were receiving a prophylaxis dose of enoxaparin, they were included in the overall category of enoxaparin therapy. Other LMWHs were not evaluated because enoxaparin was the only LMWH on the drug formulary at the time of this analysis.

Based on the disappointing results found in the initial data collection (preeducation) period (Table 4), a pharmacy-driven education program was initiated with the intent of improving both the quantity and quality of VTE prophylaxis in medically ill patients. Patients in this initial data collection period served as the historical control (comparison) group. The education program was initiated in June 2002 and was aggressively continued until June 2003. This program utilized several different methods of education and targeted multiple health care disciplines. Live (one-to-group) educational presentations were made to nursing staff, house staff, pharmacists, and physicians. All nurses were required to attend one of these presentations. Therefore, 4 presentations were given for each of the 6 nursing divisions in the hospital. Due to the rotating nature of the house staff, 4 presentations were given to get the attendance of all 32 house staff. Four presentations were given in the pharmacy department and an additional 6 presentations at different physician meetings. These presentations focused on 4 main points: (1) hospitalized medically ill patients are at risk for developing VTE, (2) how to identify medically ill patients who require VTE prophylaxis, (3) the fact that VTE prophylaxis is currently underutilized in medically ill patients, and (4) appropriate VTE prophylaxis strategies for medically ill patients. Appropriate VTE prophylaxis strategies followed the definition for optimal prophylaxis given above (SC UFH 5,000 units 3 times daily or SC enoxaparin 40 mg once daily). During the educational presentations, no preference was given to either prophylaxis regimen.

Another form of education included newsletters, which were mailed to all 260 physicians with practice privileges at this community teaching hospital. There were also 4 presentations with roundtable discussions at quality assurance meetings for the medical staff and administration. Finally, at the time this project was conducted, clinical pharmacists participated on rounds on 2 of the 4 cardiology services and 3 of the 5 internal medicine services. In the course of providing pharmaceutical care to patients on these inpatient services, recommendations on the need for prophylaxis and type of prophylaxis for individual patients were often given by the clinical pharmacists.

Clinical pharmacists and house staff often rotated to different teams at the beginning of each month. This provided the opportunity to interact with more house staff and attending physicians than if they had stayed on one team consistently. The primary outcomes desired by this pharmacy-driven education program were an increase in the quantity and quality of VTE prophylaxis provided to medically ill patients, as defined in the published literature.

A follow-up evaluation of the utilization of VTE prophylaxis in medically ill patients was then conducted. Another retrospective review was conducted on patients with discharge dates between October 2003 and March 2004 (posteducation group). Patients were identified using the same criteria as in the preeducation period (MEDENOX criteria). As in the initial evaluation, data were collected on patient demographics, presence of VTE risk factors, length of stay, use of VTE prophylaxis, and type of VTE prophylaxis utilized. Results from findings in the posteducation group were then compared with findings in the preeducation group (historical comparison group). All data collections were approved by the institution’s investigational review board.

### Table 3: Study Definitions

<table>
<thead>
<tr>
<th>Type of Prophylaxis</th>
<th>Preeducation (n = 144)</th>
<th>Posteducation (n = 297)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any prophylaxis</td>
<td>43% (148)</td>
<td>58% (172)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Suitable prophylaxis</td>
<td>38% (131)</td>
<td>49% (146)</td>
<td>0.006</td>
</tr>
<tr>
<td>Optimal prophylaxis</td>
<td>11% (38)</td>
<td>44% (131)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

* The chi-square test was used to make comparisons between the 2 groups.

### Table 4: Improvement in the Quantity and Quality of VTE Prophylaxis: Percentage of Patients Receiving VTE Prophylaxis

<table>
<thead>
<tr>
<th>Type of Prophylaxis</th>
<th>Preeducation (n = 131)</th>
<th>Posteducation (n = 146)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>UFH twice daily</td>
<td>74% (97)</td>
<td>10% (15)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>UFH 3 times daily</td>
<td>18% (24)</td>
<td>20% (29)</td>
<td>0.863</td>
</tr>
<tr>
<td>Enoxaparin once daily</td>
<td>8% (10)</td>
<td>70% (102)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

* The chi-square test was used to make comparisons between the 2 groups.

### Table 5: Breakdown of Patients Receiving “Suitable” Prophylaxis: Percentage Improvement in the Quality of VTE Prophylaxis

<table>
<thead>
<tr>
<th>Type of Prophylaxis</th>
<th>Preeducation (n = 146)</th>
<th>Posteducation (n = 297)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Optimal prophylaxis</td>
<td>38% (131)</td>
<td>49% (146)</td>
<td>0.006</td>
</tr>
</tbody>
</table>

* Defined in Table 3.

VTE = venous thromboembolism.
Effect of a Clinical Pharmacy Education Program on Improvement in the Quantity and Quality of Venous Thromboembolism Prophylaxis for Medically Ill Patients

Comparisons between the 2 groups on the use of VTE prophylaxis, type of VTE prophylaxis, primary diagnosis, presence of VTE risk factors, and dichotomous patient characteristics (age and gender) were accomplished using the chi-square test. Mean length of stay, patient weight, and patient height were compared using the Mann-Whitney U test. An a priori $P$ value of $<0.05$ was considered statistically significant.

Results

There were 437 patients identified in the preeducation period and 377 patients in the posteducation period. Of these, 93 patients (21.3%) in the preeducation period and 80 patients (21.2%) in the posteducation period were excluded from analysis due to a clear indication for already receiving warfarin therapy on admission (Table 1). No patients in either group had a contraindication to VTE prophylaxis.

Data were available for 344 patients in the preeducation period (historical comparison group) and 297 patients in the posteducation period. Patient demographics were not significantly different between the groups for all comparisons (Table 2). Overall, patients were, on average, 77 years old, weighed 75 kg, and had a length of stay of 9 to 10 days. About two thirds of the patients were female. While there were numerically more patients with the primary diagnosis of pneumonia in the preeducation group and more patients with heart failure in the posteducation group, these differences were not statistically significant. Patients in the preeducation group had, on average, 2.53 ± 0.96 VTE risk factors. Patients in the posteducation group had a similar number of mean VTE risk factors, 2.38 ± 0.88 ($P = 0.626$). While there were also small numerical differences between the groups with regard to existing risk factors for VTE, no statistically significant differences existed between the groups (Table 2).

The quantity of VTE prophylaxis was significantly improved in the posteducation period compared with the preeducation period, regardless of how VTE prophylaxis was defined (Table 4). The pharmacy-driven education program was associated with a significant 26% relative increase in the utilization of any VTE prophylaxis ($P < 0.001$) and a 22% relative increase in suitable VTE prophylaxis ($P = 0.006$). The most impressive improvement in the quantity of VTE prophylaxis was the significant 75% relative increase in the utilization of optimal VTE prophylaxis ($P < 0.001$).

In addition to improving the quantity of VTE prophylaxis, we also sought to improve the quality of VTE prophylaxis with our pharmacy-driven education program. During the initial data collection, the majority (74%) of suitable VTE prophylaxis was UFH twice daily. Based on the current literature, this was not considered optimal prophylaxis. Part of our educational program emphasized the utilization of UFH 3 times daily or LMWH once daily, and not the use of UFH twice daily. As a result of this educational program, there was a significant 86% relative reduction in the utilization of UFH twice daily (Table 5). When clinicians were given the choice between UFH 3 times daily and enoxaparin once daily, the majority chose the once-daily regimen. There was only about a 10% relative increase in the use of UFH 3 times daily ($P = 0.863$), while there was more than an 8-fold increase in the use of enoxaparin once daily ($P < 0.001$). The significant reduction in the use of UFH twice daily and the significant increase in the use of optimal prophylaxis (mainly enoxaparin once daily) represents our ability to improve both the quality of prophylaxis along with the quantity of prophylaxis in these medically ill patients.

Discussion

Several retrospective reviews have reported a 30% to 45% prophylaxis utilization rate in medically ill patients. However, few institutions have documented the success of a program that addresses the low utilization rates of prophylaxis. Furthermore, even fewer investigations have designed an educational program that targets both the quantity and quality of VTE prophylaxis. Our initial prophylaxis rates are not unusually low, as others have reported similar starting points. Coincidently, 3 independent retrospective chart reviews have reported that only 43% of their medically ill patients received any type of VTE prophylaxis.

Rahim and colleagues retrospectively evaluated VTE prophylaxis rates in medical in-patients admitted consecutively to the medicine units at 2 teaching hospitals. These medically ill patients were defined as patients admitted to the medical ward with a number of different diagnoses, including cerebrovascular disease, heart failure, general infection, diabetes, malignancy, or chronic obstructive pulmonary disease. During a period of time similar to our initial preeducation data collection period, they reported that the utilization of any prophylaxis improved according to the number of risk factors identified, from 25% in low-risk patients to 43% in high-risk patients. Their conclusion was that a risk-factor-based classification scheme might be helpful in increasing their institutions’ poor VTE prophylaxis rates by helping physicians identify those patients at risk.

