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Sports art occupies a special niche within the fine art market. In an article written for the April 2005 issue of American Artist magazine, Daniel Grant says that one of the major differences between sports art and other fine art is the subject of autographs. Not only does the depicted athlete’s autograph increase the value of the artwork, but it also creates a personal link between the fan and the athlete that most collectors desire.

Bill Hall got his start as a sports artist when he created the advertising illustrations for MasterCard at the 1994 World Cup soccer tournament. His work was very well received, and commissions by other corporations and individuals soon followed. Hall’s numerous corporate clients include Chrysler, Coca-Cola, Dow Chemical, Federal Express, and the Malibu Speed Zone Racing theme parks in Georgia, Texas, and California. “Businesses like to associate themselves with competition and success,” he says of the popularity of sports art. Hall has also created illustrations for many different organizations and events, such as the San Antonio Stock Show and Rodeo, the Special Olympics, and the New York City Marathon. He produces prints of his work which are sold through his Web site, billhall.com, and through sports-memorabilia shops. His original paintings and prints are available at the Evviva Art Gallery in Beverly Hills, California.

Hall was born and raised in the town of Bartlesville, Oklahoma, located about 45 miles north of Tulsa. “When I was very young, I realized that I liked to draw. It gave me a lot of enjoyment, so I kept doing it. Eventually I became good at drawing,” he says. “When you’re good at something, people notice, and you get positive feedback. Positive feedback gives you a feeling of worth, and reinforces the enjoyment of creating. People should enjoy what they do for a living—therefore, I decided that I would become an artist someday.” As a student, Hall was always the class artist; teachers asked him to draw decorations on the chalkboard for holidays and special occasions. When he was in his mid teens, his family moved to Dallas, Texas, where he took art classes at South Oak Cliff High School. Several of Hall’s teachers encouraged him to continue his art education and get a degree. He did just that, earning his bachelor of arts in art from the University of Texas at Arlington in 1970.

Although Hall gained much of his notoriety as a traditional painter, he has become so accomplished at working digitally that it is difficult to tell his Corel Painter X computer-generated art from his oil paintings once the images are printed. In fact, Corel uses his digital artwork to promote their Painter X digital painting software. And Wacom, the maker of the electronic drawing tablet that Hall uses, features his paintings on their Web site. In addition, his digital images have been published in several industry “how-to” books, including the Painter IX and Painter X Wow! books by Cher Threinen-Pendarvis, Digital Collage and Painting: Using Photoshop and Painter to Create Fine Art by Susan Ruddick Bloom, and Painter X Creativity by Jeremy Sutton.

Hall has become a master at capturing movement and action on his canvases. “Painting action allows me a certain amount of freedom—I don’t have to be so literal with the subject,” he explains. “I can introduce elements of abstraction into my work that make it fresh and uniquely mine.” Hall’s spectacular Baseball Pitcher digital painting is a perfect example of his signature style. Some of the broad streaks of color represent the true colors of the outdoor scene, such as the brown pitching mound and the green grass—yet other colors, like the red in the foreground, serve a decorative purpose. His compositions are quite distinctive as well. In Baseball Pitcher, the figure’s right foot extends beyond the background, which contributes to the image’s 3-dimensional effect. The blurred lines that indicate the motion of the pitcher’s arm form a half circle, and draw one’s eye toward the baseball that appears to be flying right out of the painting. In addition, the way that the artist has “colored outside the lines” of the rectangular background lends a delightful, spontaneous feeling to the picture.

Hall believes that his artistic inspiration comes from within. “Creating art is part of who I am. It’s like asking a bird why it flies. It flies because it can,” he says. Hall encourages beginning artists to find their own style by determining what interests them most. “If you find that the work of another artist appeals to you, incorporate elements of it into the mix,” he advises. “But follow your own path. Let their influence be a signpost in your personal journey, not a destination.” Hall has certainly followed his own path—one that has led to tremendous success in sports art.

Sheila Macho
Cover Editor

COVER CREDIT

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

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

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

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

Formulary Management

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

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7. In a newspaper—Reagan ME. Workers’ compensation, managed care, and reform. Poster presented at: 1995 AMCRA Midyear Managed Care Summit; March 13, 1995; San Diego, CA.


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• style guide: Journal of Managed Care Pharmacy, the International Pharmaceutical Abstracts (IPA), Science Citation Index Expanded (SCIE), Current Contents/Clinical Medicine (CC/CM), and Scopus.

Note: Please do not include author identification in the electronic manuscript document.

Disclosures and conflict of interest:

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• Title page
• Abstract, text, references, tables, and figures (see Submission Checklist for details)

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• Many articles, particularly Subject Reviews, should incorporate or at least acknowledge the relevant work of others published previously in JMCP (see Article Index by Subject Category at www.amcp.org).

• Many articles involve research that may pose a threat to either the research enterprise and the responsibility of the principal author to ensure that the manuscript is submitted with either the result of review by the appropriate institutional review board (IRB) or a statement of why the research is exempt from IRB review (see JMCP Policy for Protecting Patient Safety and Privacy at www.amcp.org).

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3. Chapter paginated by issue—Gregory DW, Malone DC. Characteristics of older adults who meet the annual prescription drug expenditure threshold for
Meta-Analysis to Assess the Quality of Warfarin Control in Atrial Fibrillation Patients in the United States

William L. Baker, PharmD, BCPS; Deborah A. Cios, PharmD; Stephen D. Sander, PharmD; and Craig I. Coleman, PharmD

ABSTRACT

BACKGROUND: Atrial fibrillation (AF) affects a significant proportion of the American population and increases ischemic stroke risk by 4- to 5-fold. Oral vitamin K antagonists, such as warfarin, can significantly reduce this stroke risk but can be difficult to dose and monitor. Previous research on the effects of setting (e.g., randomized controlled trials, anticoagulation management by specialty clinics, usual care by community physicians) on the proportion of time spent within therapeutic range for the international normalized ratio (INR) has not specifically examined anticoagulation in AF patients.

OBJECTIVES: Use traditional meta-analytic and meta-regressive techniques to evaluate the effect of specialty clinic versus usual care by community physicians on anticoagulation control, measured as the proportion of time spent in therapeutic INR range, for AF patients that received warfarin anticoagulation in the United States.

METHODS: Studies included in a previously published meta-analysis (van Walraven et al., 2006), which systematically searched reports between 1987 and 2005, were also screened for inclusion in our analysis. A subsequent systematic literature search of MEDLINE, EMBASE, and the Cochrane Central Register of Clinical Trials from January 2005 through February 2008 was conducted. Studies were included if they (a) contained at least 1 warfarin-treated group including more than 25 patients for whom INR control was monitored for at least 3 weeks; (b) included patients treated for AF in the United States; (c) used a patient-time approach (patient-year) to report outcomes; and (d) reported data on the proportion of time spent in traditional therapeutic INR ranges (i.e., a lower limit INR between 1.8 and 2.0 and an upper limit INR between 3.0 and 3.5). Studies with INR goals outside this range were excluded. The proportion of time spent within the therapeutic INR range for each study group was expressed as an incidence proportion. All studies were pooled using a random effects model and were weighted by the inverse of the variance of proportion of time spent in the therapeutic range. In order to determine how study setting influenced the proportion of time spent within a therapeutic INR range, both subgroup and meta-regression analyses were conducted.

RESULTS: This analysis included 8 studies and a total of 14 unique warfarin-treated groups; 3 of the 8 studies and 4 of the warfarin groups were not included in the previous meta-analysis (van Walraven et al, 2006). Overall, patients spent a mean 55% (95% CI=51%-58%) of their time in the therapeutic INR range. Meta-regression suggested that AF patients treated in a community usual care setting compared with an anticoagulation clinic spent 11% (95% CI=2%-20%, n=6 studies with 9 study groups) less time in range.

CONCLUSIONS: In the United States, AF patients spend only about one-half the time within therapeutic INR. Anticoagulation clinic services are associated with somewhat better INR control compared with standard community care.

J Manag Care Pharm. 2009;15(3):244-52

What is already known about this subject

- The 2008 practice guidelines from the American College of Chest Physicians include a recommendation to use long-term oral anticoagulation in patients with atrial fibrillation (AF) and a recent stroke or transient ischemic attack, to a target INR of 2.5 (range 2.0 to 3.0; Grade 1A quality of evidence).
- Van Walraven et al. (2006) evaluated 67 studies involving 50,208 patients with 57,155 patient-years of follow-up. Overall, patients taking vitamin K antagonists for a wide range of indications that included atrial fibrillation, venous thromboembolism, cardiovascular disease other than atrial fibrillation, peripheral vascular disease, valvular heart disease, and other indications were within therapeutic INR range 63.6% of the time (95% CI=61.6%-65.6%). For the patients managed in usual care (i.e., by community physicians), time in therapeutic INR was 12.2% lower (95% CI=–19.5 to –4.8%, P<0.001) compared with patients managed in anticoagulation clinics.
- Study setting is a significant predictor of the time spent in therapeutic INR range, with about 66% of the time in therapeutic range for anticoagulation therapy in both randomized controlled trials and anticoagulation clinics versus 57% for community-based care provided by physicians.

What this study adds

- Our meta-analysis assessed 8 studies including a total of 14 groups involving 22,237 warfarin-treated AF patients with 41,199 years of follow-up. Atrial fibrillation patients in the 14 groups spent 55% (95% CI=51%-58%) of their time within the therapeutic INR range.
- Of the 8 studies, 13 groups could be evaluated by setting warfarin dosing was managed by anticoagulation clinics for 4 (31%) groups and by community (physician) practice, defined as usual care, for 9 (69%). Patients in anticoagulation clinics spent on average 63% (95% CI=58%-68%) of their time in the therapeutic range versus 51% (95% CI=47%-55%) for patients in community practice. Compared with an anticoagulation clinic, patients treated in the usual care (community) setting spent 11% (95% CI=2%-20%, n=6 studies) less time in therapeutic INR range.
- 5 studies (including 8 groups) reported data on the proportion of eligible patients receiving warfarin. Overall, 48% (95% CI=43%-54%) of eligible AF patients received warfarin, including 53% of AF patients managed by anticoagulation clinics, revealing another gap in protection from ischemic stroke.
trial fibrillation (AF), the most common cardiac rhythm disorder, increases the risk for ischemic stroke 4- to 5-fold. Studies have demonstrated that use of oral vitamin K antagonists such as warfarin significantly reduces the risk of stroke by up to 68% compared with no therapy, from a range of 4.5% without warfarin to 1.4% with warfarin. For patients receiving therapy with warfarin, the proportion of time spent in the therapeutic international normalized ratio (INR) range is strongly associated with reduced risk of both bleeding and thromboembolism. However, achieving high-quality anticoagulation control can often be difficult and labor intensive with warfarin due to its indirect mode of action and a large number of factors that influence its pharmacokinetics and pharmacodynamics, including patient age, concurrent medications and diet, comorbidities, and genetics.

Understanding the overall quality of anticoagulation management in AF patients in the United States can be challenging because there is variation in the proportion of time spent within the therapeutic INR range among studies. Study-specific factors, such as study setting (randomized trial vs. observational anticoagulation clinic-based trial vs. observational community physician office-based trial) may explain at least some of the variance in reported quality of anticoagulation. A meta-analysis reported by van Walraven et al. in 2006 included studies from around the world and included warfarin as well as 4 vitamin K antagonists that are not available in the United States (acenocoumarol, dicumarol, ethyl biscoumacetate, and phenprocoumon). Van Walraven et al. evaluated 67 studies involving 50,208 patients with 57,155 patient-years of follow-up. Overall, patients taking vitamin K antagonists for a wide range of indications that included atrial fibrillation, venous thromboembolism, cardiovascular disease other than atrial fibrillation, peripheral vascular disease, valvular heart disease, and other indications were within therapeutic INR range 63.6% of the time (95% CI = 61.6%-65.6%).

Outside the United States, self-management of anticoagulation therapy has been a subject of research designed to find methods that might be more effective and efficient than usual care or anticoagulation clinics. Gadisseur et al. (2003) in a randomized trial found that patient self-management using a hand-held prothrombin time monitoring device was at least as effective as specialized physician management in anticoagulation clinics, as measured by the proportion of time spent in INR range. In the systematic review and meta-regression reported by van Walraven et al., 24.4% of the patients were managed in usual care (community physicians); 68.3% of patients were in anticoagulation clinics; and 7.3% of the patients were involved in clinical trials. Meta-regression showed that setting had a significant effect on anticoagulation control, with studies in community practices having significantly lower control than either anticoagulation clinics or clinical trials (−12.2%; 95% CI = −19.5 to −4.8; P < 0.001), and self-management was associated with a significant improvement of time spent in the therapeutic range (+7.0%; 95% CI = 0.7–13.3; P = 0.03). Study setting was a significant predictor of the time spent in therapeutic INR range, with about 66% of the time in therapeutic range for anticoagulation therapy in both randomized controlled trials and anticoagulation clinics as compared with 57% for community-based care provided by physician.