Stinnett and colleagues conducted a similar study with an objective to evaluate the impact of an awareness campaign on prophylaxis rates. A combination of interventions that included an educational component, risk-stratification guidelines, and standard admission order sets, were implemented. During the preintervention phase, 43% of medically ill patients, who were defined as patients aged 18 years or older who had been admitted to cardiology, oncology, or general medical services for greater than 48 hours, received some form of prophylaxis. Similar to our initial data collection, the majority of prophylaxis consisted of UFH twice daily. An improvement was observed in the postintervention phase, revealing that 71% of the medically ill patients received some form of VTE prophylaxis. Furthermore, the utilization of preferred regimens, UFH 3 times daily and
TABLE 6  Clinical Trials Utilizing UFH Twice Daily for VTE Prophylaxis in Medically Ill Patients

<table>
<thead>
<tr>
<th>Trial</th>
<th>Methods</th>
<th>Therapy*</th>
<th>No of Patients</th>
<th>End Points</th>
<th>Results (%)</th>
<th>P Value</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ibarrá-Perez et al.79</td>
<td>Nonrandomized, unblinded</td>
<td>UFH 5,000 BID vs. GCS, EB vs ASA</td>
<td>192</td>
<td>VTE by RFUT</td>
<td>2.6</td>
<td>26.1</td>
<td>&lt;0.05 Lack of randomization, lack of blinding, and small numbers of patient in each group present significant limitations to the influence of the trial results.</td>
</tr>
<tr>
<td>Halkin et al.17</td>
<td>Randomized, unblinded</td>
<td>UFH 5,000 BID vs. no prophylaxis</td>
<td>1,358</td>
<td>Mortality</td>
<td>7.8</td>
<td>10.9</td>
<td>&lt;0.05 Randomization by medical record number and open-label design influenced patient selection into the trial, limiting the influence of the results.</td>
</tr>
<tr>
<td>Cade et al.18</td>
<td>Randomized, double-blind, placebo-controlled</td>
<td>UFH 5,000 BID vs. placebo</td>
<td>131</td>
<td>VTE by RFUT</td>
<td>2</td>
<td>10</td>
<td>NS Well-conducted trial did not demonstrate a benefit of UFH BID in medically ill patients.</td>
</tr>
<tr>
<td>Heparin Prophylaxis Study Group19</td>
<td>Randomized, double-blind</td>
<td>UFH 5,000 BID vs. no prophylaxis</td>
<td>11,693</td>
<td>DVT at autopsy</td>
<td>49</td>
<td>49</td>
<td>NS Largest VTE prevention trial ever conducted in medically ill patients.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>PE at autopsy</td>
<td>7.7</td>
<td>8.5</td>
<td>NS No benefit of UFH BID was evident, regardless of the end point evaluated.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mortality</td>
<td>5.3</td>
<td>5.3</td>
<td></td>
</tr>
</tbody>
</table>

* All prophylaxis doses are given subcutaneously.

ASA = aspirin; BID = twice daily; DVT = deep vein thrombosis; EB = elastic bandage; GCS = graded compression stockings; NS = not significant; PE = pulmonary embolism; RFUT = radiolabeled 125I-fibrinogen-uptake test; UFH = unfractionated heparin; VTE = venous thromboembolism.

LMWH, had increased from 10% to 47%. Interestingly, UFH 3 times daily was the preferred therapy in the postintervention phase. This study illustrates the importance and value of implementing a risk assessment component to VTE prophylaxis programs.

Education is a key component to any successful prophylaxis program regardless of clinician experience. Fassiadis and colleagues evaluated the change of VTE prophylaxis during a 6-month period after local prophylaxis guidelines were put into practice. Prophylaxis utilization remained suboptimal after the institution implemented prophylaxis guidelines without an education component.12 Kucher and colleagues developed a computer-alert program to increase the prophylaxis of medically and surgically hospitalized patients with VTE risk factors.13 Prophylaxis improved from 14.5% in the nonalert arm (control group) to 33.5% in the alert arm (P <0.001). This modest improvement in prophylaxis using a computer-based reminder system further underscores the value of clinician education.

As stated previously, we defined suitable VTE prophylaxis in medically ill patients as the use of UFH twice daily, UFH 3 times daily, or LMWH once daily. This definition was chosen based on the ACCP 6th Consensus Conference recommendations for providing VTE prophylaxis in medically ill patients.14 This was the most recent version of the guidelines available at the time our project was implemented and completed. The more current ACCP 7th Consensus Conference recommendations only state that “low-dose” UFH can be used with no specific discussion of frequency as in the previous recommendations.1 This issue has also been the topic of comprehensive reviews in the medical literature, which have questioned the role of UFH twice daily as an effective prophylaxis regimen.15,16

Our definition of optimal VTE prophylaxis in medically ill patients included UFH 3 times daily and LMWH once daily, but did not include UFH twice daily. Data supporting UFH twice daily is very limited (Table 6). There are only 2 clinical trials that suggest a possible benefit of UFH twice daily in medically ill patients.17 One trial distributed 192 patients to control or 1 of 4 other treatment groups. While there were fewer DVTs in patients receiving UFH compared with the control group, the lack of randomization, blinding, and the small number of patients per group presented significant limitations to making strong conclusions about these data. The other trial by Halkin and colleagues demonstrated a significant reduction in mortality with the use of UFH compared with no therapy.17 While this may be considered an impressive finding, there are significant limitations to these data. Patients in this trial were randomized by medical record number which, combined with the open-label design, was demonstrated to have potentially influenced the number of patients considered eligible for treatment with UFH. Therefore, the clinical trials that suggest a possible benefit of UFH twice daily in medically ill patients have serious trial design flaws, limiting the use of this regimen in clinical practice.

There is a body of data that suggests a lack of benefit of UFH twice daily for VTE prophylaxis in medically ill patients (Table 6). Cade and associates failed to demonstrate a significant reduction in DVT in medically ill patients compared with placebo in a well-conducted randomized, double-blind, placebo-controlled trial.18 The Heparin Prophylaxis Study Group

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conducted the largest trial performed in medically ill patients. In this trial, there was no reduction in DVT, PE, or mortality with the use of UFH twice daily compared with placebo. The Enoxaparin in Medicine Study Group demonstrated equal efficacy between UFH twice daily and enoxaparin 20 mg daily for VTE prophylaxis in medically ill patients. These results are consistent with the findings from the MEDENOX trial in which 20 mg of enoxaparin was equal to placebo in preventing VTE in 1,102 medically ill patients. Therefore, based on the available clinical evidence, a strong evidence-based recommendation cannot be made for the routine use of UFH twice daily for prevention of VTE in medically ill patients.

The efficacy of UFH twice daily as a VTE prophylactic regimen has been questioned for surgical patients as well as for medically ill patients. A meta-analysis of 49 trials with general surgery patients demonstrated a DVT frequency of 11.8% (95% CI, 10.6%-13.1%) in patients receiving UFH twice daily vs. 7.5% (95% CI, 6.4%-8.6%) in patients receiving UFH 3 times daily. Data from gynecological oncology surgery trials have demonstrated a lack of benefit of UFH twice daily compared with placebo but have proven efficacy of UFH 3 times daily in this patient population. Therefore, the efficacy of UFH in prevention of VTE appears to be dose-related.

UFH 3 times daily has demonstrated effectiveness compared with control or placebo in medically ill patients. There are also no trials suggesting a lack of benefit with UFH 3 times daily as there are with UFH twice daily. There have been a number of trials supporting the efficacy of LMWH once daily in preventing VTE in medically ill patients. Trials comparing the efficacy of LMWH once daily with UFH 3 times daily have demonstrated similar efficacy between the regimens, with a benefit of LMWH in higher-risk patients. The evidence from these clinical trials supports our definition of optimal VTE prophylaxis in medically ill patients.

The significant increase in the utilization of optimal prophylaxis in the present study was mainly due to a more than 8-fold increase in the use of enoxaparin once daily and a minimal change in the use of UFH 3 times daily. Since the pharmacy-driven education program did not differentiate between these options in terms of efficacy, this difference is based on clinician preference and convenience. It might be expected that the use of UFH 3 times daily would have been higher because of its lower acquisition cost compared with LMWH. On the other hand, VTE prophylaxis with LMWH offers several advantages over UFH 3 times daily. The pharmacologic profile of LMWH is superior to UFH, providing a more consistent and predictable anticoagulant response. Some, but not all, of the clinical trials comparing the 2 regimens in medically ill patients suggest better efficacy with enoxaparin 40 mg once daily over UFH 3 times daily. The use of LMWH also has a preferred safety profile with less bleeding and less heparin-induced thrombocytopenia compared with UFH. Finally, a once-daily SC LMWH injection has more convenient dosing for patients and nurses compared with a 3-times-a-day regimen of UFH. In terms of nursing time, there may be a cost advantage of a once-daily SC injection over a 3-times-a-day regimen.

While our pharmacy education program was associated with improved VTE prophylaxis rates at our institution, we believe further improvements are possible. The clinical pharmacy department has developed and implemented a point-based VTE risk assessment form that will be included in our standard admission packet. This risk assessment form will be completed by nurses and verified by physicians. The VTE risks have been divided into a 5-point system based upon the severity of each risk factor. The cumulative VTE risk score will then be used to determine an appropriate prophylactic strategy. Placement of this VTE risk assessment form in patient charts will be accompanied by additional hospital education. The clinical pharmacy department will review the initial program objectives as well as provide instruction for the risk assessment form. We believe that this 2-pronged approach to VTE prophylaxis, consisting of general VTE education and a patient-specific assessment, can further improve the quantity and quality of VTE prophylaxis at our institution.

Limitations

The foremost limitation of this study was the absence of a control group. Therefore, we cannot fully attribute the changes in quantity and quality of VTE prophylaxis solely to the educational program intervention. When implementing an institution-wide program, it is difficult to have a coincident control group that is not influenced by the intervention program. Therefore, we choose to use a historical control (preeducation) group to measure the results of the intervention program. While historical comparison groups do have the limitation of not being able to control for other possible influences on the outcome being measured, they have been the main study design for trials evaluating clinical pathways.

Since there was no control group in the present study, it is possible that other factors contributed to these study findings. However, the time periods for data collection in this study are important since information on the importance of VTE prophylaxis in medically ill patients had already been available. The MEDENOX trial was published in 1999, which was almost 2 years before the start of the in the preeducation period in the present study. The ACCP 6th Consensus Conference on Antithrombotic therapy, which specifically addressed the importance of VTE prophylaxis in medically ill patients, was published in early 2001, about one year before the initial data collection in the present study. Despite this information being available for a significant period of time before the preeducation period of the present study, the utilization of VTE prophylaxis was still low in the preeducation period.

The second most important limitation is that this was a
study of care processes not care outcomes. We did not collect data on either the incidence of VTE in the patients in our institution or the clinical outcomes for patients who did or did not receive VTE prophylaxis. Most clinical trials of VTE in medically ill patients employ contrast venography for the identification of VTE. Since venography is not commonly used in clinical practice, many more patients would be needed to demonstrate differences in symptomatic VTE. It can be argued that it is not necessary to demonstrate a difference in the rate of VTE for there to be success of our pharmacy-driven education program. Clinical trials in different patient populations have already demonstrated the efficacy and importance of providing VTE prophylaxis. Therefore, improving the utilization of VTE prophylaxis is an appropriate end point in a study of this size.

A third limitation was the retrospective collection of data. It was also not possible to measure the effects of any one component of the educational intervention program since several education methods were used. While we believe the educational presentations to nurses, pharmacists, and physicians and the presence of clinical pharmacists on patient-care rounds had the largest impact, we have no way of making that conclusion definitively.

Fourth, we did not address the patients’ smoking status as a risk factor for VTE. Smoking status was newly identified as a risk factor for VTE in the most recent publication of the ACCP Consensus Conference on Antithrombotic Therapy in 2004. This publication was made available in September 2004, after the data collection period for this study. Despite this fact, we do not believe that there would have been significant differences between the groups for this risk factor since there were no statistically significant differences for any other VTE risk factor collected.

We also did not measure administrative costs of the educational interventions or the cost outcomes of VTEs or avoided VTEs in our institution. In a recent article in this Journal, Bullano et al. reported a prevalence of VTE of 2.04 per 100,000 study-eligible health plan members. For the incident hospital VTE events, average costs were $7,712 ± $18,339 (median, $3,131) per incident DVT event, $9,566 ± $13,512 (median, $6,424) per PE event, and $12,200 ± $24,038 (median, $6,678) per incident DVT+PE event.

**Conclusions**

Our pharmacy-driven educational program was associated with a significant improvement in the quantity of use of all 3 categories (any, suitable, and optimal) of VTE prophylaxis. The quality of VTE prophylaxis was also improved, with less UFH twice daily, and more utilization of UFH 3 times daily or once daily LMWH. Institutions implementing a comprehensive educational program may derive more value from measuring changes in both quantity and quality of VTE prophylaxis.

**DISCLOSURES**

No outside funding supported this study. This paper was presented in part as a poster at the American College of Clinical Pharmacy (ACCP) Annual Meeting in Dallas, Texas, on Tuesday, October 26, 2004. Author Paul P Dobesh discloses that he is a consultant to sanofi-aventis, the manufacturer of enoxaparin. Author Zachary A Stacy discloses no potential bias or conflict of interest relating to this article. Dobesh served as principal author of the study. Study concept and design were contributed primarily by Dobesh, with input from Stacy. Data collection was the work of Stacy, with input from Dobesh, data interpretation was the work of both authors. Drafting of the manuscript and its critical revision was the work of both authors.

**REFERENCES**

Effect of a Clinical Pharmacy Education Program on Improvement in the Quantity and Quality of Venous Thromboembolism Prophylaxis for Medically Ill Patients


Lipid Levels and Use of Lipid-Lowering Drugs for Patients in Pharmacist-Managed Lipid Clinics Versus Usual Care in 2 VA Medical Centers

TIMOTHY A. MAZZOLINI, PharmD, BCPS; BRIAN K. IRONS, PharmD, BCPS; EVANS C. SCHELL, PharmD, BCPS; and CHARLES F. SEIFERT, PharmD, FCCP, BCPS

ABSTRACT

OBJECTIVE: The objective of this study was to assess the effectiveness of pharmacist-managed dyslipidemia clinics at 2 Veterans Affairs medical centers since the release of the 2001 National Cholesterol Education Panel Adult Treatment Panel III (NCEP ATP III) guideline compared with the usual care (UC) provided by other health care professionals in the same setting.

METHODS: Analysis was performed through retrospective chart review of patients with a diagnosis of dyslipidemia who received care in either the Amarillo or Lubbock, Texas, pharmacist-managed lipid clinics (LCs) or UC from a primary care physician. Data from medical charts were abstracted for dates of service from July 2001 to December 2003 for 115 patients selected randomly from LC rolls matched with 115 patients with a diagnosis of dyslipidemia selected randomly from UC. All patients had to have had at least 3 visits with the LC or 3 visits in UC with a billing code of dyslipidemia; they were followed for at least 6 months after an initial visit in July 2001 or thereafter and were enrolled in the VA health care system for at least 1 year. Baseline lipid values were available for LC but not UC patients. Cholesterol target goals were determined according to NCEP ATP III guideline.

RESULTS: After an average of 21.6 months of follow-up, the proportion of patients in the LC group that attained goal level increased from 45.2% at baseline to 82.6% for total cholesterol (TC) and from 36.5% at baseline to 64.3% for low-density lipoprotein cholesterol (LDL-C) (P < .001 for both comparisons). There was an average 24.5 mg/dL absolute reduction (relative reduction, 19.4%) in LDL-C along with significant improvements in the other lipid levels (P < .001 for TC and LDL-C, P = .007 for triglycerides [TGs]) with the exception of high-density lipoprotein cholesterol (HDL-C), which declined from 40.0 mg/dL to 36.3 mg/dL (P < .001). A total of 50 patients (43.5%) were on lipid-lowering pharmacotherapy at baseline versus 108 patients (93.9%) at follow-up. Compared with UC, LC patients were more likely to have achieved goal LDL-C (64.3% vs. 15.7% for UC, P < .001) and TC (82.6% vs. 40.9%, P < .001), but there was no difference in the proportion of patients at TG goal for LC (65.2%) compared with UC (62.2%, P = .061) or at HDL-C goal (23.5% for LC vs. 33.0% for UC, P = .143). A higher proportion of LC patients (93.9%) used lipid-lowering agents compared with UC patients (24.3%, P < .001). Subanalysis of patients on a lipid-lowering agent found that a significantly higher proportion (85.2%) in the LC group were at goal total cholesterol compared with 60.7% for UC (P = .012) and at goal LDL-C (66.7% for LC vs. 39.3% for UC, P = .016). However, a lower proportion were at goal HDL-C for LC (21.3%) versus 42.9% for UC (P = .043). Overall, only 11 LC patients (9.6%) attained goal levels for all 4 serum lipid values by the end of follow-up versus 2 UC patients (1.7%, P = .019).

CONCLUSIONS: Nearly two thirds of patients diagnosed with dyslipidemia and enrolled in a pharmacist-managed LC had LDL-C levels at or below NCEP ATP III target goal compared with 16% of dyslipidemia patients who received UC from their primary care provider. The pharmacist-managed LC patients were also twice as likely (83 vs. 41%) to have attained the TC target goal, but there was no difference between the 2 groups in the proportion of patients who attained either TG or HDL-C target goals. Only 9.6% of LC patients were at goal for all 4 individual lipid measures at the end of follow-up.

KEYWORDS: Lipid clinics, Pharmacist, Dyslipidemia

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medication use, although those who do receive drug therapy are more likely to reach these goals.10,11

Shortly after publication of NCEP ATP III guidelines in 2001, a group of investigators evaluated the impact of these guidelines versus the previous NCEP ATP II guidelines on a sample of NHANES III participants with known cardiovascular risk factors.12 The investigators found a 140% increase in the number of patients eligible for LDL-C-lowering therapy, a 157% increase among males versus a 122% increase among females.

Among the ever-expanding roles pharmacists perform in the health care system, collaborative drug therapy management is one particular role where pharmacists can have a significant impact in improving patient care outcomes. Studies assessing the impact of pharmacist management of dyslipidemia have shown improved lipid goal attainment and appropriate medication use either compared with a baseline or a control group.13-20 However, only one of these studies was performed on intermediate outcomes that occurred after the release of the most recent NCEP guidelines in 2001.20 These guidelines significantly altered LDL-C goals for patients newly classified as having an increased risk for a CHD event (e.g., diabetics and those with a >20% 10-year risk), altered classifications for other lipid parameters (e.g., triglycerides [TGs] and high-density lipoprotein cholesterol [HDL-C]), and increased the number of patients who require lipid-lowering therapy as a result.7 Quilliam et al. found that 21% of 1,962 managed care organization (MCO) patients on a statin drug moved to a more stringent LDL-C goal when the ATP III criteria were applied over ATP II, and substituting the ATP III criteria for ATP II criteria resulted in a 7% decrease in the percentage of patients who had their most recent LDL-C value below the suggested goal, from 69% under ATP II to 53% under ATP III.21 The objective of this study was to compare the outcomes of care provided by the pharmacist-managed clinic with the care provided by other health care professionals in the same setting in the context of the NCEP ATP III guidelines.

## Methods

### Design and Patient Selection

This study was a retrospective review of medical charts for patients who received lipid management care at the Veterans Administration Medical Center (VAMC) in Amarillo, Texas, or the Lubbock, Texas, VA Outpatient Clinic. The population served by the VAMC in Amarillo is approximately 95,000 and approximately 63,000 at the Outpatient Clinic in Lubbock. The study design was approved by the Texas Tech University Health Sciences Center Institutional Review Board and the Amarillo VA Research and Development Committee.

The pharmacist-managed referral lipid clinics (LCs) at these sites were initiated in 1995 and, combined, they currently serve more than 3,500 patients. Patients are referred for enrollment in the LC after a diagnosis of dyslipidemia has been made by their primary care provider. Patients are typically referred to the LC with abnormal lipid levels and/or a history of CHD. The referral process is voluntary, and the primary care provider can manage the patient's dyslipidemia without the involvement of the LC. Primary care providers at these VAMCs are composed of physicians, physician assistants, and nurse practitioners.

Patients included in the LC group were randomly selected from a generated list of all patients who had been seen in the lipid education class between July 2001 and December 2003. This time period was chosen to coincide with the publication of the NCEP ATP III Executive Summary to make sure that all patients without known CHD would be evaluated for the presence of other CHD REs. Patients included in the usual care (UC) groups were randomly selected from a generated list of patients seen by a primary care provider with an International Classification of Disease, Ninth Revision (ICD-9) code for dyslipidemia (either 272.0 [pure hypercholesterolemia], 272.1 [pure hypertriglyceridemia], 272.2 [mixed hyperlipidemia], 272.3 [severe mixed hyperlipidemia], or 272.5 [low HDL-C]). Criteria for inclusion into the study were as follows: had a diagnosis of dyslipidemia; had a minimum of 3 visits with the pharmacist-managed specialty clinic or 3 visits with the primary care provider, with an ICD-9 billing code listed above; were followed in either clinic for at least 6 months with an initial clinic visit on or after July 2001; and were enrolled in the VA health care system for at least 1 year. Patients were excluded from the study if they had documented noncompliance in their medical records as defined by missing 2 or more scheduled routine appointments. Patients were also excluded if they had a thyroid-stimulating hormone level >4.5 m IU/ml at any time during study period, to eliminate patients with uncontrolled hypothyroidism. Charts were reviewed until there were 115 patients in each group.