The findings reported by van Walraven et al. are informative but not specific to AF patients and perhaps not generalizable to the United States for warfarin therapy. Health system infrastructures and practice patterns vary greatly between nations, which can lead to differences in degrees of management. Pengo et al. (2006) highlighted differences in anticoagulation care between countries in a recently published International Study of Anticoagulation Management (ISAM) study. They found superior INR control in Spain and Italy versus the other countries; however, hematologists ran all the clinics in Spain and primarily cardiologists and hematologists ran those in Italy. The studies conducted in the United States, Canada, and Italy used predominantly warfarin, while studies in Spain and France, respectively, usedacenocoumarol and fluiniene.

The purpose of our analysis was to identify and assess (using traditional meta-analytic and meta-regressive techniques) data from all published randomized trials or cohort studies evaluating the quality of management of warfarin use by AF patients in the United States.

### Methods

In order to ensure comparability between our results and those of the previous meta-analysis by van Walraven et al., we utilized similar study selection and statistical analytic methodologies.

#### Study Selection

We first examined the full-text versions of all 67 studies included in the meta-analysis by van Walraven et al., which searched reports between 1987 and 2005, for inclusion in our analysis using the entry criteria described below. A subsequent systematic literature search was conducted in MEDLINE, EMBASE, and the Cochrane Central Register of Clinical Trials from January 1, 2005, through the end of February 2008 to identify additional studies (either prospective randomized or observational in design) evaluating warfarin as an anticoagulant in patients with AF. The search used the following Medical Subject Headings (MeSH) and text keywords: warfarin, vitamin K antagonist, VKA, anticoagulant and international normalized ratio, INR, prothrombin time, PT, PTR. The resulting citations were then limited to human subjects, clinical trials, and English language publications. Furthermore, a manual search of references from reports of clinical trials or review articles was performed to identify additional relevant trials.

Two investigators (Cios and Coleman) reviewed all potentially relevant articles independently, with disagreement resolved by a third investigator (Baker). To be included in this meta-analysis, studies had to (a) contain at least 1 warfarin-treated group including at least 25 patients for whom INR control was monitored for
at least 3 weeks; (b) include only patients treated for AF within the United States; (c) use a patient-time approach that requires the measurement of serial INRs in each study subject and an interpolation (any interpolation method was accepted, but linear was used preferentially when available) of the values between actual measures so that anticoagulation status could be estimated for each day of observation; and (d) report data on the proportion of time spent in traditional therapeutic INR ranges (i.e., a lower limit INR between 1.8 and 2.0 and an upper limit INR between 3.0 and 3.5). Studies with INR goals outside this range were excluded).\(^2\) Finally, if studies reported INR control on the same patient group at different time periods, only the time period of the longest duration was included. Studies were excluded if serial INRs were measured after the systemic administration of vitamin K, as these measurements may not be a true marker of anticoagulation status.

### Data Abstraction

Two investigators (Cios, Coleman) used a common data abstraction tool but independently abstracted all data. If a disagreement arose it was resolved by a third investigator (Baker). The following information was obtained from each study: author identification, year of publication, geographic location of the study, type of anticoagulant used, and the study setting (designated as anticoagulation clinic, randomized trial, or community practice). The setting was designated using the following definitions: (a) an anticoagulation clinic if the study took place in an anticoagulation clinic or if the stated role of the study clinicians in patient care was limited to managing anticoagulation; (b) a randomized trial if random allocation was employed to assign subjects to receive warfarin or another non-warfarin therapy; and (c) all others were classified as community practice. All of the preceding definitions were similar to those used by van Walraven et al.\(^8\)

### Statistical Analysis

The proportion of time spent within the therapeutic INR range for each study group was expressed as an incidence density using a person-time approach (in years). The numerator was calculated as the proportion of time that the group spent within the INR range multiplied by the observation time. The denominator was the total observation time for each study group (or the total study observation time multiplied by the proportion of patients in each study group, if the observation time for the individual study group was not reported in a given study). Ninety-five percent confidence intervals (CI) were calculated for each incidence density using the Wilson score method without continuity correction.\(^11\) For the purposes of this meta-analysis, all studies were pooled using a random effects model and were

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Warfarin Indication</th>
<th>Number of Warfarin-Treated Patients</th>
<th>Follow-Up</th>
<th>Study Group</th>
<th>Interpolation Method</th>
<th>Patient Years of Follow-Up(^a)</th>
<th>Proportion (95% CI)(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Samsa et al., 2000(^17)</td>
<td>RD</td>
<td>AF—identified by new ECG, chart documentation of AF, diagnostic code for AF+warfarin</td>
<td>43, 61, 125</td>
<td>NR</td>
<td>AC Clinic Community Linear</td>
<td>Linear</td>
<td>32.3(^c) (45.8(^c), 93.8(^c))</td>
<td>0.60 (0.43-0.75)</td>
</tr>
<tr>
<td>McCormick et al., 2001(^18)</td>
<td>RD</td>
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<td>174</td>
<td>1 year</td>
<td>Community Linear</td>
<td>174(^d)</td>
<td>0.51 (0.44-0.58)</td>
<td></td>
</tr>
<tr>
<td>Matchar, 2003(^2)</td>
<td>PD</td>
<td>AF</td>
<td>363, 363, 317, 317</td>
<td>9 months</td>
<td>Clinic/Comm Community Other Other Other</td>
<td>Other</td>
<td>272 (^d) (373.8(^d))</td>
<td>0.56 (0.30-0.61)</td>
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<td>Go et al., 2003(^2)</td>
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<td>2.35 years (1.83-2.81)(^c)</td>
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<tr>
<td>Menzin et al., 2005(^2)</td>
<td>RD</td>
<td>Nonvalvular AF</td>
<td>600</td>
<td>10.5 ± 3.2 months(^c)</td>
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<td>3.3 years (1.0-5.1)(^c)</td>
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<td>1 year</td>
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<td>Nichol et al., 2008(^3)</td>
<td>RD</td>
<td>Nonvalvular AF</td>
<td>756, 351</td>
<td>NR</td>
<td>Community AC Clinic Halving Halving</td>
<td>1,164 (24, 919)(^e)</td>
<td>0.42 (0.39-0.45)</td>
<td></td>
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</tbody>
</table>

\(^a\)For the indicated studies, patient-years of follow-up were estimated using number of patients in each group and the length of follow-up reported in the study.

\(^b\)Mean (95% confidence interval) proportion of time spent within the therapeutic INR range; none of these patients self-managed their own warfarin regimens.

\(^c\)Data reported as median (interquartile range).

\(^d\)Data reported as mean ± standard deviation.

AC = anticoagulation; AF = atrial fibrillation; CI = confidence interval; Comm = community; ECG = electrocardiogram; Method = International Normalized Ratio interpolation method used in the study; NR = not reported; PD = prospective design; RD = retrospective design.

### Characteristics of U.S. Atrial Fibrillation Warfarin Studies and Groups

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weighted by the inverse of the variance of proportion of time spent in the therapeutic range.8,12

In order to determine how study setting influenced the proportion of time spent within a therapeutic INR range, both subgroup and meta-regression analyses were conducted. Meta-regression analysis allows evaluating the effect of study setting independent of other influencing study design aspects (i.e., year, etc.). A multiple linear mixed model method using both random- and fixed-effects was utilized for meta-regression, which was weighted by the inverse of the variance of proportion of time spent in the therapeutic range.13,14 By conducting a mixed linear model, we accounted for the potential lack of independence of INR control within studies. Thus, study groups were treated as dependent within studies, but as independent across studies. The use of mixed linear models helps to avoid the biased estimation of variable deviation (i.e., standard error) that can arise due to the potential lack of independence among multiple groups within the same study.8 Random effects were assumed for study-level factors, including the covariates listed below, and fixed effects for patient-level factors. Study level covariates incorporated into the model include study design (community vs. anticoagulation clinic), study year (from 1998-2002 and 2003-2008), use of self-management or not,9 and interpolation method (linear or other). No hierarchy was used in the model for these covariates. Statistical analysis was performed using StatsDirect version 2.4.6 (StatsDirect Ltd., Cheshire, England) and SPSS, version 15.0 (SPSS Inc., Chicago, IL).

Results

Our review of studies included in the van Walraven et al. study8 yielded 14 studies meeting our preliminary inclusion criteria (conducted in the United States, evaluating warfarin, and limited to patients with AF).15-28 Our updated systematic search from January 2005 through February 2008 (as depicted in Figure 1) identified an additional 536 studies for full text review, of which 526 were excluded. Of the studies excluded, most were excluded because they were not conducted in the United States, or they were not a primary study. Our preliminary screening process resulted in a total of 24 studies, including a total of 43 separate groups.15-38 Of these, 16 studies were excluded because patients were included for indications other than AF.24,15,19,22,23,27,30,32,34,36,37 Thus, 8 studies, including a total of 14 study groups, met all of the inclusion criteria and were included in the final analysis (Table 1).17,18,20,21,26,31,35,38

The study groups enrolled a median of 317 patients (inter-quartile range, 150 to 482 patients; total = 22,237 warfarin-treated patients),19 who were followed for a median of 272.3 patient-years (range, 123.9 to 980.8 patient-years; total = 41,471.9 patient-years). Patients spent a median of 146.6 patient-years (range, 74.9 to 524 patient-years; total = 23,752.1 patient-years) within the therapeutic INR range. Patient-years data were calculated in 5 of the included studies17,18,20,26,38 whereas the other 3 studies reported the required data.21,31,35 Four groups (31%) were treated in anticoagulation clinics,17,26,35,38 while 9 (69%) were treated in community practice.17,18,20,21,31,38 One group in the study by Matchar (2003)20 could not be classified as either an anticoagulation clinic or community practice because warfarin control was reported in this group of patients prior to their use or nonuse of an anticoagulation clinic. No randomized controlled trials (RCTs) met our inclusion criteria; thus, no RCTs were available for evaluation in our study.

Overall, patients within the 14 included groups spent 55% (95% CI = 51%-58%) of their time within the therapeutic INR range (Figure 2). Differences by study setting were observed, with patients in an anticoagulation clinic spending a mean 63% (95% CI = 58%-68%) of their time in the therapeutic range versus 51% (95% CI = 47%-55%) for patients in community practice. As no RCTs met our inclusion criteria, we could not evaluate this subgroup. After controlling for covariates, meta-regression analyses showed similar results to that of the subgroup analyses. Compared with an anticoagulation clinic, patients treated in a community setting spent 11% (95% CI = 2%-20%, n = 6 studies, with 9 study groups) less time in range. Although the differences were not statistically significant, recently reported studies showed more improved INR control than older ones (difference of 9% [95% CI = –4% to 21%]); prospective studies showed more improved control than retrospective ones (2% [95% CI = –10% to 14%]); and studies using linear interpolation methods showed more improved control than studies using other methods (2% [95% CI = –10% to 15%]).

We also evaluated the proportion of warfarin-eligible patients who received warfarin in studies that measured that outcome. A total of 5 trials (including 8 study groups) reported data on the proportion of eligible patients receiving warfarin (Figure 3).17,18,20,21,31 Overall, 48% (95% CI = 43%-54%) of eligible AF patients received warfarin.

Discussion

Warfarin has been shown in clinical trials to significantly reduce the risk of stroke in AF patients by 64% (absolute risk reduction 2.7% for primary prevention, 8.4% for secondary prevention) versus control (placebo or no treatment).30 Based on these findings, evidence-based practice guidelines consistently recommend vitamin K antagonists for all patients with AF and at least 1 other risk factor. Rates of efficacy, unfortunately, have not translated into the real world. A recent analysis of Medicare beneficiaries with AF showed a disappointing 35% reduction in ischemic strokes among patients exposed to warfarin versus those that did not receive warfarin, revealing a discrepancy between effectiveness in clinical trials and actual clinical practice.40 The results of our analysis help provide insight into reasons for this discrepancy.

In our meta-analysis of studies evaluating anticoagulation
control in AF patients in the United States, we found that patients spent a relatively low percentage of their time within the therapeutic INR range while on warfarin (55%, 95% CI = 51%-58%). In addition, meta-regression showed that studies of usual care in the community found poorer control as measured by time within INR therapeutic range than did studies of anticoagulation clinics.