### The Lipid Clinic Intervention

Upon enrollment in the LC, the clinical pharmacists assessed and treated the patients' dyslipidemia to achieve goal lipid levels based on the NCEP ATP III guideline and recent recommendations.7,22 The clinical pharmacists in these clinics have prescribing authority for all VA formulary lipid-lowering agents. Any changes made to lipid-lowering medications can be performed only by one of the clinical pharmacists once the patient has been enrolled in the LC.

The initial visit to the specialty LC included an educational class session where the patients received information about the treatment of dyslipidemia and therapeutic lifestyle modifications. Education at these classes was provided by a dietitian and one of the clinic pharmacists. After this visit, patients were scheduled for appropriate follow-up visits (20-minute appointments) in the LC, during which the patient's lifestyle (diet and exercise), changes in health status, and current lipid profile were reviewed with the patient and any necessary changes in lipid-lowering medications were made. Patients were discharged from
the clinic after they had achieved and maintained goal lipid levels for 2 or more consecutive visits and no longer required the focused services of the specialty clinic.

**Outcome Measures**

The primary outcomes of this study were the absolute values and the percentage changes in serum LDL-C at the most recent fasting lipid panel (FLP) and the proportion of patients who attained goal LDL-C for the LC compared with UC and for the LC group compared with baseline. Secondary outcomes of interest included the absolute values and percentage changes in the other FLP values and the proportions of patients who attained, goal TC, HDL-C, TGs, TC to HDL-C ratio (TC/HDL-C), and non–HDL-C. A Framingham risk analysis score was calculated for all patients with no known history of CHD or other CHD RE and 2 or more CAD risk factors. Calculation was performed with the Web-based Framingham risk calculator provided by the National Heart, Lung, and Blood Institute (http://hin.nhlbi.nih.gov/atpiii/calculator.asp).

**Data Collection**

Electronic medical records were reviewed and data were collected as described below. Patient's age, gender, and weight were recorded for the patient’s most recent visit. The most recent FLP values were recorded for the LC and UC groups, and the FLP values at enrollment in the pharmacist-managed specialty clinic (baseline) were recorded. CHD or CHD RE diseases (e.g., myocardial infarction, diabetes) and coronary artery disease risk factors (e.g., tobacco use, hypertension), as defined by NCEP III guidelines, were recorded. The number of clinic visits and duration of enrollment in the clinic (months) were recorded to determine the number of visits per year. Use of a lipid-lowering agent was determined through review of electronic medical records as well as documentation in any clinic note that the patient was using an agent obtained outside of the VA from a private physician.

**Data Analysis**

The data are presented as mean ± standard deviation or as proportions when appropriate. When available, a 95% confidence interval is presented. This study required 80 patients in each group to have an 80% power to detect a 20% difference in the primary outcome (percentage obtaining goal LDL-C) between LC and UC (α = 0.05). All statistical analyses were performed using Analyse-It version 1.71 electronic software (Leeds, United Kingdom). All comparisons of nominal data were performed using chi-square or Fisher's exact test when appropriate. For comparison of all continuous variables, the assessment of the LC for values at the most recent visit compared with baseline was done using a paired t test. When these variables were not normally distributed, comparisons were made using a Wilcoxon signed rank test. Comparisons of all continuous variables between groups were performed with the Student’s t test. If these variables were not normally distributed, comparisons were made using a Mann-Whitney U test. A P value of <0.05 was considered significant.

**TABLE 1**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Lipid Clinic (n = 114)</th>
<th>Usual Care (n = 115)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) [mean ± SD]</td>
<td>67.9 ± 9.8</td>
<td>66.4 ± 11.4</td>
<td>0.285†</td>
</tr>
<tr>
<td>Gender</td>
<td>2 females</td>
<td>1 female</td>
<td></td>
</tr>
<tr>
<td>Weight (lbs.)</td>
<td>198.3 ± 37.43</td>
<td>196.8 ± 39.2</td>
<td>0.722†</td>
</tr>
<tr>
<td>Average annual number of visits</td>
<td>2.96 ± 0.71</td>
<td>2.98 ± 1.34</td>
<td>0.055†</td>
</tr>
<tr>
<td>CHD or CHD RE</td>
<td>85.2% (98)</td>
<td>80.0% (92)</td>
<td>0.388†</td>
</tr>
<tr>
<td>CAD RFs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years) &gt;45 male, &gt;55 female</td>
<td>98.3% (113)</td>
<td>98.3% (113)</td>
<td>0.614‡</td>
</tr>
<tr>
<td>Tobacco use</td>
<td>16.5% (19)</td>
<td>30.4% (35)</td>
<td>0.020‡</td>
</tr>
<tr>
<td>Family history §</td>
<td>19.1% (22)</td>
<td>7.0% (8)</td>
<td>0.011‡</td>
</tr>
<tr>
<td>HTN or HTN-med</td>
<td>73.9% (85)</td>
<td>81.7% (94)</td>
<td>0.204‡</td>
</tr>
<tr>
<td>HDL-C &lt;40 mg/dL</td>
<td>52.2% (60)</td>
<td>66.1% (76)</td>
<td>0.044‡</td>
</tr>
<tr>
<td>Average number of CAD RFs</td>
<td>2.65 ± 0.974</td>
<td>2.83 ± 0.700</td>
<td>0.110‡</td>
</tr>
<tr>
<td>CHD or CHD RE type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MI</td>
<td>26.1% (30)</td>
<td>20.9% (24)</td>
<td>0.464‡</td>
</tr>
<tr>
<td>DM</td>
<td>28.7% (33)</td>
<td>26.1% (30)</td>
<td>0.768‡</td>
</tr>
<tr>
<td>CABG</td>
<td>18.3% (21)</td>
<td>8.7% (10)</td>
<td>0.052‡</td>
</tr>
<tr>
<td>FRAM &gt;20%</td>
<td>17.4% (20)</td>
<td>22.6% (26)</td>
<td>0.506‡</td>
</tr>
<tr>
<td>PAD/PVD</td>
<td>6.1% (7)</td>
<td>2.6% (3)</td>
<td>0.333‡</td>
</tr>
<tr>
<td>PTCA</td>
<td>13.0% (15)</td>
<td>9.6% (11)</td>
<td>0.533‡</td>
</tr>
<tr>
<td>LDL-C goal¶</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>100 mg/dL</td>
<td>84.3% (97)</td>
<td>80.0% (92)</td>
<td>0.491‡</td>
</tr>
<tr>
<td>130 mg/dL</td>
<td>9.6% (11)</td>
<td>19.1% (22)</td>
<td>0.060‡</td>
</tr>
<tr>
<td>160 mg/dL</td>
<td>6.1% (7)</td>
<td>0.9% (1)</td>
<td>0.072‡</td>
</tr>
</tbody>
</table>

* Plus-minus values are means ± standard deviation.
† Student’s t-test.
‡ Chi-square test.
§ Family history = family history of premature heart disease (primary relative; male <55 years, female <65 years).
|| Patient could have CHD (coronary heart disease) or CHD RE (risk equivalent) disease documented more than once. CHD RE = diabetes mellitus, symptomatic carotid artery disease, peripheral arterial disease, abdominal aortic aneurysm, and/or Framingham risk score >20%.
¶ LDL target goal according to NCEP ATP III.
CABG = coronary artery bypass graft; CAD = coronary artery disease; CAD RFs = coronary artery disease risk factors; DM = diabetes mellitus; FRAM = Framingham risk analysis score; HDL = high-density lipoprotein; HTN = hypertension; HTN-med = antihypertensive medication; MI = myocardial infarction; NCEP ATP III = National Cholesterol Education Panel Adult Treatment Panel III; PAD/PVD = peripheral arterial disease; PTCA = percutaneous transluminal coronary angioplasty; PVD = peripheral vascular disease.
Results

LC and UC Comparison Analysis

There were 115 patients in the LC group and 115 in the UC group. Patient characteristics were similar between the groups with the exception of the percentage of patients who had documented tobacco use, a documented family history of premature heart disease, and a low HDL-C (Table 1). There were no differences in the type of CHD or CHD RE diseases between the groups. The annual number of clinic visits was not significantly different between patients enrolled in the LC (2.97) and UC (2.98) group ($P = 0.055$).

All measured lipid levels at the most recent FLP were found to be significantly lower in patients enrolled in the LC ($P < 0.001$) (Table 2): 48.6% more patients in the LC were at goal LDL-C compared with UC (64.3% vs. 15.7%, $P < 0.001$). Significant differences were also seen in TC and those at all goal lipid levels ($P < 0.001$ and $P = 0.019$, respectively), but not in the proportion at goal HDL-C ($P = 0.143$), and the UC group had a significantly higher mean HDL-C (39.0 vs. 36.2 for LC, $P < 0.001$).

Use of a lipid-lowering agent was found in 28 patients (24.3%) in the UC group compared with 108 (93.9%) in the LC group, nearly a 4-fold difference (Table 3). Based on the large difference in medication use between the groups, further analysis was performed evaluating the same outcomes in those patients from both LCs that were known to be on one or more lipid-lowering agents. The proportion attaining goal LDL-C in the LC group remained significantly different compared with UC, 66.7% versus 39.3%, a 27.4% absolute difference between the groups ($P = 0.016$).

Further analysis was performed between and within both groups for patients who had a Framingham 10-year analysis risk score calculated. For 20 patients in LCs and 26 patients in UC with a Framingham risk score >20%, the LC patients had lower absolute TC, LDL-C, and TG values but not higher HDL-C values (Table 4). For the proportion of patients at goal, the LC patients were more likely to be at goal for TC, LDL-C, and TGs but not for HDL-C or for all 4 values.

The mean age for the 115 LC patients who satisfied the inclusion criteria was 67.9 years. The group included only 2 females and 85.2% had CHD or a CHD RE disease (Table 1). The mean duration of enrollment in the clinic was 21.56 ± 5.2 months, with an average of 5.16 ± 1.3 visits to clinic (data not presented). Compared with baseline, TC, LDL-C, HDL-C, and TGs were reduced by 16.2%, 19.5%, 9.3%, and 14.6%, respectively ($TC, LDL-C, and HDL-C, P < 0.001; TGs, P = 0.007$) (Table 5). The proportion of patients attaining goal TC and LDL-C at the most recent LC visit increased by an absolute 37.4% and 27.8% from baseline ($P < 0.001$). The proportion of patients attaining goal HDL-C decreased by an absolute 20% from baseline ($P = 0.002$), and the mean HDL-C level dropped from 40.0 mg/dL to 36.3 mg/dL ($P < 0.001$) although the TC/HDL-C ratio decreased by a relative 8%, from 5.1 at baseline to 4.7 at follow-up ($P < 0.001$). At enrollment, 8 patients (7.0%) were found to be at all 4 goal lipid levels, and all 8 of these patients were on a

### Table 2: Comparison of Lipid Level Outcomes for Pharmacist-Managed Lipid Clinic Versus Usual Care*

<table>
<thead>
<tr>
<th>Lipid Clinic (n = 115)</th>
<th>Usual Care (n = 115)</th>
<th>Difference Between Means</th>
<th>95% CI of Difference Between Means</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting lipid panel (mg/dL) mean ± SD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TC 166.4 ± 31.1</td>
<td>209.7 ± 43.5</td>
<td>43.4</td>
<td>35.5-53.2</td>
<td>&lt;0.001†</td>
</tr>
<tr>
<td>LDL-C 101.7 ± 28.2</td>
<td>135.4 ± 11.9</td>
<td>33.7</td>
<td>25.3-42.1</td>
<td>&lt;0.001†</td>
</tr>
<tr>
<td>HDL-C 36.2 ± 7.6</td>
<td>39.0 ± 11.9</td>
<td>2.7</td>
<td>0.2-5.3</td>
<td>&lt;0.001†</td>
</tr>
<tr>
<td>TG 143.5 ± 77.8</td>
<td>181.9 ± 137.0</td>
<td>38.4</td>
<td>9.5-67.4</td>
<td>&lt;0.001†</td>
</tr>
<tr>
<td>TC/HDL-C ratio 4.7 ± 1.1</td>
<td>5.7 ± 1.7</td>
<td>1.0</td>
<td>0.6-1.3</td>
<td>&lt;0.001†</td>
</tr>
<tr>
<td>Non–HDL-C§ 130.1 ± 29.5</td>
<td>170.7 ± 42.9</td>
<td>40.6</td>
<td>31.1-50.2</td>
<td>&lt;0.001†</td>
</tr>
<tr>
<td>Proportion of patients at goal</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TC 82.6% (95/115)</td>
<td>40.9% (47/115)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDL-C 64.3% (74/115)</td>
<td>15.7% (18/115)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HDL-C 23.5% (27/115)</td>
<td>33.0% (38/115)</td>
<td>0.143</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TG 65.2% (75/115)</td>
<td>52.2% (60/115)</td>
<td>0.061</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All at goal¶ 9.6% (11/115)</td>
<td>1.7% (2/115)</td>
<td>0.019</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Plus-minus values are means ± standard deviation.
† Students t test.
‡ Mann-Whitney U test.
|| Fisher exact test.
§ Non–HDL-C = total cholesterol minus high-density lipoprotein cholesterol.
¶ All = all measured lipid levels at goal.
CI = confidence interval; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; TC = total cholesterol; TC/HDL-C ratio = total cholesterol to high-density lipoprotein cholesterol ratio; TG = triglycerides.
Lipid Levels and Use of Lipid-Lowering Drugs for Patients in Pharmacist-Managed Lipid Clinics Versus Usual Care in 2 VA Medical Centers

Table 3: Comparison of Lipid Clinic and Usual Care Patients on a Lipid-Lowering Medication*

<table>
<thead>
<tr>
<th></th>
<th>Lipid Clinic (n = 108, 93.9%)</th>
<th>Usual Care (n = 28, 24.3%)</th>
<th>Difference Between Means</th>
<th>95% CI of Difference</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average annual visits</td>
<td>2.96 ± 0.7</td>
<td>2.98 ± 1.5</td>
<td>0.02</td>
<td>0.036 to 0.040</td>
<td>0.9137†</td>
</tr>
<tr>
<td>Fasting lipid panel (mg/dL) mean ± SD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TC</td>
<td>164.0 ± 28.9</td>
<td>189.3 ± 57.2</td>
<td>25.25</td>
<td>9.8-40.5</td>
<td>0.029‡</td>
</tr>
<tr>
<td>LDL-C</td>
<td>99.4 ± 26.3</td>
<td>109.4 ± 38.7</td>
<td>10.08</td>
<td>2.5-22.7</td>
<td>0.241‡</td>
</tr>
<tr>
<td>HDL-C</td>
<td>35.9 ± 6.9</td>
<td>39.9 ± 12.5</td>
<td>3.95</td>
<td>0.5-7.7</td>
<td>0.231‡</td>
</tr>
<tr>
<td>TG</td>
<td>145.2 ± 79.2</td>
<td>194.1 ± 190.3</td>
<td>48.91</td>
<td>2.4-95.5</td>
<td>0.653‡</td>
</tr>
<tr>
<td>TC/HDL-C ratio</td>
<td>4.7 ± 1.1</td>
<td>5.10 ± 2.2</td>
<td>0.409</td>
<td>0.2-1.0</td>
<td>0.162‡</td>
</tr>
<tr>
<td>Percentage achieving goal levels</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TC</td>
<td>85.2% (92/108)</td>
<td>60.7% (17/28)</td>
<td>0.012</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDL-C</td>
<td>66.7% (72/108)</td>
<td>39.3% (11/28)</td>
<td>0.016</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HDL-C</td>
<td>21.3% (23/108)</td>
<td>42.9% (12/28)</td>
<td>0.043</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TG</td>
<td>64.8% (70/108)</td>
<td>60.7% (17/28)</td>
<td>0.847</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All at goal</td>
<td></td>
<td></td>
<td>10.2% (11/108)</td>
<td>7.1% (2/28)</td>
<td>0.947‡</td>
</tr>
</tbody>
</table>

* Plus-minus values are means ± standard deviation.
† Independent samples t test.
‡ Mann-Whitney U test.
§ Fisher exact test.
|| All = all measured lipid levels at goal.
CI = confidence interval; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; TC = total cholesterol; TC/HDL-C ratio = total cholesterol to high-density lipoprotein cholesterol ratio; TG = triglycerides.

Discussion
To our knowledge, this report is the first published study evaluating the effectiveness of a pharmacist-managed LC in the treatment of patients with dyslipidemia, including those without known CHD or CHD REs, based on NCEP ATP III guidelines. The findings of this study demonstrated significant improvements in the level of care provided to patients enrolled in the pharmacist-managed LCs as defined by the proportion of patients who attained goal lipid levels at follow-up compared with baseline for TC and LDL-C but not for HDL-C, TGs, or patients at goal for all 4 serum lipid values. Comparison of these patients to randomly identified patients who were treated in UC by the primary care provider demonstrated significantly lower lipid levels, a higher percentage of patients achieving goal TC and LDL-C, and a greater utilization of lipid-lowering agents; there was no difference for LC versus UC for the proportion of patients at goal for HDL-C or TGs. Therefore, by these outcomes, the pharmacist-managed clinics were able to make effective drug therapy selection as well as provide important lifestyle education, resulting in a larger proportion of patients attaining LD and TC goals of therapy compared with UC.

The results of the subgroup analysis of patients with a calculated Framingham CHD Risk Analysis Score >20% are shown in Table 4.

Table 4: Comparison of Patients With Calculated Framingham CHD Risk Analysis Score >20%*

<table>
<thead>
<tr>
<th></th>
<th>Lipid Clinic &gt;20% Risk (n = 20)</th>
<th>Usual Care &gt;20% Risk (n = 26)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) mean ± SD</td>
<td>72.1 ± 6.8</td>
<td>68.7 ± 11.8</td>
<td>0.026†</td>
</tr>
<tr>
<td>No. of CAD risk factors</td>
<td></td>
<td>2.9 ± 0.8</td>
<td>2.9 ± 0.7</td>
</tr>
<tr>
<td>Fasting lipid panel (mg/dL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TC</td>
<td>161.6 ± 25.9</td>
<td>223.4 ± 47.4</td>
<td>&lt;0.001†</td>
</tr>
<tr>
<td>LDL-C</td>
<td>102.6 ± 24.7</td>
<td>145.3 ± 41.4</td>
<td>&lt;0.001†</td>
</tr>
<tr>
<td>HDL-C</td>
<td>34.8 ± 6.9</td>
<td>36.6 ± 8.4</td>
<td>0.448‡</td>
</tr>
<tr>
<td>TG</td>
<td>121.7 ± 44.2</td>
<td>207.5 ± 152.5</td>
<td>0.019‡</td>
</tr>
<tr>
<td>Percentage of patients at goal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TC</td>
<td>95.0% (19/20)</td>
<td>38.5% (10/26)</td>
<td>&lt;0.001§</td>
</tr>
<tr>
<td>LDL-C</td>
<td>50.0% (10/20)</td>
<td>3.85% (1/26)</td>
<td>&lt;0.001§</td>
</tr>
<tr>
<td>HDL-C</td>
<td>10.0% (2/20)</td>
<td>23.1% (6/26)</td>
<td>0.448‡</td>
</tr>
<tr>
<td>TG</td>
<td>75.0% (15/20)</td>
<td>34.6% (9/26)</td>
<td>0.014§</td>
</tr>
<tr>
<td>All at goal¶</td>
<td>5.0% (1/20)</td>
<td>0.0% (0/26)</td>
<td>0.870§</td>
</tr>
<tr>
<td>% patients on lipid lowering</td>
<td>85.0% (17/20)</td>
<td>3.85% (1/26)</td>
<td>&lt;0.001§</td>
</tr>
</tbody>
</table>

* Plus-minus values are means ± standard deviation.
† Independent samples t test.
§ Fisher exact test.
¶ All = all measured lipid levels at goal.
CAD = coronary artery disease; CHD = coronary heart disease; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; TC = total cholesterol; TG = triglycerides.
calculated Framingham CHD risk score showed significant differences between the LC and UC patients, with a Framingham risk score >20%. Perhaps the health care providers in the UC group are not utilizing the Framingham risk analysis score as a clinical tool in the care of their patients. On the other hand, only 50% of the LC patients with a Framingham risk score >20% attained LDL-C goal, only 10% attained HDL-C goal, and only 5% attained all 4 serum lipid goals.