Our meta-analytic methods differed from those of van Walraven et al.¹⁸ and Dolan et al. (2008)¹⁴ in notable ways. By including only studies evaluating anticoagulation control in AF patients in the United States and limiting the evaluation exclusively to warfarin, the information is more readily applicable to the U.S. population (greater external validity). The 2 prior meta-analyses conducted by van Walraven et al. and Dolan et al. included studies evaluating a variety of warfarin indications (e.g., atrial fibrillation, venous thromboembolism, stroke), thus limiting the ability to apply their results to a particular population. We also included published U.S. trials to ensure that our observations apply to U.S. practice patterns. Since we found better INR control with anticoagulation clinics compared with community-based care, our findings help
An additional prior meta-analysis conducted by Reynolds et al. (2004) reported the overall impact of warfarin anticoagulation on clinical outcomes in patients with AF. They showed that, in studies with an INR range of 2-3, patients spent 61% of their time within the therapeutic INR range. These results are similar to ours and demonstrate the lack of adequate anticoagulation control in patients treated with oral vitamin K antagonists for AF.

The low achievement of anticoagulation control seen in our study is of concern. Unfortunately, a significant portion of
the time that patients spend on oral anticoagulants is outside of the therapeutic range. Economic modeling studies have projected improved outcomes and cost-savings from increasing the proportion of time spent within range. Chiquette et al. (1998) estimated that with improvements in time spent within the therapeutic range (64.0% vs. 51.0%) patients experienced lower rates of significant bleeding (defined as a decrease in hematocrit greater than 3% or hemoglobin level greater than 1.2 milligrams per deciliter; 8.1% vs. 35.0%) and thromboembolic events (3.3% vs 11.8%), as well as significant cost savings ($162,058 per 100 patient-years), driven mainly by reduced hospitalizations and emergency room visits.\textsuperscript{13}

However, as we saw in the present study of 4 groups managed by anticoagulation clinics, patients still spend over one-third of their time out of the therapeutic range.\textsuperscript{31,45-45} Even within clinics, newer warfarin dosing strategies—including computer-aided dosing (time within therapeutic INR range = 56% vs. 32% with usual care),\textsuperscript{16} specialty-pharmacy clinics (71% of time spent within range),\textsuperscript{23} and genotype-guided dosing\textsuperscript{32} (30.7% of INRs were out of range with genotype dosing vs. 33.1% with standard dosing)—have been investigated, with only modest improvement in overall time spent within the therapeutic INR range.

### FIGURE 3

<table>
<thead>
<tr>
<th>Study Description</th>
<th>Proportion of Eligible Patients Receiving Warfarin (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AC Clinic-Based Warfarin Dosing</strong></td>
<td></td>
</tr>
<tr>
<td>Samsa, 2000\textsuperscript{17} (n = 43)</td>
<td>0.44 (0.35-0.54)</td>
</tr>
<tr>
<td>Matchar, 2003\textsuperscript{30} (n = 363)</td>
<td>0.61 (0.55-0.67)</td>
</tr>
<tr>
<td>Subtotal</td>
<td>0.53 (0.38-0.72)</td>
</tr>
<tr>
<td><strong>Community-Based Warfarin Dosing</strong></td>
<td></td>
</tr>
<tr>
<td>Samsa, 2000\textsuperscript{17} (n = 61)</td>
<td>0.33 (0.29-0.38)</td>
</tr>
<tr>
<td>Samsa, 2000\textsuperscript{17} (n = 125)</td>
<td>0.33 (0.27-0.40)</td>
</tr>
<tr>
<td>McCormick, 2001\textsuperscript{18} (n = 174)</td>
<td>0.42 (0.37-0.47)</td>
</tr>
<tr>
<td>Go, 2003\textsuperscript{21} (n = 7,445)</td>
<td>0.55 (0.54-0.56)</td>
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<td>Subtotal</td>
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**Overall Effect**  
0.48 (0.43-0.54)

\textsuperscript{a}The squares represent individual studies, and the size of the square represents the weight given to each study in the meta-analysis. Error bars represent 95% confidence intervals. The diamond represents the combined results. The solid vertical line extending upwards from 1 is the null value. None of these studies were randomized controlled trials. List of studies shows name of first author and year of publication.

AC = anticoagulation.
Meta-Analysis to Assess the Quality of Warfarin Control in Atrial Fibrillation Patients in the United States

Limitations
The results of our study must be taken within the context of its limitations. As with all meta-analyses, publication bias is a potential concern. However, given the systematic nature of our literature search from January 2005 until February 2008, this risk was minimized. A second limitation of our meta-analysis is that the INR control in RCTs could not be evaluated, since none were identified by our search. Since no significant differences were seen in the results between RCTs and anticoagulation clinics in the previous van Walraven study (2006), it might be concluded that anticoagulation clinics and RCTs provide similar control, both of which are superior to community practice. However, according to Go et al. (2003), clinical trials evaluating warfarin in patients with nonvalvular AF translated well into their clinical practice. In addition, Matchar (2003) found no differences in INR control between patients randomized to either anticoagulation clinics or usual care. An additional limitation to this study is the differing interpolation methods used to report the time in therapeutic range among the studies. Although our model showed that the interpolation method used did not significantly impact the overall study results, caution must be used when interpreting these data. It should also be noted that the included study samples were clinically and methodologically heterogeneous, as can be seen in Table 1. For example, studies included various settings (e.g., community, clinic, and hospital) and types of AF (e.g., nonvalvular atrial fibrillation and atrial flutter).

Conclusions
In the United States, patients who receive warfarin anticoagulation spend only about one-half the time within therapeutic INR. The use of anticoagulation clinic services by patients with AF improves INR control to 63% of the time on warfarin therapy versus 51% for usual community care.

Authors
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DISCLOSURES
This study was sponsored by Boehringer Ingelheim Pharmaceuticals, and Stephen Sander is an employee of Boehringer Ingelheim Pharmaceuticals.

Study concept and design were contributed primarily by Sander and Coleman. Data collection was performed by Cios with assistance from Baker and Coleman. Data interpretation was performed primarily by Baker and Coleman. Baker wrote the manuscript with the assistance of the other authors. The revision was made primarily by Baker and Coleman.

REFERENCES
Meta-Analysis to Assess the Quality of Warfarin Control in Atrial Fibrillation Patients in the United States


Analysis of Drug Content and Weight Uniformity for Half-Tablets of 6 Commonly Split Medications

Shaynan W. Hill, PharmD; Andrew S. Varker, PharmD; Kelly Karlage, BS; and Paul B. Myrdal, PhD

BACKGROUND: Cost savings can be achieved with the practice of tablet splitting. Previous research has shown weight nonuniformity within tablet halves. However, limited research to date has found that the potential dose inaccuracy resulting from splitting tablets does not significantly affect clinical outcomes.

OBJECTIVE: To determine the drug content and weight in split half-tablets of 6 commonly split medications using drug assay analysis.

METHODS: This study was performed by 2 fourth-year pharmacy students using 30 randomly selected tablets of each of the following 6 medications: warfarin sodium 5 milligrams (mg), simvastatin 80 mg, metoprolol succinate 200 mg, metoprolol tartrate 25 mg, citalopram 40 mg, and lisinopril 40 mg. A randomly selected half of the tablets were split by a single pharmacy student using a tablet cutter, and the remaining tablets were kept whole. Drug content was analyzed for 15 whole tablets and 30 half-tablets for each of the 6 drugs using high performance liquid chromatography, an analytical tool used to identify and quantify substances in solution. Drug content uniformity was assessed by comparing drug content within half-tablets with one-half of the drug content mean found for all whole tablets in the sample. Weight uniformity was assessed by comparing half-tablet weights, as determined by a Mettler analytical balance, with one-half of the mean weight for whole tablets in the sample. The percentages by which each whole tablet’s or half-tablet’s drug content and weight differed from sample mean values were compared with proxy United States Pharmacopeia (USP) specification ranges for drug content (95%-105% for warfarin sodium and 90%-110% for the other 5 drugs). Additionally, these outcomes were compared for nonscored versus scored tablets. The percent relative standard deviation (%RSD, ratio of the standard deviation to the mean), a commonly used measure of the repeatability and precision of assays used to analyze drug content, was also calculated in order to determine whether the drugs met proxy USP specification for %RSD (less than 6% for all drugs studied).

RESULTS: A total of 43 of 180 half-tablets (23.9%) differed from sample mean values by a percentage that fell outside of proxy USP specification for drug content; warfarin sodium (11 of 30 half-tablets, 36.7%), simvastatin (3 of 30 half-tablets, 10.0%) metoprolol succinate (10 of 30 half-tablets, 33.3%), metoprolol tartrate (4 of 30 half-tablets, 13.3%), citalopram (5 of 30 half-tablets, 16.7%), and lisinopril (10 of 30 half-tablets, 33.3%). Half-tablets outside of proxy USP specification for weight included warfarin sodium (10 of 30 half-tablets, 33.3%), metoprolol succinate (6 of 30 half-tablets, 20%), and lisinopril (7 of 30 half-tablets, 23.3%). The %RSDs for drug content and weight fell outside of the proxy USP specification for %RSD for metoprolol succinate (drug content = 8.98%, weight = 7.70%) and lisinopril (drug content = 10.41%, weight = 8.13%). Mean percent weight loss after splitting was less than 1% for all drugs except lisinopril, which had an average weight loss of 1.25%. The total numbers of scored (nonscored) tablet halves that fell outside of proxy USP specification were 20 (23) for drug content and 10 (13) for weight. When measuring drug content, the numbers of out-of-range half-tablets for scored (nonscored) drugs were 36 (44) at 95%-105%, 9 (23) at 90%-110%, 0 (10) at 85%-115%, and 0 (1) at 75%-125%. When measuring weight, the numbers of out-of-range half-tablets for scored (nonscored) drugs were 28 (38) at 95%-105%, 0 (14) at 90%-110%, 0 (3) at 85%-115%, and 0 (0) at 75%-125%.

CONCLUSION: Dose variation exceeded a proxy USP specification for more than one-third of sampled half-tablets of warfarin sodium, metoprolol succinate, and lisinopril and appeared to be greater for nonscored tablets as compared with scored tablets. Drug content variation in half-tablets appeared to be attributable primarily to weight variation occurring when tablets powder or fragment during the splitting process. Therefore, equal daily doses will be determined by the ability of patients to split tablets perfectly in half.

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What is already known about this subject

• Manufacturers of FDA-approved medications are required to adhere to the United States Pharmacopeia (USP) established ranges for drug content of whole tablets. The USP has created guidelines to compare drug content for whole tablets; however, no guidelines have been established to assess the drug content of half-tablets.

• Teng et al. (2002) found that only 3 of 11 medications passed an adapted USP uniformity test when half-tablet drug content uniformity was estimated from half-tablet weight after splitting of tablets by hand or razor blade.

• To date, 4 published studies have shown that the potential inaccuracy of dose resulting from splitting tablets does not significantly affect clinical and humanistic outcomes.

What this study adds

• This is the first study to determine drug content uniformity within half-tablets using drug assay; target drug content was defined as one-half of the per-tablet mean drug content for all half-tablets in a sample of 15 whole tablets each of 6 commonly split medications.

• More than 30% of measured half-tablets (n = 30 each drug) of warfarin sodium, metoprolol succinate, and lisinopril differed from the target drug content by a percentage that fell outside of the proxy USP specification (95%-105% for warfarin sodium and 90%-110% for the other 5 drugs). For all other medications studied (simvastatin, metoprolol tartrate, and citalopram), 10%-17% of half-tablets fell outside of proxy USP specification for drug content.

• Only 5 of 180 (2.8%) half-tablets in a weight-adjusted analysis, as compared with 43 of 180 (23.9%) half-tablets in an analysis that was not weight-adjusted, fell outside of the proxy USP specification for drug content. Thus, drug content variation in half-tablets appears to be attributable primarily to weight variation occurring when tablets powder or fragment during the splitting process.

Note: This article is the subject of a commentary that appears on pages 272-274 of this issue.
Tablet splitting has become increasingly common, especially within the geriatric and psychiatric communities, as a means of reducing medication dose and/or cost. Physicians frequently write prescriptions for half-tablets in order to achieve doses less than the smallest available manufactured strength. Prescribers also write for half- and quarter-tablet doses of higher-strength tablets in order to reduce costs because parity pricing (the use of flat rates for medications independent of dose strength) is common. Cohen and Cohen (2000) showed that an annual savings of $1.45 billion could be achieved when tablet splitting was performed for 12 specific psychotropic medications, while annual savings of $725 million and $325 million could be achieved from splitting one-half and one-fourth of prescriptions written, respectively. Cohen and Cohen later (2002) estimated potential cost savings of $1.7 billion nationally if tablet splitting was performed for 7 antidepressant medications. Miller et al. (2007) found that tablet splitting contributed $342,239 (about $1.30 per member per month [PMPM]) or 17.3% of total annualized savings of $1,983,153 attributed to 4 managed care interventions that included (a) moving certain brand name drugs in 6 drug classes to nonpreferred status, (b) removing low-sedating antihistamines from the formulary, (c) limiting the quantity supplied for sedative sleep aids, and (d) tablet splitting for 9 brand name drugs (6 antidepressants and 3 statins). Stafford and Radley (2002) estimated that tablet splitting for 11 drugs was infrequent, accounting for annual savings of only $0.03 PMPM compared with potential savings of $1.14 PMPM.