Patients enrolled in the LC had a significant decrease in mean HDL-C levels. This is an unfavorable outcome in these patients, but there were offsetting favorable findings in the significant decrease in the non–HDL-C and a significant increase in the TC/HDL-C ratio. Overall, there were generally favorable serum lipid values for the LC patients, with a presumed lowering of the CHD risk in these patients.

The results of our study are in accordance with other previously published results in similar settings. Bozovich et al. prospectively evaluated the level of care provided by a pharmacist-managed LC as compared with standard care provided by cardiologists in the same private practice clinic in the treatment of patients with a known history of CHD. The investigators found that after 6 months of treatment, 69% of patients enrolled in the LC were at goal LDL-C compared with 50% of patients being treated by the cardiologists (P = 0.016), which compares favorably with our finding of 64.3% of LC patients but much higher for UC patients in Bozovich et al. (50%) compared with 16% in the present study. Bozovich et al. attributed the significant difference to more aggressive treatment and follow-up for patients enrolled in the pharmacist-managed LC.

Cording et al. investigated the efficiency of their pharmacist-managed LC approximately 12 months after its inception in the treatment of patients with dyslipidemia; there was no comparison with a control group. The proportion of patients attaining goal LDL-C based on the NCEP ATP II guidelines increased from 40% at enrollment to 77% at the most recent visit, a 92.5% relative increase (P value was not provided).

A study with a similar design and similar outcomes by O’Donnell et al. found that 73% of patients enrolled in their pharmacist-managed LC were at goal LDL-C compared with 64.3% in the present study. O’Donnell et al. concluded that patients were more likely to achieve and maintain goal LDL-C in their clinic if (1) the goal was attained in the clinic, (2) the patient had known CHD (i.e., lipid-lowering pharmacotherapy for secondary prevention), and (3) the patient had fewer risk factors.

Geber et al. compared the care provided by their pharmacist-managed pharmacotherapy clinic with that provided by primary care providers at their institution in patients with a known history of CHD and a baseline LDL-C above goal (100 mg/dL) level. The proportion of patients attaining NCEP LDL-C goal (<100 mg/dL) in the pharmacist-managed clinic was 72% compared with 39% in the primary care group (P <0.001).

| TABLE 5 | Comparison of Fasting Lipid Panel Levels Among Patients (n = 115) Enrolled in Pharmacist-Managed Lipid Clinic* |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|
| Fasting lipid panel (mg/dL)     | Baseline        | Most Recent     | Mean Change     | 95% CI          | P Value         |
| TC                             | 198.6 ± 43.5    | 166.4 ± 31.1    | -32.2 ± 42.2    | 24.4-40.0       | <0.001†         |
| LDL-C                          | 126.3 ± 39.2    | 101.7 ± 28.2    | -24.5 ± 37.7    | 17.4-31.5       | <0.001†         |
| HDL-C                          | 40.0 ± 9.1      | 36.3 ± 7.6      | -3.7 ± 7.6      | 2.5-5.0         | <0.001†         |
| TG                             | 168.1 ± 113.7   | 143.5 ± 77.8    | -24.6 ± 96.6    | 6.7-42.4        | 0.007†          |
| TC/HDL-C ratio                 | 5.1 ± 1.3       | 4.7 ± 1.1       | -0.4 ± 1.2      | 0.2-0.6         | <0.001†         |
| Non–HDL-C§                     | 158.6 ± 41.6    | 130.1 ± 29.5    | -28.5 ± 40.5    | 21.0-36.0       | <0.001†         |
| Percentage of patients at goal level(s) |           |                 |                 |                 |                 |
| TC                             | 45.2% (52/115)  | 82.6% (95/115)  |                 |                 | <0.001||        |
| LDL-C                          | 36.5% (42/115)  | 64.3% (74/115)  |                 |                 | <0.001||        |
| HDL-C                          | 43.5% (50/115)  | 23.5% (27/115)  |                 |                 | 0.022||          |
| TG                             | 56.5% (65/115)  | 65.2% (75/115)  |                 |                 | 0.242||          |
| All at goal¶                   | 7.0% (8/115)    | 9.6% (11/115)   |                 |                 | 0.639||          |

* Plus-minus values are means ± standard deviation.
† Paired t test.
‡ Wilcoxon signed rank test.
§ Non–HDL-C = total cholesterol minus high-density lipoprotein cholesterol.
|| Chi-square test.
¶ All = all measured lipid levels at goal.
CI = confidence interval; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; TC = total cholesterol; TC/HDL ratio = total cholesterol to high-density lipoprotein cholesterol ratio; TG = triglycerides.
An additional 18% of patients in the pharmacist-managed clinic were on a lipid-lowering medication (P value was not provided).

Till et al. compared a pharmacist-managed LC versus UC provided by primary care providers in the primary care clinics at the William Jennings Bryan Dorn VA Medical Center in South Carolina.20 They evaluated 47 patients in the pharmacist-managed group and 41 patients in the UC group. There was an 18.5% reduction in LDL-C in the pharmacist-managed patients compared with a 6.5% reduction in those patients treated in the UC group (P = 0.049). In that study, the mean LDL-C between the 2 groups was not found to be significantly different. However, the magnitude of LDL-C reduction was found to be related to the number of clinical pharmacy visits in a fairly linear manner and statistically different from the nonlinear relationship of LDL-C reduction and the number of UC visits (P = 0.038). Similar to the findings of our study, the proportion of patients with goal HDL-C (>40 mg/dL) was significantly lower in the pharmacist-managed patients (36%) compared with UC patients (56%, P = 0.037).

The multicenter IMPROVE (Impact of Managed Pharmaceutical Care on Resource Utilization and Outcomes in Veterans Affairs Medical Centers) Study investigated efficacy of pharmacist-managed ambulatory care clinics in the treatment of a multitude of problems as compared with care provided by a control group of primary care providers.24 The investigators found that 39.5% of patients with known CHD in the pharmacist-managed clinics were at goal LDL-C compared with 34.5% of those receiving UC.

Limitations

The foremost limitation of the present study was the absence of baseline fasting lipid panel values for patients enrolled in the UC group. This limitation makes the precomparison and postcomparison for the LC group more robust than the comparison of the LC with the UC group. For the patient characteristics other than lipid values, the LC group and the UC group were significantly different. The UC group had a much higher proportion of use of tobacco (30.4% vs. 16.5%, P = 0.02) but a lower proportion with a family history of premature heart disease (7.0% vs. 19.1%, P = 0.011). The lower proportion of patients in the UC group with a family history of premature heart disease may explain the lower use of lipid-lowering drugs in this group.

Second, these study results are not generalizable since the patient population served at these 2 VA clinics is predominantly male and older than patients in most private MCOs. Third, we did not measure medication compliance in this study, and it is also possible that some of the patients obtained a lipid-lowering agent outside of the VA system that was not documented in the medical record. Fourth, the retrospective chart review did not permit elimination of the possibility that the recorded lipid values could have been nonfasting (i.e., there was no documentation in the record to confirm that the patient followed the explicit instructions to fast 8 to 12 hours prior to the medical visit to determine serum lipid values). There is also the possibility that the primary care provider could have deferred lipid management in patients who were concurrently seeing a private physician and/or specialist.

This study measured only the intermediate clinical outcomes of serum lipid values. There was no assessment of direct and administrative costs of providing pharmacist-managed LC services. Therefore, it was not possible to estimate a return on investment or to suggest that the pharmacist-managed LC service was cost effective.

Despite these limitations, the effectiveness of pharmacist-managed specialty clinics has been demonstrated in numerous studies establishing the ability of similar specialty clinics to deliver appropriate care based on specific goals of therapy.16-21 These clinics are likely successful because of their ability to have a focused visit devoting the majority of time on patient assessment and education.29 In addition to these factors, the pharmacist services have demonstrated significant cost savings to both the patient and the health care organization.20,32 A pharmacist’s time is often less costly to the patient and health care organization than is a physician’s. Thus, if a pharmacist is able to achieve a similar or improved level of care in treating a specific disease state, then a pharmacist-managed specialty clinic could be a cost-effective method to improve the efficiency of a health care system.

Based largely on these factors, physicians have voiced support of collaborative drug therapy management agreements between themselves and appropriately trained pharmacists.33 Yet, there are additional potential roles for pharmacists in the treatment and identification of patients with dyslipidemia.20,34 Such roles outside of drug therapy management can include providing education to patients and health care providers, community screening projects, and the traditional role of dispensing medications. Community pharmacists are a source of information for many patients, giving the pharmacist numerous educational opportunities. In a community setting, the access to pharmacists has been associated with significant improvements in the level of care provided to patients with dyslipidemia through screening projects and recommendations provided to the patients’ primary care providers.10-13,15-17

Conclusions

The operation of pharmacist-managed LCs was associated with improved serum lipid values of enrolled patients compared with baseline for 5 of 6 measures and for the proportion of patients at goal levels for TC and LDL-C but not for HDL-C, TGs, or for all 4 goal levels. A smaller proportion of patients in the UC group, treated only by their primary care provider, received drug therapy for their dyslipidemia, contributing to a
comparatively higher proportion of patients in the LC group that attained goal lipid levels. After nearly 2 years of follow-up, these 2 pharmacist-managed VA LCs had an effect on some but not all lipid panel values for enrolled patients. These pharmacist-managed LCs, in which pharmacists had prescribing authority for referred patients, received more pharmacotherapy for dyslipidemia compared with UC groups.

DISCLOSURES
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Who Needs XR, LA, SR, XL, ER, or CR?

Most managed care pharmacists have quipped at one time or another that SR (sustained release) at the end of a drug name stands for sustained revenue, ER (extended release) really means extended revenue, and CR (controlled release) really means continued revenue. In this issue of JMCP, Hong et al. applied logistic regression analysis to the prices of 27 drugs that lost patent protection and concluded that price rigidity was more likely to occur in brands with product-line extensions (such as SR, ER, LA [long-acting], etc.) compared with brands without extensions. Hong et al. raise the obvious point about public policy surrounding a business practice that contributes to rising prescription drug expenditures. The authors cite, for example, Cardizem CD (diltiazem), which earned more than $735 million in community pharmacy sales during the 12 months ended May 1999, and Procardia XL (nifedipine, extended release), with sales of $299.7 million during the 12 months ended October 2000, combined pharmacy sales of more than $1 billion per year despite the fact that generic versions of the these 2 drugs had been available for 8 to 10 years in the immediate-release (IR) dose form.