Although cost savings may be accomplished, problems may arise with tablet splitting such as poor cognitive function or memory, the inability of patients to effectively split tablets, and the fear of inaccurate dose. The “Uniformity of Dosage Units” section in the U.S. Pharmacopeia (USP) manual states that each unit within a single lot of a given medication should have drug substance content that is within a narrow range around the labeled claim. Several studies have looked at weight variation of split tablets as a means of estimating drug content uniformity. Teng et al. (2002) evaluated the weight uniformity of 11 commonly split medications through an analysis of half-tablet weights, using a uniformity test adapted from the USP specifications. Eight medications were split using a single-edged razor blade, and 3 were split by hand (i.e., using only tensile strength of the fingers or hands). Results revealed that only 3 of 11 medications passed their adapted USP specifications, and there were no obvious tablet features (e.g., scoring) that determined whether a tablet would pass or fail the uniformity test. This study also found that tablets split by hand showed less uniformity than did tablets split using a razor blade, even though splitting tablets by hand produced cleaner splits with less tablet crumbling.

A similar study performed by Polli et al. assessed content uniformity through the analysis of half-tablet weights using the same adapted USP methods as used by Teng et al. In contrast to the results found by Teng et al., this study, performed at a Department of Veterans Affairs (VA) center, found that 8 out of 12 medications split with a tablet-splitting device passed the adapted uniformity test. Another study analyzed the drug weight uniformity of cyclobenzaprine tablets split in half using either a tablet splitter or a kitchen knife. The results showed that both methods resulted in a wide variation in fragment weight between 49.9% to 149.5% of the theoretical weight (defined as one-half of the mean weight of the intact tablet) using a kitchen knife and 69.4% to 130.2% using the tablet splitter. Thus, both methods failed the quality standards for dosage uniformity of manufactured drugs as outlined by Teng et al.

Rosenberg et al. (2002) evaluated content uniformity of discontinued pharmacist-dispensed split-tablet samples taken from 4 long-term care facilities using a total of 560 fragments. These authors found that 2 of 22 medications had significantly different fragment weights as compared with the theoretical weight of the half-tablets. The researchers also found that 30 of the 560 fragments deviated by more than 15% of the sample mean fragment weight, and 32 of the 560 fragments deviated by more than 15% of the theoretical weight. Lastly, 15 of the 22 medications were found to have relative standard deviations for weight expressed as a percentage (%RSDs) in excess of 6%, the upper limit of the USP specification.

Although studies of weight differences among split tablets have been performed, the more important analysis of drug content has yet to be explored. Studies to date have assessed drug content uniformity only as variation in half-tablet weights. These studies adapted the USP manual section entitled “Uniformity of Dosage Units”—criteria developed to ensure that actual drug content is equivalent to manufacturer-labeled drug content—and indirectly measured half-tablet drug content by measuring half-tablet weight. Although USP guidelines enforce strict adherence to drug content per dosage unit for whole tablets, guidelines for the drug content of split tablets have yet to be established.

In the present study, we defined the target drug content and weight of a half-tablet as equal to one-half of the mean drug content and weight, respectively, for all whole tablets in a sample of 6 commonly split medications. To assess the acceptability of variation in the half-tablets, defined as the percentage by which each individual whole tablet and half-tablet differed from the sample mean values, we adapted USP specifications for drug content and weight of whole tablets (proxy USP specification). We hypothesized that the drug content and weight of half-tablets would deviate from these proxy specifications.

Methods

Six drugs were studied: warfarin sodium 5 milligrams (mg), simvastatin 80 mg, metoprolol succinate 200 mg, metoprolol tartrate 25 mg, citalopram 40 mg, and lisinopril 40 mg (Table 1). These drugs were chosen because they were observed to be commonly split within a single VA health care network. A total of 30 whole tablets were randomly selected from each medication lot for each of the 6 drugs. All 30 whole tablets were weighed using a Mettler
Toledo AG204 (Mettler Toledo, Inc., Columbus, Ohio) analytical balance that is accurate to 0.1 mg. Fifteen of the 30 randomly selected tablets were split in half by a single pharmacy student (SH), using a Locking Tablet Cutter (Apothecary Products, Inc.), and weighed with the Mettler Toledo analytical balance.

The 15 whole tablets and 30 half-tablets for each of the 6 drugs were then dissolved separately using a combination of manual agitation and sonication techniques in an appropriate diluent adapted from respective USP official monographs. All tablets were assayed in accordance with USP methodology for determining content uniformity for whole tablets. Assay parameters for each drug were taken directly from USP monographs; customarily changes were made to allow for column optimization (Appendix). After the tablets were completely dissolved, samples of each solution were assayed for drug concentration via a Waters Alliance High Pressure Chromatography system, consisting of a 2695 Separations Module coupled with a 2487 Dual Wavelength ultraviolet (UV) detector (Waters Corporation, Milford, MA). A standard curve was created for each drug, using pure drug powder (obtained from LKT Laboratories, St. Paul, MN, or Sigma-Aldrich, St. Louis, MO) diluted to 5 known concentrations. These standard curves were established to verify accurate analysis of the drug, as opposed to any inactive tablet constituents, and to quantify drug content by calculating concentration from area under the curve data obtained through high performance liquid chromatography (HPLC) analysis of whole- and half-tablet samples.

The following parameters were assessed for each of the 6 medications (Table 2):

1. Measured drug content:
   a. Each whole tablet’s drug content (n = 15) was compared with the target drug content for whole-tablets, defined as one-half of the mean measured drug content for all whole tablets in the sample.
   b. Each half-tablet’s drug content (n = 30) was compared with the target drug content for half-tablets, defined as one-half of the mean measured drug content for all whole tablets in the sample.

2. Weight-adjusted target drug content: To account for tablet powdering/fragmenting and the inability to split tablets into perfectly equal halves, each half-tablet’s target drug content (n = 30) was adjusted for the weight of the fragment. The adjustment formula assumed that within a single half-tablet of known weight, the half-tablet’s proportion of the whole-tablet drug content should equal the half-tablet’s proportion of the whole-tablet weight (e.g., if a half-tablet was 51% of the whole-tablet weight, it should equal 51% of the whole-tablet target drug content).

3. Measured weight:
   a. Each whole tablet’s weight (n = 15) was compared with the target weight for whole tablets, defined as the mean measured weight for all whole tablets in the sample.
   b. Each half-tablet weight (n = 30) was compared with one-half of the target weight for whole tablets.

4. For each tablet, the percentage weight loss due to fragmenting and/or powdering was calculated as [(measured weight of whole tablet – measured weight of both half-tablets] / measured weight of whole tablet) x 100.

5. Nonscored drug tablets (n=90; simvastatin, metoprolol succinate, and lisinopril) were compared with scored drug tablets (n=90; warfarin sodium, citalopram, and metoprolol tartrate) on 2 outcome measures, half-tablet drug content and half-tablet weight.

To assess the amount and acceptability of variations in drug content and weight, several measures were calculated. The measured drug content expressed as a percent of target drug content was calculated for both whole and half-tablets using the following equation: ([target drug content – measured drug content] / target drug content) x 100. Individual values for whole tablets should...
TABLE 2 Definitions of Terms

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>United States Pharmacopeia (USP)</td>
<td>A publication that contains legally recognized standards of identity, strength, quality, purity, packaging, and labeling for drug substances, dosage forms, and other therapeutic products, including nutritionals and dietary supplements.</td>
</tr>
<tr>
<td>Percent (%) RSD</td>
<td>Ratio of the standard deviation to the mean measured variable ( \times ) 100 standard deviation for measured variable ( \times ) 100 measured variable mean.</td>
</tr>
<tr>
<td>5-point standard curve</td>
<td>A curve consisting of 5 known concentrations of the drug created using pure drug—used to determine that the drug was isolated by HPLC as opposed to other tablet constituents.</td>
</tr>
<tr>
<td>High Performance (Pressure) Liquid Chromatography (HPLC)</td>
<td>A form of liquid chromatography used to separate compounds that are dissolved in solution.</td>
</tr>
<tr>
<td>Measured drug content</td>
<td>The amount of drug (mg) determined to be within the whole or half-tablet analyzed using HPLC.</td>
</tr>
<tr>
<td>Measured weight</td>
<td>The weight (mg) of the whole or half-tablet as measured using a Mettler analytical balance.</td>
</tr>
<tr>
<td>Target drug content for individual tablet or half-tablet (measured drug content mean per tablet for sample)</td>
<td>Whole tablets: ( \sum \text{drug content for whole tablets} ) ( \text{number of whole tablets} ) Half-tablets: ( \sum \text{drug content for half-tablets} ) ( \text{number of half-tablets} )</td>
</tr>
<tr>
<td>Target weight for individual tablet or half-tablet (measured weight mean per tablet for sample)</td>
<td>Whole tablets: ( \sum \text{weight for whole tablets} ) ( \text{number of whole tablets} ) Half-tablets: ( \sum \text{weight for half-tablets} ) ( \text{number of half-tablets} )</td>
</tr>
<tr>
<td>Weight-adjusted target drug content</td>
<td>The amount expected to be found within a single half-tablet of known weight, assuming that the half-tablet's proportion of whole tablet drug content equals the half-tablet's proportion of whole tablet weight.</td>
</tr>
<tr>
<td>Percent of weight-adjusted drug content</td>
<td>Measured half-table drug content as a percent of weight-adjusted target drug content. ( \frac{\text{measured drug content for half-table #1}}{\text{weight-adjusted target drug content}} \times 100 )</td>
</tr>
<tr>
<td>Percent of target drug content</td>
<td>For each tablet or half-tablet, expresses measured drug content as a percentage of target drug content. Whole tablets: ( \frac{\text{measured drug content for whole tablet #1}}{\text{target drug content for whole tablets}} \times 100 ) Half-tables: ( \frac{\text{measured drug content for half-table #1}}{\text{target drug content for half-tables}} \times 100 )</td>
</tr>
<tr>
<td>Percent of target weight</td>
<td>For each tablet or half-tablet, expresses measured weight as a percentage of target weight. Whole tablets: ( \frac{\text{measured weight for whole tablet #1}}{\text{target weight for whole tablets}} \times 100 ) Half-tables: ( \frac{\text{measured weight for half-table #1}}{\text{target weight for half-tables}} \times 100 )</td>
</tr>
<tr>
<td>Mean percent weight loss</td>
<td>The amount of drug loss caused by the splitting process. ( \frac{\text{weight of whole tablet #1} - \text{weight of half-table #1} - \text{weight of half-table #2}}{\text{weight of whole tablet}} \times 100 )</td>
</tr>
<tr>
<td>Proxy USP specification for drug content</td>
<td>Measured drug content of whole or half-tablets within 95%-105% of target drug content for half-tables for warfarin sodium and within 90%-110% of target drug content for half-tables for simvastatin, metoprolol succinate, metoprolol tartrate, citalopram, and lisinopril.</td>
</tr>
<tr>
<td>Proxy USP specification for weight</td>
<td>Measured weight of whole or half-tables within 95%-105% of target weight for half-tables for warfarin sodium and within 90%-110% of target weight for half-tables for simvastatin, metoprolol succinate, metoprolol tartrate, citalopram, and lisinopril.</td>
</tr>
</tbody>
</table>
| Proxy USP specification for %RSD                                     | %RSD for whole or half-tables less than 6%. \( HPLC = \text{high performance liquid chromatography; mg = milligrams; RSD = relative standard deviation.} \)

fall within 95%-105% for warfarin sodium and 90%-110% for the other 5 drugs studied (proxy USP specification for drug content) according to the individual USP drug monographs. Because no USP criteria for drug content uniformity of half-tablets have yet been established, this study applied the proxy USP specification for whole tablets to half-tablets. It should be noted that the proxy USP specification ranges chosen for this study are the more stringent of ranges described within the individual USP monographs. The tighter range is typically applied to samples of 20 or greater. However, individual tablets are typically subjected to a specification range of 85%-115%.