Is there a clinical argument, beyond the convenience associated with the use of fewer doses per day, that might provide support for price rigidity and sales revenue expansion attained through product extension via SR dose forms? Researchers at the Wake Forest University School of Medicine reported in 1995 that short-acting calcium channel blockers (CCBs) caused more harm than benefit in patients, and followed that report with results of a meta-analysis of 9 randomized controlled trials presented in August 2000 that showed a 27% higher risk of heart attack and a 26% higher risk of heart failure in patients on all (including LA) CCBs versus alternative therapies (diuretics, angiotensin-converting enzyme inhibitors [ACEIs], beta-blockers) for hypertension: diuretics, ACEIs, or beta-blockers. And, according to the combined results of 42 clinical trials involving 192,478 patients, low-dose diuretics are the most effective first-line treatment for preventing the occurrence of cardiovascular disease morbidity and mortality. Compared with CCBs, low-dose diuretics were found to be associated with reduced risks of cardiovascular disease events (relative risk [RR], 0.94; 95% confidence interval [CI], 0.89-1.00) and congestive heart failure (RR, 0.74; 95% CI, 0.67-0.81). So, it is not clear whether LA CCBs are any safer than short-acting CCBs, but they are more expensive in direct drug cost and are not first-line therapy for hypertension.

This matter of product (line) revenue extension is significant in the U.S. pharmaceutical market. For pharmacy claims with dates of service in 2005 in the third quarter ended September 30 (2005 Q3), venlafaxine XR (extended release) was ranked #4 in total expenditure for small employers, accounting for 1.7% of total drug benefit expenditures, surpassed in expenditure by only 3 drugs: atorvastatin, lansoprazole, and esomeprazole. The average allowed price (drug cost plus dispense fee, before copay) was $123 per 30-day supply of venlafaxine XR, a 43% price premium compared with the average allowed price per 30-day supply ($86) for the IR form of venlafaxine. This is perhaps the best measure of the market-determined value (aided, of course, by direct-to-consumer and physician promotion) of the XR form of the drug, which is taken once daily compared with the IR form of the drug, which is taken 2 or 3 times daily. An economist, or a self-paying consumer for that matter, might ponder the value added by 1 less dose per day of venlafaxine for an incremental cost of $1.23 per day, $37 per month, or $444 per year of therapy.

One does not have to look far today for a second example of the market value of an ER (or XR or XL) form of an old drug. Bupropion was approved by the U.S. Food and Drug Administration (FDA) 20 years ago, on December 30, 1985. In 2005 Q3, bupropion XL was ranked #9 in total drug plan expenditure, accounting for 1.3% of total drug benefit costs for small employers at an average allowed price (before copay) of $116 per 30-day supply; a price premium of more than 60% compared with generic bupropion (about $70 per 30-day supply). The market value of these 2 drugs, venlafaxine XR and bupropion XL, is enormous, each with more than $1 billion in pharmacy sales per year in the United States, despite lower-cost therapeutic alternatives of the same chemical composition of the drug. One is compelled to wonder about the true market value of these drugs absent effective direct-to-consumer advertising and physician promotion, including free drug samples and education programs.

Longing for a third contemporary example, there is paroxetine CR, at $88 per 30-day supply in 2005 Q3, a 91% price premium to generic paroxetine IR. This example does indeed help to frame the matter since both the IR and CR forms of the drug are indicated (approved by the FDA) for once-daily dosing. So, paroxetine IR was approved by the FDA 13 years ago, on December 29, 1992, at an initial (and often end) dose of 20 mg per day. Paroxetine CR is indicated for once-daily dosing in an initial dose of 25 mg per day and is available only in 12.5 mg, 25 mg, and 37.5 mg CR formulations (a noteworthy fact since all 3 clinical trials for panic disorder cited in the product labeling had a mean dose of 50 mg per day for completers at end point).4 The price differential for these alternate dose forms is also informative, but perhaps in a more poignant manner. In this case, the consumer would pay nearly twice as much for the same drug, both dose forms taken once per day. Does life really get better than this for a pharmaceutical manufacturer, selling a clone product for about $3.00 per day of drug therapy to achieve the same therapeutic outcome as the generic IR formulation of the drug at a cost of $1.50 per day taken in the same dosing frequency?

In 2004, approximately 10% of the top 200 drugs by sales volume in community pharmacies were either SR, LA, XL, CR,
XR, or ER dose forms. Venlafaxine XR led the list at rank #7 with sales of $2.281 billion, up 19% from 2003. Buproprion XL had sales of $949 million, and, when combined with sales of bupropion SR ($529 million), the combined SR and XL forms of buproprion had sales of $1.478 billion, which would have ranked #19 in total community pharmacy sales in 2004. Paroxetine CR had sales of $824 million in 2004, nearly 5 times the sales of $172 million for (brand) paroxetine IR.

Additional perspective is provided by Lee, who compared the price of the first or second drug introduced in each of 5 high-expenditure prescription drug therapeutic categories with the price of 1 or 2 drugs introduced to the market at a later time. Using average wholesale price in October 2003, Lee concluded that the “me-too” drugs were each a better value (see table) since they produce the same or similar clinical outcomes at a lower average drug acquisition price. More to the point of the article by Hong et al., first-in-class manufacturers do not lower the price of the innovator product, preferring instead to make profits by selling the higher-priced drug to fewer patients rather than selling a price-reduced drug to more patients. Note, for example, that 21 years after its market introduction in 1982, Capoten had a price more than 3 times the price of Mavik, introduced 14 years later, in 1996.

This year, researchers from the Centre for Health Services and Policy Research at the University of British Columbia evaluated 1,147 newly patented drugs appraised by the Canadian Patented Medicine Prices Review Board between 1990 and 2003, finding that only 68 (5.9%) were breakthrough drugs (defined as “the first drug to treat effectively a particular illness or which provides a substantial improvement over existing drug products”). The overwhelming proportion (87.6%, N=1,005) of new drug introductions were classified as “me-too” drugs, and researchers concluded that 80% of the increase in drug expenditure between 1996 and 2003 in British Columbia was explained by the use of new, patented drug products that did not offer substantial improvements over less-expensive alternatives available before 1990.

In May 2002, the National Institute for Health Care Management (NIHCM) concluded that only 39% of the 17.1% ($22.5 billion) increase in total community pharmacy sales in 2001 was contributed by an increase in the number of prescriptions (utilization). Of the 61% contributed by “price,” about four tenths (24% of the total) was contributed by a shift to higher-cost drugs, led by bupropion SR in the antidepressant drug class. In the previous year, NIHCM found that 36% of the $20.8 billion increase in community pharmacy sales was contributed by a shift in the mix of drugs, including bupropion SR and venlafaxine XR, both top 25 drugs by sales volume, increasing 37% and 64% in sales, respectively, in the year 2000. Two thirds of the new drugs approved by the FDA in the 12-year period between 1989 and 2000 used active ingredients that were already on the market. NIHCM researchers concluded that, in 85% of the cases, product-line extensions of brand-name drugs did not provide significant improvement over currently marketed therapies while contributing 36% of the growth in total spending on pharmaceuticals between 1995 and the year 2000.

In the first quarter of 2005, sales of bupropion IR and SR were down 75% because of generic drug competition, but sales of bupropion XL were up 56%. Venlafaxine sales, led in a ratio of more than 10-to-1 by the XR dose form, were $3.3 billion worldwide in 2004, making it the largest selling antidepressant in the world. So, there appears to be some truth in the notion that XL really means e(x)tended life, SR really means sustained revenue, and XR stands for e(x)tended revenue. But there is more to product-line extensions than dose-form manipulation. Venlafaxine was approved for marketing in the U.S. market on December 28, 1993, and patent protection will expire on June 13, 2008. Not to worry. Long before 2008, perhaps as early as the first quarter of 2006, a New Drug Application (NDA) is expected for desvenlafaxine, a metabolite of venlafaxine, and radafaxine, a metabolite of bupropion, enters Phase 3 clinical trials in 2006, with an NDA filing expected in 2007.

### Table 1: Price Comparisons for “ME-too” Drug

<table>
<thead>
<tr>
<th>Class</th>
<th>Drug and Dose</th>
<th>FDA Approval Date</th>
<th>Average AWP Cost/ Month ($)</th>
<th>Price Reduction of Newer Agent (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statins</td>
<td>Simvastatin (Zocor) 80 mg/day</td>
<td>Dec. 1991</td>
<td>138</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Atorvastatin (Lipitor) 40 mg/day</td>
<td>Dec. 1996</td>
<td>109</td>
<td>-21.0</td>
</tr>
<tr>
<td></td>
<td>Rosuvastatin (Crestor) 10 mg/day</td>
<td>Aug. 2003</td>
<td>76</td>
<td>-44.9</td>
</tr>
<tr>
<td>ARBs</td>
<td>Losartan (Cozaar) 100 mg/day</td>
<td>Apr. 1995</td>
<td>65</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Olmesartan (Benicar) 40 mg/day</td>
<td>Apr. 2002</td>
<td>40</td>
<td>-38.5</td>
</tr>
<tr>
<td>PPIs</td>
<td>Omeprazole (Prilosec) 20 mg/day</td>
<td>Jan. 1999</td>
<td>138</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Pantoprazole (Protonix) 40 mg/day</td>
<td>Feb. 2000</td>
<td>110</td>
<td>-20.3</td>
</tr>
<tr>
<td>COX-2s</td>
<td>Celecoxib (Celebrex) 200 mg 2X/day</td>
<td>Dec. 1998</td>
<td>171</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Valdecoxib (Bextra) 10 mg/day</td>
<td>Nov. 2001</td>
<td>115</td>
<td>-32.7</td>
</tr>
<tr>
<td>ACEIs</td>
<td>Captopril (Capoten) 25 mg 3X/day</td>
<td>Jan. 1982</td>
<td>106</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Trandolapril (Mavik) 4 mg/day</td>
<td>Apr. 1996</td>
<td>30</td>
<td>-71.7</td>
</tr>
</tbody>
</table>

Developed from data presented by Lee TH. “Me-too” products—friend or foe? N Engl J Med. 2004;350:211-12, including prices in October 2003 obtained from Drug Topics Red Book. Statins are 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors. Note that simvastatin 80 mg was approved by the U.S Food and Drug Administration in 1998, but the lower-dose product was approved by the FDA in December 1991.

ACEIs = angiotensin-converting enzyme inhibitors; ARBs = angiotensin receptor blockers; PPIs = proton pump inhibitors.
Selectivity and Specificity Are the Keys to Cost-Effective Use of Omalizumab for Allergic Asthma

Omalizumab (Xolair) was approved by the U.S. Food and Drug Administration (FDA) on June 20, 2003, for subcutaneous (SC) treatment of adults and adolescents (aged 12 years and older) (a) who have moderate or severe persistent asthma, (b) who have a positive skin test or in vitro reactivity to a perennial aeroallergen, and (c) whose symptoms are inadequately controlled with inhaled corticosteroids.1 It is associated with off-label (unapproved use) for seasonal allergic rhinitis.

Omalizumab was the first humanized therapeutic antibody approved by the FDA for treatment of asthma and the first approved therapy designed to target immunoglobulin E (IgE). Omalizumab labeling includes the results of 3 clinical trials involving 1,368 allergic asthma patients who were randomized to receive either subcutaneous weight-adjusted doses of omalizumab or placebo every 2 or 4 weeks.18 Doses were determined based on patients’ body weight and IgE level. Inhaled corticosteroid doses were kept stable over the initial 16 weeks of treatment (stable-steroid phase) and tapered during a further 12-week treatment period (steroid-reduction phase).

So, how does omalizumab stack up by the measures of efficacy, safety, and cost? Efficacy compared with placebo is not inspiring. In the 2 multicenter clinical trials, 86% to 88% of 542 omalizumab patients experienced no exacerbations of asthma at 16 weeks during the stable steroid phase versus 70% to 77% of patients who received placebo. During the 12-week steroid-reduction phase, 79% to 84% of omalizumab patients experienced no exacerbations compared with 68% to 70% of placebo patients.10,20

By the measure of at least 50% reduction in symptom score, the response ratio was 50% at 20 weeks for high-dose omalizumab (5.8 mcg per kilogram [kg] of body weight per nanogram of IgE per milliliter [mL]), 47% for low-dose (2.5 mcg per kg per nanogram of IgE per mL) patients, and 45% for placebo.21 In this third multicenter clinical trial involving 317 allergic asthma patients who required inhaled or oral corticosteroids (or both), Milgrom et al., for the rhuMAB-E25 Study Group, found that 30% of high-dose patients, 28% of low-dose patients, and 45% of patients who received placebo experienced exacerbations of asthma. Treatment with oral corticosteroids for exacerbations of asthma was required in 13% of patients in the high-dose group, 16% in the low-dose group, and 28% in the placebo group. The absolute improvement in forced expiratory volume in 1 second (FEV1) at 12 weeks in the study by Milgrom et al. was 1.9% in the high-dose group, 2.1% in the low-dose group, and 1.0% in the placebo group.

In their review of omalizumab in this issue of JMCP, Belliveau and Lahoz found that the drug is not only expensive (generally in the range of $1,000 to $3,000 per month, there is an obvious need to identify the patient selection criteria to determine the subset of moderate-to-severe allergic asthma patients who would be most likely to respond favorably to treatment with omalizumab. As pointed out by Belliveau and Lahoz, high utilization of medical care resources might help to justify the high direct cost of the drug.

Bousquet et al. provide additional guidance by pooling the results from the 2 principal multicenter clinical trials (Study 1 and Study 2) with omalizumab.23 Of the 1,070 allergic asthma patients who were symptomatic regardless of moderate-to-high doses of inhaled beclomethasone dipropionate (BDP, mean dose of 75 mcg per day), 542 patients received omalizumab and 528 patients received placebo, administered at a 4-weekly subcutaneous dose of at least 0.016 mg per kg of IgE (IU/mL) for 16 weeks in addition to stable BDP therapy. Univariate logistic regression was performed to explore baseline variables predictive of best response, and 4 aspects of response were assessed (reduced symptom scores, reduced use of rescue medication, improved lung function, improved quality of life [QoL]) as well as a composite definition of response (response in at least 1 of these 4 aspects with no asthma exacerbation during 16 weeks of treatment). For the composite measure of response, the factor most predictive was a history of emergency asthma treatment in the past year (P = 0.015), 67% for omalizumab versus 42% for placebo; for those without a history of emergency asthma treatment, the response rate with omalizumab was 63% versus 54% for placebo. High BDP dose (≥800 mcg per day) was also a predictive factor (P = 0.037) in response to treatment with omalizumab (65%) compared with 40% for placebo; for those treated with <800 mcg per day of BDP 63% of omalizumab patients had a clinically significant response to treatment versus 55% for placebo. A low FEV1 (≤65%) was not predictive (P = 0.072) of response to omalizumab (60%, versus 40% for placebo).
On February 7, 2005, the National Institute for Clinical Excellence announced that its nearly 3-year-old plan to evaluate omalizumab for uncontrolled asthma was being suspended since omalizumab had not been approved for marketing in the United Kingdom. Sin et al. concluded in their systematic review and meta-analysis that the precise role of monoclonal anti-IgE antibody therapy with omalizumab in the management of chronic asthma was not clear.

All 4 clinical trials were short-term—the longest in duration of omalizumab treatment at full dose was 28 weeks—so the value of omalizumab beyond 7 months of therapy is not known. What is more certain is that omalizumab has been tested only in patients with severe allergic asthma treated with inhaled corticosteroids, with allergy skin test results that are positive for at least 1 or 2 perennial (and common) allergens, and who have elevated serum IgE levels, ≥30 IU/mL. Second, Salvi and Babu pointed out in a follow-up to the first published clinical trial results for omalizumab in December 1999 that a acute anaphylaxis can occur in the absence of IgE in laboratory animals; (b) humanized monoclonal antibody can significantly reduce concentrations of free IgE in patients with allergic rhinitis without improving symptom scores; (c) the role of IgE in the pathogenesis of asthma is not known; (d) corticosteroids and beta-agonists, the most effective drugs for asthma treatment, improve symptoms while increasing IgE serum levels; (e) the increased concentration of IgE in allergic asthma may be a phenomenon unrelated to the disease; and (f) symptom scores for the patients treated with omalizumab were only slightly better than those for placebo; and (g) the first clinical trial results with omalizumab did not include any objective measures of asthma such as the standard tests of lung function (FEV1 and peak expiratory flow).

From an evidence-based perspective, there is a distinct lack of evidence to support the use of omalizumab even in severe allergic asthma patients and, therefore, insufficient support to develop useful clinical criteria for a prior authorization/medical exception process for health plan coverage of omalizumab therapy. On the other hand, the dilemma for managed care organizations in setting selective and specific criteria for the appropriate use of omalizumab may be moot since most patients do not use the drug beyond a few months. An analysis of pharmacy claims with dates of service from January 1, 2003, through October 32, 2005, showed that 36% of omalizumab patients used the drug for 2 months or less, 64% used the drug for 6 months or less, and only 2% of patients received omalizumab for 12 months or more.

Frederic R. Curtiss, PhD, RPh, CEBS  
Editor-in-Chief  
fcurtiss@amcp.org

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28. Data search performed November 11, 2005, of the data warehouse of a national pharmacy benefits manager (PBM) representing approximately 500,000 beneficiaries of small employer drug benefit plans for pharmacy claims with dates of service from January 1, 2003, through October 31, 2005.
Pharmacist Intervention in Safe and Effective Conversion of Brand to Generic Drugs

The article by Billups et al. in the October 2005 issue of JMCP is another good example of how the application of pharmacists’ services can bring efficiency to our health care system. It answers a very timely question about the economic impact of a brand-to-generic conversion. In this study, the authors used a cost-minimization analysis to determine cost savings associated with the conversion of patients currently taking simvastatin to generic lovastatin. Given the ever-growing role of statins in a wide range of therapeutic situations, this study is especially important. Although the authors used a cost-minimization approach, they also evaluated laboratory values for cholesterol concentration to assess the validity of the underlying assumption of therapeutic equivalency of simvastatin and generic lovastatin. Further, they evaluated alanine aminotransferase (ALT) levels in laboratory values to consider the safety of their conversion efforts. Armed with this information, pharmacists are now in a much better position to justify their services in this area when discussing such opportunities with patients, physicians, and plan administrators.

This article is notable for its use of a very large population to evaluate the application of pharmacists’ services to reduce costs for both patients and the health plan, while maintaining the quality of pharmacotherapy through the monitoring of laboratory values indicative of safety and efficacy. As with most intervention efforts in normal clinical practice, this study was subject to several limitations that were duly noted. In the future, it would be interesting to consider the total cost of conversion, net of pharmacists’ services. With the evolution of electronic laboratory data, paired with paid claims data, we might anticipate future research using cost-effectiveness analyses to provide insight regarding the efficiency of relevant alternatives to managing the prescription benefit. For example, we might want to know how an intervention such as this one involving significant pharmacist resources compares with a more open design. Specifically, we might want to compare the efficiency of an alternative such as this one with a less intrusive approach, such as changes in the tiered copay to increase usage of the generic, along with a targeted mail communication explaining the rationale. Direct comparisons of this nature can help us to more efficiently manage the prescription drug benefit. Further, it would be interesting to evaluate projects such as this in other populations. For example, the Centers for Medicare & Medicaid Services is undoubtedly interested in brand-to-generic conversions under the new Medicare Part D benefit administered by prescription drug plans and Medicare Advantage prescription drug benefits.

As we go forward, we will continue to need sources of information such as this to improve economic efficiency in our plans. This will help build a preponderance of evidence to support the role of pharmacists as pivotal contributors to the health of our health care system.

Kent H. Summers, RPh, PhD
Purdue University School of Pharmacy
R. Heine Pharmacy Bldg., Rm. 502
575 Stadium Mall Dr.
West Lafayette, IN 47907-2091
ksummers@pharmacy.purdue.edu

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