Relative standard deviation expressed as a percentage (%RSD), which is a ratio of the standard deviation to the mean of the variable being analyzed, was calculated for whole tablets (drug content and weight) and for half-tablets (drug content, weight-adjusted drug content, and weight). The %RSD is widely used to...
assess the repeatability and precision of the assays used to analyze drug content. The %RSD for drug content for all drugs studied was calculated using the following equation: (standard deviation for measured drug content / measured drug content mean) x 100. The %RSD for weight for all drugs studied was calculated using the following equation: (standard deviation for measured weight / measured weight mean) x 100. Individual medication lots for whole tablets are targeted to have a %RSD less than 6% (proxy USP specification for %RSD).3

The percentage by which weight-adjusted drug content differed from target drug content was calculated using the following equation: (measured drug content for half-tablet / weight-adjusted target drug content for half-tablet) x 100.

### Results

#### Drug Content

For all whole tablets studied, measured drug content expressed as a percent of target drug content was found to fall within the proxy USP specification percentage range (Table 3). All whole tablets also met the proxy USP specification for %RSD. The measured drug content expressed as a percent of target drug content for half-tablets fell outside of the proxy USP specification for drug content for at least 3 half-tablets of each drug studied. A total of 43 of 180 half-tablets (23.9%) fell outside of the proxy USP specification for drug content; warfarin sodium (11 of 30 half-tablets, 36.7%), simvastatin (3 of 30 half-tablets, 10.0%) metoprolol succinate (10 of 30 half-tablets, 33.3%), metoprolol tartrate (4 of 30 half-tablets, 13.3%), citalopram (5 of 30 half-tablets, 16.7%), and lisinopril (10 of 30 half-tablets, 33.3%). The measured drug content variations expressed as a percent of target drug content for half-tablets were, from smallest to the largest, warfarin sodium (90.01-109.40%), simvastatin (95.21%-111.35%), metoprolol succinate (82.77%-115.92%), metoprolol tartrate (94.83%-112.37%), citalopram (96.50-111.93%), and lisinopril (81.15%-125.72%). Metoprolol succinate and lisinopril were the only agents analyzed that fell outside of the proxy USP specification for %RSD, with %RSD values of 8.98% and 10.41%, respectively.

Weight-adjusted drug content expressed as a percent of target drug content for half-tablets fell outside of the proxy USP specification for drug content for at least 1 half-tablet of 3 drugs—warfarin sodium, citalopram, and lisinopril (Table 3). A total of 5 of 180 half-tablets (2.78%) fell outside of the proxy USP specification for drug content for at least 3 half-tablets of each drug studied. A total of 43 of 180 half-tablets (23.9%) fell outside of the proxy USP specification for drug content; warfarin sodium (11 of 30 half-tablets, 36.7%), simvastatin (3 of 30 half-tablets, 10.0%) metoprolol succinate (10 of 30 half-tablets, 33.3%), metoprolol tartrate (4 of 30 half-tablets, 13.3%), citalopram (5 of 30 half-tablets, 16.7%), and lisinopril (10 of 30 half-tablets, 33.3%). The measured drug content variations expressed as a percent of target drug content for half-tablets were, from smallest to the largest, warfarin sodium (90.01-109.40%), simvastatin (95.21%-111.35%), metoprolol succinate (82.77%-115.92%), metoprolol tartrate (94.83%-112.37%), citalopram (96.50-111.93%), and lisinopril (81.15%-125.72%). Metoprolol succinate and lisinopril were the only agents analyzed that fell outside of the proxy USP specification for %RSD, with %RSD values of 8.98% and 10.41%, respectively.

Weight-adjusted drug content expressed as a percent of target drug content for half-tablets fell outside of the proxy USP specification for drug content for at least 1 half-tablet of 3 drugs—warfarin sodium, citalopram, and lisinopril (Table 3). A total of 5 of 180 half-tablets (2.78%) fell outside of the proxy USP specification for drug content for at least 3 half-tablets of each drug studied. A total of 43 of 180 half-tablets (23.9%) fell outside of the proxy USP specification for drug content; warfarin sodium (11 of 30 half-tablets, 36.7%), simvastatin (3 of 30 half-tablets, 10.0%) metoprolol succinate (10 of 30 half-tablets, 33.3%), metoprolol tartrate (4 of 30 half-tablets, 13.3%), citalopram (5 of 30 half-tablets, 16.7%), and lisinopril (10 of 30 half-tablets, 33.3%). The measured drug content variations expressed as a percent of target drug content for half-tablets were, from smallest to the largest, warfarin sodium (90.01-109.40%), simvastatin (95.21%-111.35%), metoprolol succinate (82.77%-115.92%), metoprolol tartrate (94.83%-112.37%), citalopram (96.50-111.93%), and lisinopril (81.15%-125.72%). Metoprolol succinate and lisinopril were the only agents analyzed that fell outside of the proxy USP specification for %RSD, with %RSD values of 8.98% and 10.41%, respectively.

### Table 3: Whole- and Half-Tablet Drug Content

<table>
<thead>
<tr>
<th>Drug</th>
<th>Target Drug Content (mg)</th>
<th>Measured Drug Content Mean (mg)</th>
<th>%RSD</th>
<th>Percent of Target Drug Content - Range</th>
<th>Outside of Proxy USP Specification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin sodium</td>
<td>Whole (n=15)</td>
<td>2.56</td>
<td>1.81</td>
<td>97.39 – 102.66</td>
<td>0</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>Whole (n=15)</td>
<td>98.04</td>
<td>8.98</td>
<td>82.77 – 115.92</td>
<td>10 (33.3%)</td>
</tr>
<tr>
<td>Metoprol succinate</td>
<td>Whole (n=15)</td>
<td>14.64</td>
<td>4.73</td>
<td>94.83 – 112.37</td>
<td>4 (13.3%)</td>
</tr>
<tr>
<td>Metoprol tartrate</td>
<td>Whole (n=15)</td>
<td>19.13</td>
<td>4.50</td>
<td>96.50 – 111.93</td>
<td>5 (16.7%)</td>
</tr>
<tr>
<td>Citalopram</td>
<td>Whole (n=15)</td>
<td>19.13</td>
<td>10.41</td>
<td>81.15 – 125.72</td>
<td>10 (33.3%)</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>Whole (n=15)</td>
<td>20.46</td>
<td>10.0%</td>
<td>95.21 – 107.15</td>
<td>3 (10.0%)</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>Half (n=30)</td>
<td>98.04</td>
<td>8.98</td>
<td>82.77 – 115.92</td>
<td>10 (33.3%)</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>Half (n=30)</td>
<td>19.13</td>
<td>4.50</td>
<td>96.50 – 111.93</td>
<td>5 (16.7%)</td>
</tr>
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<td>Half (n=30)</td>
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<td>Half (n=30)</td>
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<td>96.50 – 111.93</td>
<td>5 (16.7%)</td>
</tr>
<tr>
<td>Citalopram</td>
<td>Half (n=30)</td>
<td>19.13</td>
<td>4.50</td>
<td>96.50 – 111.93</td>
<td>5 (16.7%)</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>Half (n=30)</td>
<td>19.13</td>
<td>4.50</td>
<td>96.50 – 111.93</td>
<td>5 (16.7%)</td>
</tr>
</tbody>
</table>

### Table 3 Notes

- Target drug content for whole tablets is equal to the measured drug content mean per tablet for the sample. Target drug content for half-tablets is one-half of the measured drug content mean.
- Mean drug content values per whole tablet or half-tablet as determined by HPLC.
- A range (smallest to largest) representing measured drug content for whole or half-tablets expressed as a percent of target drug content.
- Number of whole or half-tablets with measured drug content not within 95%-105% of target drug content for warfarin sodium or 90%-110% of target drug content for simvastatin, metoprolol succinate, metoprolol tartrate, citalopram, and lisinopril.
- HPLC = high performance liquid chromatography; mg = milligram; %RSD = relative standard deviation expressed as a percentage; USP = United States Pharmacopeia; wt adj = weight-adjusted.
USP specification for drug content after weight adjustment; these included warfarin sodium (3 of 30 half-tablets, 10%), citalopram (1 of 30 half-tablets, 3.33%), and lisinopril (1 of 30 half-tablets, 3.33%). Metoprolol succinate and lisinopril were the only agents analyzed that fell outside of the proxy USP specification for %RSD after weight adjustment, with %RSD values of 7.67% and 8.07%, respectively.

### Weight

For all whole tablets studied, measured weight expressed as a percent of target weight was found to fall within the proxy USP specification for weight (Table 4). All whole tablets also met the proxy USP specification for %RSD. Measured weight expressed as a percent of target weight for half-tablets fell outside of the proxy USP specification for weight for at least 6 half-tablets of warfarin sodium, metoprolol succinate, and lisinopril. A total of 23 of 180 half-tablets (12.8%) fell outside of the proxy USP specification for weight; these included warfarin sodium (10 of 30 half-tablets, 33.3%), metoprolol succinate (6 of 30 half-tablets, 20.0%), and lisinopril (7 of 30 half-tablets, 23.3%). Metoprolol succinate and lisinopril were the only agents analyzed that fell outside of the proxy USP specification for %RSD, with %RSD values of 7.70% and 8.13%, respectively.

Mean percent weight loss, after splitting, was less than 1% for all drugs with the exception of lisinopril: warfarin sodium (0.50%), simvastatin (0.08%), metoprolol succinate (0.17%), metoprolol tartrate (0.57%), citalopram (0.24%), and lisinopril (1.25%; Table 4).

### Scored Versus Nonscored Tablets

A total of 20 of 90 (22.2%) half-tablets of scored medications, and a total of 23 of 90 (25.6%) half-tablets of nonscored medications fell outside of the proxy USP specification for drug content (Table 5). The numbers of half-tablets for scored (nonscored) drugs falling outside of range for drug content were 36 (44) for 95%-105%, 9 (23) for 90%-110%, 0 (10) for 85%-115%, and 0 (1) for 75%-125%.

A total of 10 of 90 (11.1%) half-tablets of scored medications, and a total of 13 of 90 (14.4%) half-tablets of nonscored medications fell outside of the proxy USP specification for weight (Table 6). The numbers of half-tablets for scored (nonscored) drugs falling outside of range for weight were 28 (38) for 95%-105%, 0 (14) for 90%-110%, 0 (3) for 85%-115%, and 0 (0) for 75%-125%.

### Discussion

When measured half-tablet drug content was compared against target drug content (one-half of the sample mean drug content) for each of 6 study medications, 43 of 180 half-tablets (23.9%) fell outside of a proxy USP specification percentage range. Warfarin sodium had the highest number of half-tablets falling out of its proxy specification range, most likely due to its narrower specification window of 95%-105%. Metoprolol succinate and lisinopril were found to have a relatively large number of half-tablets with drug content falling outside of the range of 90%-110%. Variation in half-tablet drug content was greatest with lisinopril, which had tablet halves ranging from 81.15% to 125.72% of the target drug.
content for half-tablets. Thus, when tablet splitting is performed for this lot of lisinopril, patients may receive daily doses that vary by as much as 45%.

Several potential reasons could explain the observed variation in lisinopril half-tablet drug content. Inaccuracy during the tablet splitting process may have produced variability between tablet halves due to unequal half-tablet size. This argument is supported by the weight-adjusted data: Only a single lisinopril half-tablet fell outside of the range of 90%-110% when half-tablet drug content was adjusted for weight as compared with 10 half-tablets when the data were not adjusted for weight. The results for lisinopril may also have been affected by weight loss due to the powdering and fragmenting that occurred during tablet splitting. Although lisinopril half-tablets were shown to have a mean percent weight loss of 1.25%, the majority of lisinopril half-tablets did not fall outside the proxy USP specification for drug content until the weight loss was greater than 1.72%.

Both metoprolol succinate and metoprolol tartrate may also have been affected by the inaccuracy of the tablet splitting device to accurately split medications into 2 equal halves. Additionally, for metoprolol succinate, a greater percent of drug content variation may be attributed to tablet formulation, specifically regarding the sustained release mechanism. This drug is found within nondisolving pellets intended to provide a slow release of the drug. Without the ability to visualize the inside of individual drug pellets, complete dissolution could not be easily determined.

Metoprolol succinate and lisinopril were shown to have %RSD values greater than 6% with regard to drug content and weight. This finding indicates that tablets of these medications are not easily split into equal halves when using a tablet-splitting device. Lisinopril had the greatest degree of drug content variability, with a %RSD of greater than 10%, perhaps in part because lisinopril had the greatest amount of weight loss from splitting. The high level of variability for metoprolol succinate may be due to the extended release drug delivery system.

Following the splitting process, half-tablet weight measurements revealed unequal splitting; this finding is likely a result of tablet powdering and limitations of the tablet splitter, person, and device. When half-tablet drug content was adjusted for weight, a large reduction in drug content variation was found. Thus, half-tablet weight appears to be directly correlated with drug content. When compared with the target drug content of a perfectly split tablet half, 43 of 180 half-tablets (23.9%), but only 5 of 180 weight-adjusted half-tablets (2.8%) fell outside of proxy USP specification for drug content. Warfarin sodium accounted for the majority of weight-adjusted half-tablets falling outside of proxy

### Table 5: Comparison of Scored and Nonscored Half-Tablets: Drug Content

<table>
<thead>
<tr>
<th>Tablet type</th>
<th>n</th>
<th>Percent of Target Drug Content - Range</th>
<th>Outside of Proxy USP Specification</th>
<th>Out of Range (95% - 105%)</th>
<th>Out of Range (90% - 110%)</th>
<th>Out of Range (85% - 115%)</th>
<th>Out of Range (75% - 125%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scored</td>
<td>90</td>
<td>89.85 – 112.37</td>
<td>20 (22.2%)</td>
<td>36 (40.0%)</td>
<td>9 (10.0%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Nonscored</td>
<td>90</td>
<td>81.15 – 125.72</td>
<td>23 (25.6%)</td>
<td>44 (48.9%)</td>
<td>23 (25.9%)</td>
<td>10 (11.1%)</td>
<td>1 (1.1%)</td>
</tr>
</tbody>
</table>

4A range (smallest to largest) representing measured drug content for whole or half-tablets expressed as a percent of target drug content.

5Number of half-tablets with measured drug content not within 95%-105% of target drug content for half-tablets for warfarin sodium or 90%-110% of target drug content for half-tablets for simvastatin, metoprolol succinate, metoprolol tartrate, citalopram, and lisinopril.

6Determined by HPLC. The number (%) of half-tablets that fell outside of the range listed for drug content expressed as a percentage of target half-tablet drug content.

7Warfarin sodium, metoprolol succinate, and citalopram tablets were scored.

8Simvastatin, metoprolol succinate, and lisinopril tablets were not scored.

HPLC = high performance liquid chromatography; USP = United States Pharmacopeia.

### Table 6: Comparison of Scored and Nonscored Half-Tablets: Weight

<table>
<thead>
<tr>
<th>Tablet type</th>
<th>n</th>
<th>Percent of Mean Weight - Range</th>
<th>Outside of proxy USP Specification</th>
<th>Out of Range (95% - 105%)</th>
<th>Out of Range (90% - 110%)</th>
<th>Out of Range (85% - 115%)</th>
<th>Out of Range (75% - 125%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scored</td>
<td>90</td>
<td>90.69 – 109.05</td>
<td>10 (11.1%)</td>
<td>28 (31.1%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Nonscored</td>
<td>90</td>
<td>82.16 – 113.27</td>
<td>13 (14.4%)</td>
<td>38 (42.2%)</td>
<td>14 (15.6%)</td>
<td>3 (3.3%)</td>
<td>0</td>
</tr>
</tbody>
</table>

4A range (smallest to largest) representing measured weight for whole or half-tablets expressed as a percent of target weight.

5Number (%) of half-tables with measured weight not within the 95%-105% specification range for warfarin sodium or 90%-110% for the other 5 drugs.

6Determined by Mettler analytical balance. The number (%) of half-tablets that fell outside of the range listed for drug weight expressed as a percentage of target half-tablet drug weight.

7Warfarin sodium, metoprolol tartrate, and citalopram tablets were scored.

8Simvastatin, metoprolol succinate, and lisinopril tablets were not scored.

USP = United States Pharmacopeia.
USP specification for drug content (3 of the 5 half-tablets). It was also observed that the %RSD for weight-adjusted drug content for all medications was reduced in comparison with non-weight-adjusted drug content. These results would appear to indicate that the drug is uniformly dispersed within single whole tablets.

The data suggest greater variability in half-tablet drug content and weight for nonscored medications than for scored medications. Although nonscored and scored tablets produced roughly an equivalent number of half-tablets falling outside of proxy USP specification for drug content and weight, it was found that greater variability existed with the nonscored drug tablets. More nonscored drug half-tablets were found to have drug content and weight within the ranges of 85%-115% and 75%-125%. This finding suggests that when a tablet-splitting device is used, dose administration may be more accurate and consistent for scored than nonscored medications; however, a larger sample of scored and nonscored tablets is needed to determine if there is a significant difference between scored and nonscored tablets.

The pharmacokinetics and the mechanisms by which these medications act would appear to dictate that half-tablet regimens may or may not have a clinical impact on long-term patient outcomes. Metoprolol succinate, lisinopril, and citalopram are agents with long durations of action, in which minor dose variation should have no significant impact on steady state plasma concentrations. Additionally, citalopram efficacy is highly subjective; thus, daily efficacy measurements can be variable regardless of small dose variation. Statins, including simvastatin, are agents designed to prevent downstream medical problems such as acute coronary syndromes and stroke; thus, small changes in daily dose should have no significant impact on long-term clinical endpoints. Lastly, antihypertensives, including angiotensin-converting enzyme inhibitors and beta blockers, are used to prevent medical problems associated with an elevated blood pressure over an extended period of time, thus, daily fluctuations in dose would be expected to affect blood pressure measurements and side effects and have no effect on long-term clinical end points.

In contrast, caution should be taken when splitting warfarin sodium due to the potential for significant adverse events with minimal change in daily dose. However, daily variation of international normalized ratio (INR) values, the parameter used to monitor warfarin sodium efficacy, can result from food interactions, drug interactions, and variations in daily dose. For this reason, it cannot be stated that the minor differences in warfarin sodium half-tablet drug content will predict clinical outcomes.

Comparison With Previous Research and Clinical Significance
In order to determine true clinical significance of tablet splitting, studies looking at clinical outcomes must be examined. Four studies known to these authors have evaluated the clinical impact of half-tablet regimens: 3 assessing statins and 1 assessing lisinopril.10-13 All 4 studies have shown that the dose inaccuracy experienced from splitting tablets does not significantly affect primary outcomes. The study by Duncan et al. (2002) performed at a VA medical center examined triglycerides, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and total cholesterol values for 109 patients enrolled in a statin (atorvastatin and simvastatin) tablet splitting program.10 The study concluded that there was a significant decrease in total cholesterol (187.6 mg per deciliter [dl] to 179.7 mg per dl; \( P = 0.005 \)) and LDL-C (111.6 mg per dl to 105.1 mg per dl; \( P = 0.004 \)) after at least 6 weeks following the initiation of the split tablet program. Duncan et al. concluded that there was no clinically significant difference comparing the time periods before and after the initiation of the tablet-splitting program.

A similar study performed at a different VA medical center assessed clinical endpoints before and after the initiation of a tablet-splitting program for 2,019 patients.11 This study by Gee et al. (2002) also found no clinically significant changes in serum lipid levels before and after implementation of the tablet-splitting program. A more recent retrospective chart review was performed across 6 VA medical centers, comparing 3,196 patients assigned to a split-tablet regimen with a whole-tablet regimen of varying simvastatin doses.12 Similar to the other previously mentioned studies, no statistically significant difference in LDL-C was found between patients in the split-tablet group and in the whole-tablet comparison group (\( P = 0.304 \)). A randomized crossover study performed at another VA medical center found no statistically significant differences in systolic or diastolic blood pressure for patients treated with whole- and half-tablet regimens for lisinopril.13 No studies to date have been performed that assess the clinical impact of half-tablet regimens for citalopram, metoprolol tartrate, metoprolol succinate, or warfarin sodium; thus, no conclusions about the clinical impact of half-tablet regimens for these agents can be made.

Limitations
First, the USP has not created a method for assessing half-tablet drug content uniformity; thus, previous studies assessing half-tablet drug content uniformity have used adapted USP methods for assessing weight variability as a means of estimating drug content uniformity. Second, all of the medications in this study are now available generically, and there is little financial value in splitting these particular drugs today. Third, the medications chosen for analysis were determined by prevalence of tablet splitting within a single health care network. The medications studied may not be representative of the most commonly split medications, and the purpose of the present research is not to suggest which drug classes may or may not be split. For these reasons, health care practitioners may not extrapolate the findings of this study to medications not studied. Fourth, the only tablet-splitting technique studied was the use of a tablet-splitting device. Splitting by hand or with sharp instruments including knives and razor blades are also commonly used techniques.
in the outpatient setting. With greater precision and accuracy, tablet-splitting devices generally provide greater consistency in half-tablet doses. Thus, tablets split using other techniques may lead to greater variability than that observed in this study. Fifth, a single pharmacy student performed all tablet splitting and weight measurements in an intentional effort to eliminate variability that might be introduced by multiple testers. However, this tester’s technique may not be representative of tablet-splitting when performed by patients in the general population. In particular, certain patient populations may have increased difficulty splitting tablets, such as the elderly and patients with arthritis, movement disorders, or poor cognitive function. Lastly, this research does not permit clinical conclusions since no clinical end points were assessed.

Conclusion

Dose variation, measured as the difference between actual half-tablet drug content and sample mean drug content, exceeded a proxy USP specification for more than one-third of sampled half-tablets of warfarin sodium, metoprolol succinate, and lisinopril. The percentages of half-tablets exceeding a proxy USP specification for drug content were roughly equal for scored and nonscored tablets; however, dose variation appeared to be greater with nonscored tablets. Fewer half-tablets in a weight-adjusted analysis than in an analysis that was not weight-adjusted fell outside of the proxy USP specification for drug content. Thus, drug content variation in half-tablets appears to be attributable primarily to weight variation occurring when tablets powder or fragment during the splitting process. Therefore, equal daily doses will be determined by the ability of patients to split tablets perfectly in half.

DISCLOSURES

The authors reported no external funding for this research and no financial or other conflicts of interest related to the subject of this manuscript.

Hill was primarily responsible for the study concept and design, with assistance from Karlage and Myrdal. The data were collected primarily by Hill and Varker, with assistance from Karlage. Hill and Myrdal interpreted the data, with assistance of the other 2 authors. Hill and Varker wrote the manuscript, and Varker was primarily responsible for revision of the manuscript, with assistance from the other 3 authors.

REFERENCES


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Adherence to International Antimicrobial Prophylaxis Guidelines in Cardiac Surgery: A Jordanian Study Demonstrates Need for Quality Improvement

Nairooz H. Al-Momany, MSc; Amal G. Al-Bakri, PhD; Zeid M. Makahleh, MD, MRCS; and Mayyada M.B. Wazaify, PhD

ABSTRACT

BACKGROUND: Antimicrobial prophylaxis in cardiac surgery has been demonstrated to lower the incidence of surgical site infection (SSI). Inappropriate antimicrobial prophylaxis, such as inappropriate selection of the antimicrobial agent or inappropriate dosing regimen, can increase the prevalence of antibiotic resistant strains, prolong hospital stay, cause adverse reactions, and negatively affect an institution’s pharmacy budget for antibiotics. In developing countries such as Jordan, where the role of clinical pharmacists is still in its primary stages, the first step in establishing an organized clinical pharmacy service is the evaluation of current practice to determine the need for improvement.

OBJECTIVE: To assess the degree of adherence to international guidelines for antimicrobial prophylaxis practice in cardiac surgery performed at Queen Alia Heart Institute (QAHI) in Amman, Jordan, as part of an attempt to determine opportunities for clinical pharmacist intervention.

METHODS: For a total of 236 patients who were admitted for cardiac surgery to QAHI—the only official referral hospital for cardiac patients in Jordan—between November 19, 2006, and January 22, 2007, the antimicrobial prophylaxis indication, choice, duration, dose, dosing interval, and timing appropriateness were assessed against 3 international guidelines using a pre-tested, structured clinical data collection form that was completed by 2 of the authors who work at QAHI. The study design was prospective. All patients who were scheduled for surgery were monitored daily during their inpatient stay until discharge and then were tracked in the outpatient clinic for 2 months following surgery. Data regarding antimicrobial prophylaxis indication, choice, duration, dose, dosing interval, and timing appropriateness were collected during the patient’s inpatient stay; data collection was performed periodically thereafter as data became available until the end of the 2-month follow-up. The 3 guidelines agreed for antimicrobial prophylaxis indication, choice, duration, dose, dosing interval, and none of the doses of antimicrobial prophylaxis used at QAHI were within the half-life of the antibiotic used; and (6) the duration of antimicrobial prophylaxis should not be more than recommended by guidelines, but 97.0% of patients received an unnecessary midnight dose of intravenous antibiotic the night before surgery.

RESULTS: Adherence to all antimicrobial prophylaxis guidelines was not achieved for any study patients. For the 6 evaluated criteria, (1) indication: in 100% of patients the appropriate decision was made to use antimicrobial prophylaxis in concordance with guidelines; (2) choice: only 1.7% of patients received the antibiotic of choice; (3) duration: 39.4% of patients received antimicrobial prophylaxis for a total duration of 48 hours or less in concordance with guidelines, and for 58.9% of patients, duration was longer than recommended; (4) dose: 27.9% of patients received an appropriate dose; (5) dosing interval: only 13.0% of patients received an appropriate dosing interval, and none of the doses of antimicrobial prophylaxis used at induction of anesthesia was repeated in operations that lasted longer than the half-life of the antibiotic used; and (6) timing: 99.1% of patients received antimicrobial prophylaxis dose within 60 minutes prior to skin incision as recommended by guidelines, but 97.0% of patients received an unnecessary dose within 60 minutes prior to skin incision. Adherence rates in the other studied parameters were 39.4% for total duration of antimicrobial prophylaxis use, 27.9% for dose, and 13.0% for dosing interval.

CONCLUSION: Study findings indicate that adherence to international guidelines for antimicrobial prophylaxis is far from optimal in QAHI, leading to the inappropriate administration of many antibiotics. Developing local hospital guidelines, as well as giving the clinical pharmacist a central role in the administration, monitoring, and intervention of antimicrobial prophylaxis may improve the current practice.

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What is already known about this subject

- Several studies worldwide have described adherence to international guidelines in antimicrobial prophylaxis in different countries. Gorecki et al. (1999) found that in 74% of 211 patients undergoing elective or emergency surgery in a New York private teaching hospital, the antimicrobial prophylaxis administration was inappropriate according to Surgical Infection Society guidelines. Problems included excessive duration (66%), switch to inappropriate antibiotics (32%), spectrum (31%), and timing (i.e., no pre-operative dose, 22%).
- In a study of the application of guidelines on pre-operative antibiotic prophylaxis in León, Nicaragua, van Disseldorp et al. (2006) estimated that antibiotic choice was discordant with the hospital guidelines in 69% of the cases, dose in 20% of the cases, and both the timing of administration and duration in 78% of the cases. Overall adherence was achieved in 7% of patients.

What this study adds

- This study represents the first attempt to assess the degree of adherence to antimicrobial prophylaxis practice standards in cardiac surgery performed in the only official referral hospital for cardiac patients in Jordan. This is an important step in developing strategies in Jordan and in other hospitals with similar conditions.
- Complete adherence to international antimicrobial prophylaxis guidelines was not achieved for any study patients. The lowest measured adherence rate (1.7%) was for antibiotic choice, and the highest (100%) was for appropriate decision making regarding use or nonuse of antimicrobial prophylaxis (indication), followed by timing of the first dose at a fixed time before incision (99.1%). Adherence rates in the other studied parameters were 39.4% for total duration of antimicrobial prophylaxis use, 27.9% for dose, and 13.0% for dosing interval.
- The study indicates the need for interventions to improve the rational use of antibiotic prophylaxis to prevent the complications of inappropriate administration of antimicrobials.
Although cardiac surgery is generally considered a clean procedure, antibiotic prophylaxis has been demonstrated to lower the incidence of surgical site infection (SSI). SSIs of the sternal wound and underlying mediastinum occur in 0.4%–4% of cardiac surgical procedures, with over 50% due to the coagulase-positive *Staphylococcus aureus* or the coagulase-negative *Staphylococcus epidermidis*. Patients who develop SSIs after coronary artery bypass graft (CABG) surgery have a mortality rate of 22% at 1 year compared with 0.6% for those who do not develop an SSI.

Practice guidelines are intended to assist physicians and other health care providers in clinical decision making by describing a range of generally acceptable approaches for the diagnosis, management, or prevention of specific diseases or conditions. The last decade has seen a proliferation of evidence-based clinical practice guidelines. Antibiotic guidelines and associated interventions have been demonstrated to be effective in improving antibiotic use. Organizations that have promulgated guidelines for antimicrobial prophylaxis in cardiac surgery include the National Surgical Infection Prevention Project (NSIPP), the Society of Thoracic Surgeons (STS), and the American College of Cardiology/American Heart Association (ACC/AHA).

The main recommendations of the 3 guidelines are as follows: (a) antimicrobial prophylaxis should be given to all patients undergoing cardiac surgeries; (b) the first- or second-generation cephalosporins (cefazolin or cefuroxime) are the antibiotics of choice, and vancomycin use is reserved for cases of allergy to beta-lactams or if presumed or known methicillin-resistant *Staphylococcus aureus* (MRSA) colonization is present; (c) the duration of antimicrobial prophylaxis use should not be longer than 48 hours; and (d) the timing of the first dose should be within 60 minutes prior to the skin incision (Table 1). The practice of giving a midnight (on call) dose of intravenous (IV) antibiotic the night prior to surgery as part of antimicrobial prophylaxis is inconsistent with guidelines; moreover, it has been frankly discouraged by the Centers for Disease Control (CDC).

Some countries have incorporated these guidelines into a national drug policy and provided government funding for a range of activities aimed at improving rational drug use. Health organizations have become interested in such policies because of concerns about inappropriate antibiotic prescribing and reported increase in the prevalence of antibiotic-resistant organisms. Antibiotic resistance has been described as a major threat to global public health by the World Health Organization (WHO) because there are now few and, in some cases, no antibiotics available to treat certain life threatening infections.

Despite the availability of these guidelines, recent studies assessing the current practice of prophylaxis throughout the world have shown that inappropriate antibiotic choice, excessive duration of use, and inappropriate timing of antimicrobial drugs remains a problem in surgical prophylaxis. In an Italian teaching hospital, Motola et al. (1998) found that third-generation cephalosporins were the most frequently used antibiotics both in patients undergoing clean (74.1%) and clean-contaminated (73.0%) surgical procedures. The resulting costs were about 10-fold higher than estimated costs of antibiotic prophylaxis carried out according to international guidelines. In Belgium, Kurz et al. (1993) found that antimicrobial prophylaxis was given in 57% of the procedures for which prophylaxis is generally not recommended, was not used in 14% of procedures for which it is generally recommended and in 14% of contaminated procedures, and was prolonged by more than 2 days postoperatively after 23% of the procedures and by more than 4 days in 8%. In a Canadian survey of antimicrobial prophylaxis use among patients who underwent surgical repair of a fractured hip with insertion of prosthetic material, Zoutman et al. (1999) reported that 70% of cases did not receive a dose of antimicrobial prophylaxis within 2 hours pre-operatively; instead, antimicrobial prophylaxis was administered either too early or during the procedure. In 39% of cases receiving antibiotic prophylaxis, the first dose was not administered until the end of the procedure. Antimicrobial prophylaxis consisted of a parenteral first-generation cephalosporin for 94% of cases.

Monitoring and intervention can be effective in increasing the adherence to guidelines. In descriptive studies lacking a control group, stricter implementation of the existing antimicrobial prophylaxis protocols was associated with an increase in the appropriateness of antibiotic prophylaxis from approximately 50% to 95%–100%.

In Jordan in general and, specifically, in the Queen Alia Heart Institute (QAHI), in which the present study was conducted, antimicrobial prophylaxis in cardiac surgery is not governed either by national or by local guidelines. This problem is typical of other developing countries. Studies that assess the current clinical practice of antimicrobial prophylaxis in Jordan were lacking until the present study. Previous research in this topic area focused on the prevalence of antibiotic misuse among the Jordanian population. In light of this absence of local or institutional antimicrobial prophylaxis guidelines, the present study used the aforementioned 3 international guidelines—NSIPP, STS, and ACC/AHA—to assess the appropriateness and compliance of antibiotic prophylaxis practices in cardiac surgery within QAHI.

**Methods**

**Setting and Study Design**

Patients enrolled in the present study were admitted to QAHI for cardiology services and cardiac surgery. QAHI is the only official referral hospital for cardiac patients in Jordan, performing an average of 30 cardiac surgeries per week. Eligible patients were enrolled in the study between November 19, 2006, and January 22, 2007. Generally, the study evaluated practitioner adherence to antibiotic prophylaxis guidelines using a clinical data collection form. The study was approved by the Career Ethics Committee,
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### TABLE 1
Summary of 3 International Guideline Recommendations for Antimicrobial Prophylaxis in Cardiothoracic Surgery

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Antibiotic Choice</th>
<th>Dose and Route of Administration</th>
<th>Total Duration of AMP Use</th>
<th>Timing of First Dose at Fixed Time Before Incision; Dosing Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antimicrobial Prophylaxis for Surgery: An Advisory Statement from the National Surgical Infection Prevention Project (NSIPP), 2005&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Cefazolin, cefuroxime, or cefamandole If the patient has a beta-lactam allergy, vancomycin or clindamycin</td>
<td>Cefazolin IV: 1-2 gm (20-30) mg per kg standard dose. If &lt;80 kg, use 1 gm; if &gt;80 kg, use 2 gm. End stage renal disease t½ = 40-70 hours. Cefuroxime IV: 1.5 gm standard dose, 50-90 mg/kg adjusted dose. End stage renal disease t½ = 15-22 hours. Cefamandole IV: 1 gm standard dose. End stage renal disease t½ = 12.3-18 hours. Vancomycin IV infusion: 1 gm over 60 minute standard dose, 10-15 mg per kg (adult) adjusted. End stage renal disease t½ = 44.1-406.4 hours. Clindamycin IV: 600-900 mg standard dose. If &lt;10 kg, use at least 37.5 mg; if &gt;10 kg, use 3-6 mg/kg. End stage renal disease t½ = 3.5-5.0 hours.</td>
<td>24 hours or less</td>
<td>Within 60 minutes before incision. For vancomycin the infusion should begin within 120 minutes before incision. Doses should be repeated intraoperatively if the operation is still in progress 2 half-lives after the first dose.</td>
</tr>
<tr>
<td>The Society of Thoracic Surgeons (STS) Practice Guideline Series: Antibiotic Prophylaxis In Cardiac Surgery, 2006-2007&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Cefazolin If presumed or known MRSA colonization, vancomycin (1-2 doses) + cefazolin In patients with beta-lactam allergy, vancomycin (up to 48 hours) + aminoglycoside (1 pre-operative and 1 post-operative dose).</td>
<td>Cefazolin IV: 1 gm pre-operative prophylactic dose; for a patient &gt;60 kg, 2 gm is recommended. Vancomycin IV infusion over 1 hour: dose of 1-1.5 gm or a weight-adjusted dose of 15 mg per kg. Aminoglycoside IV; (usually gentamicin, 4 mg per kg) in addition to vancomycin prior to cardiac surgery.</td>
<td>48 hours or less</td>
<td>For cefazolin: administration within 60 minutes prior to the skin incision; second dose of 1 gram should be administered every 3-4 hours, if long procedure. For vancomycin: administration slowly over 1 hour, with completion within 1 hour of the skin incision. For aminoglycosides: the initial dose should be administered within 1 hour of the skin incision.</td>
</tr>
<tr>
<td>American College of Cardiology/ American Heart Association (ACC/AHA) Guideline Update for Coronary Artery Bypass Surgery, 2004&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Cephalosporin class: cefuroxime (superior efficacy compared with the other cephalosporins), cefazolin or cefamandole. Vancomycin: reserved for penicillin-allergic and justified in periods of MRSA outbreaks.</td>
<td>Cefuroxime: 1.5 gm pre-operatively, 1.5 gm after cardiopulmonary bypass, 1.5 gm every 12 hours. Cefamandole, cefazolin: 1 gm pre-operatively, 1 gm at sternotomy, 1 gm after cardiopulmonary bypass, 1 gm every 6 hours. Vancomycin: 1 gm every 12 hours until lines/tubes are out. At least 2 doses.</td>
<td>48 hours or less</td>
<td>Initial dose to be given 30-60 minutes before skin incision. Vancomycin: 30- to 60-minute infusion timed to end before skin incision.</td>
</tr>
</tbody>
</table>


AMP = antimicrobial prophylaxis; gm = gram; IV = intravenous; kg = kilogram; mg = milligram; MRSA = methicillin-resistant Staphylococcus aureus; t½ = elimination half-life.

the equivalent of an institutional review board in Jordan, in the Royal Medical Services.

**Patients**

Patients scheduled for any type of cardiac surgery were eligible for the study with a few exceptions. Patients diagnosed with human immunodeficiency virus (HIV) infection, tuberculosis, or cystic fibrosis were excluded from the study. To avoid difficulties in discriminating prolonged prophylaxis from post-operative therapy, patients with suspected or established infection during surgery were also excluded. Patients who died due to a cause other than SSI before the end of the follow up period were not included in the data analysis. Patients were enrolled in the study if informed consent was obtained from the patient or his/her representative.

**Data Collection**

Data were collected from patients’ verbal self-reports, files, medication sheets, and prescriptions using a clinical data collection form (summarized in Table 2). The form had been pre-tested on a small pilot scale (n=10) and subsequently modified to ensure that the data would provide valid information. The entire clinical data collection form is available from the authors upon request.
All parts of the form were completed by 2 of the authors (NM, a clinical pharmacist and ZM, a cardiac surgeon) who work at QAHI. All patients who were scheduled for surgery were monitored daily during their inpatient stay until discharge and then tracked in the outpatient clinic for 2 months following surgery. Data regarding antimicrobial use in the hospital were collected during the patient’s inpatient stay; additional data collection was performed periodically thereafter as data became available, until the end of the 2-month follow-up period.

Analysis of Prophylactic Antibiotic Use

The compliance of current prophylactic antibiotic practices in cardiac surgery at QAHI with 3 published international guidelines was assessed. These guidelines were from the NSIPP (Antimicrobial prophylaxis in surgery: an advisory statement),6 the STS (Antibiotic prophylaxis in cardiac surgery, part I: duration, and part II: antibiotic choice),1,3 and the ACC/AHA (2004 guideline update for coronary artery bypass graft surgery).7 The following 6 aspects of antimicrobial prophylaxis were assessed: (1) indication—appropriate decision making regarding use or nonuse of antimicrobial prophylaxis; (2) choice—antibiotic choice for patients with and without allergy; (3) total duration of use; (4) dose; (5) dosing interval—includes both repeating of doses in procedures with durations longer than the half-life of the antibiotic used, and interval between doses; and (6) timing of dose given at a fixed time before incision (within 60 minutes prior to skin incision). The criteria for evaluation of adherence are summarized in Table 3.

If more than 1 drug was prescribed for a single procedure, all parameters were evaluated separately for each drug. Final assessment of the antibiotic course was composed by combining these separate drug evaluations. Any divergence from the guidelines in the prescription of 1 of the drugs led to a final assessment of the prophylactic course as discordant with the guidelines. If no antibiotic orders or prescriptions had been recorded, it was assumed that antibiotics were not given. If data on a certain parameter of the antibiotic prescription were lacking, the case was classified as missing data on this parameter only. We defined an antibiotic administered the day before surgery (e.g., in a midnight dose the night before surgery) as not indicated, and for these events, the parameters of antibiotic choice, duration, dose, dosing interval, and timing were not evaluated for that nonindicated drug; however, if the same patient received an antibiotic on the day of the surgery, all parameters were evaluated for that drug because it was indicated.

All data were coded, entered, and analyzed using SPSS for Windows, version 14.0 (SPSS Inc., Chicago, IL). Frequency and percentages were calculated and presented.
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### Results
Between November 19, 2006, and January 22, 2007, 252 cardiac surgeries were conducted in QAHI. After the application of inclusion and exclusion criteria, 236 patients were enrolled in the study (Figure 1). Patients’ characteristics and types of cardiac surgeries are presented in Table 4.

### Overall Assessment of All Parameters
Adherence to guidelines in antimicrobial prophylaxis for all parameters was not fulfilled in any of the 236 cardiac surgeries assessed in this study. Two common deviations from the guidelines were observed: (a) the unexplained switch from an appropriate or inappropriate agent(s) to an inappropriate agent(s) in the same patient in 230 (97.5%) patients; and (b) the practice of giving a midnight dose of IV antibiotic the night prior to surgery as part of antimicrobial prophylaxis in 229 (97.0%) patients.

### Assessment of Individual Parameters
Parameters were also evaluated separately, so that nonadherence to 1 parameter did not preclude assessment of the others. Rates of adherence to international guidelines for indication, choice, total duration, dose, dosing interval, and timing are presented in Table 5.

### Indication: In concordance with the guidelines, antimicrobial prophylaxis was given for all of the 236 (100%) patients who underwent cardiac surgeries (Table 5). However, a midnight dose of IV antibiotic on the night before surgery was given to 229 (97.0%) of patients (third-generation cephalosporin in 85% of patients, second-generation in 10%, other antibiotics in 2%). As this antibiotic dose was given while not indicated, and because the midnight antibiotic might have differed from the antibiotic that was given later at induction of anesthesia, the parameters of antibiotic choice, dose, dosing interval and timing were not evaluated for the drug given at midnight; however, these parameters were evaluated for any antibiotics given to the patient on the surgery date.

### Antibiotic Choice: Overall, antibiotic choice was concordant with guidelines for only 4 (1.7%) patients (Table 5), almost entirely because of post-operative treatment decisions. In the operating room and during induction of anesthesia, the antibiotic choice (cefuroxime) was concordant with guidelines in 226 (95.8%) patients and discordant in 10 patients. The reasons for discordance were the following:
- Suspicion of beta-lactam allergy in 5 patients where cefuroxime was given.
- Use of a vancomycin and cefuroxime combination in 3 patients who did not have either beta-lactam allergy or presumed colonization with MRSA.
- Missing induction-antimicrobial prophylaxis dose in 2 patients to whom a third-generation cephalosporin was given 8 hours after the end of the operation.

After surgery, for nearly all patients, there was an unexplained switch from an appropriate or inappropriate agent(s) to an inappropriate agent(s). Switches were made from a second-generation cephalosporin cefuroxime (or combination of cefuroxime with vancomycin) to (a) a combination of a third-generation cephalosporin with 1 of these antibiotics: vancomycin, amikacin, flucloxacillin, or imipenem in 145 (61.4%) patients; (b) a combination of vancomycin with amikacin or flucloxacillin or imipenem in 34 (14.4%) patients; (c) a third-generation

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**TABLE 3** Criteria to Assess Adherence and Compliance With Current Antimicrobial Prophylaxis Practices Within QAHI Compared With International Guidelines

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Concordant if</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Antibiotic indication</td>
<td>• Decision was made to use antimicrobial prophylaxis.</td>
</tr>
<tr>
<td>2. Antibiotic choice</td>
<td>• Agent recommended by guidelines.</td>
</tr>
<tr>
<td>3. Total duration of prophylactic antimicrobial use</td>
<td>Duration as recommended by guidelines (48 hours or less).</td>
</tr>
<tr>
<td>4. Dose</td>
<td>Dose as recommended by guidelines. For pediatric patients, doses calculated according to body weight using Drug Information Handbook.</td>
</tr>
<tr>
<td>5. Dosing interval</td>
<td>Additional dose was given in surgical procedure longer than the half-life of the prophylactic antibiotic used, and dosing interval did not exceed the guideline by more than 30 minutes.</td>
</tr>
<tr>
<td>6. Timing</td>
<td>Timing of dose did not deviate from the recommended time (within 30-60 minutes prior to skin incision).</td>
</tr>
</tbody>
</table>

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aGuidelines used: National Surgical Infection Prevention Project; bThe Society of Thoracic Surgeons; cAmerican College of Cardiology/American Heart Association.

QAHI = Queen Alia Heart Institute.

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cephalosporin alone in 32 (13.6%) patients; or (d) vancomycin alone in 19 (8.1%) patients. Cefuroxime was maintained as a single prophylactic antibiotic in only 4 (1.7%) patients, and the third-generation cephalosporin ceftriaxone was maintained as a single prophylactic antibiotic in only 2 (0.8%) patients.

**Total Duration of Antimicrobial Prophylaxis Use:** In 93 of 236 patients (39.4%), total duration of all agents used as antimicrobial prophylaxis was concordant with the guidelines (48 hours or less). In 139 (58.9%) patients, duration was longer than recommended. In 4 cases (1.7%), duration could not be evaluated because medication charts were incomplete.

**Dose:** Only doses of antibiotics used in concordance with the guidelines were evaluated. The dose was concordant with the guidelines in only 63 (27.9%) of 226 evaluated doses. In all of the 163 (72.1%) discordant doses, the dose was lower than what is recommended, either because (a) a lower dose (e.g., 750 milligrams instead of 1.5 grams) was given to an adult patient; (b) no dose adjustment was made for an obese patient; or (c) the dose per kilogram calculated for a child was lower than recommended.

**Dosing Interval:** Only dosing intervals of agents used in concordance with the guidelines were evaluated (n=230, Table 5). Of these, only the dosing interval of antibiotics repeated during surgery or in the ward could be calculated. Of the 226 doses of antimicrobial prophylaxis used at induction of anesthesia, none was repeated, even though antimicrobial prophylaxis should have been repeated in 196 surgeries because the duration of the surgery was longer than the half-life of the antibiotic used. In the 4 patients for whom cefuroxime was maintained as a single prophylactic antibiotic in the ward after surgery (in compliance with the guidelines), the dosing interval was discordant with the guidelines (every 8 hours instead of every 12 hours). Thus, only 30 (13.0%) out of 230 evaluated agent dosing intervals were concordant with the guidelines.

**Timing of Doses Given on the Surgery Date:** For doses given on the day of the surgery, timing was concordant with the guidelines (at induction of anesthesia within 30 minutes before incision) in 224 of 226 (99.1%) of the evaluated cardiac surgeries. For the 2 surgeries in which antimicrobial prophylaxis timing was discordant with the guidelines, no antimicrobial prophylaxis was given in the hours prior to or during the surgery; instead, a third-generation cephalosporin was given 8 hours after the end of the operation.

### Discussion

**Adherence in Current Practice**

The present study demonstrates that adherence to the international guidelines for antimicrobial prophylaxis is disappointingly far from optimal. One of the most striking findings of this study was that no patient’s care adhered to all guideline parameters. While this result is consistent with those of similar studies in Iran and Nicaragua, where rates of complete adherence to practice guidelines were 0.3% and 7%, respectively, higher percentages of adherence to antimicrobial prophylaxis guidelines have been reported in other studies. Gorecki et al. (1999, United States), van Kasteren et al. (2003, the Netherlands), Lallemand et al. (2002, France), and Voit et al. (2005, United States) found in their studies that overall adherence was achieved in 26%, 28%, 41.1%, and approximately 50% of surgical patients, respectively.17-20-31

Interestingly, although the present study reported lower adherence to all parameters than did earlier studies, the rate of adherence to timing of antimicrobial prophylaxis at a fixed time before incision (99.1%) is higher than that reported in most other studies. Paradiso-Hardy et al. (2002), Lallemand...
et al. (2002), van Kasteren et al. (2003), and van Disseldorp et al. (2006) reported in their studies that timing of the first dose was concordant with guidelines in 72%, 61.4%, 50%, and 22% of cases, respectively.

It is noteworthy that adherence in all of the previously mentioned studies, except ours and that of Askarian et al. (2006, Iran), was compared with local, rather than international, guidelines. The higher adherence rates in studies that used local guidelines (7%-50%) as opposed to studies that used international guidelines because of lack of national or local guidelines (0%-0.3%), suggest that adherence to local guidelines may be easier to achieve than adherence to international guidelines.

One potential strategy to improve antimicrobial practice in hospitals is standardization, either by adopting an international guideline or by developing a local hospital guideline. Standardization efforts should be overseen by a committee that includes surgeons, anesthesiologists, microbiologists, pharmacists, and members of hospital epidemiology and infection control departments. Guidelines should be based on hospital-specific bacterial epidemiology patterns, the best literature evidence, and surgeon preference. Standardized protocols should then be provided to surgeons, in an effort to achieve consensus, before implementation.

The present study revealed several areas for improvement at the study hospital. At QAHI, the on-call surgeon (usually a junior surgeon) routinely prescribes a midnight antimicrobial prophylaxis dose the night before surgery and records it on the follow-up sheet in the patient’s file. The anesthesiologist gives the intraoperative antibiotic dose and records it only on the anesthesia chart. After surgery, the consultant, or senior surgeon, prescribes post-operative antimicrobial doses and records them on the follow-up sheet in the patient’s file. The absence of a standardized antimicrobial practice guideline creates a lack of communication between anesthesiologists, surgeons, and even among the members of the surgical team. This lack of communication produced poor monitoring, resulting in 2 main deviations that led to 100% nonadherence in this study. These deviations from the guidelines are as follows:

(a) Unexplained switch to inappropriate antibiotic(s) without microbiological or clinical indication. The most common antimicrobial prophylaxis agents used in this study were a combination of a third-generation cephalosporin with another antibiotic (vancomycin, amikacin, flucloxacillin, or imipenem); a combination of vancomycin with amikacin, flucloxacillin, or imipenem; or a third-generation cephalosporin alone. Third-generation cephalosporins and broad spectrum combinations should not be used for SSI prophylaxis because they have less activity against Staphylococci than does cefazolin. Such use induces the emergence of resistant organisms and is more costly.

(b) Giving a midnight dose of IV antibiotic the night prior to surgery. This practice should be strongly discouraged in group education and consensus meetings. One method of preventing this practice is to assign the prescription of antimicrobials to the anesthesiologist in charge only. Prevention could also be achieved by providing better staff training as to the benefits of adherence to standard international antimicrobial prophylaxis guidelines and the risks of unnecessarily dispensing antibiotics.
Adherence to International Antimicrobial Prophylaxis Guidelines in Cardiac Surgery: A Jordanian Study Demonstrates Need for Quality Improvement

Potential solutions to avoid both of these mistakes include better organization of work and specification of tasks among individuals on the surgical team, introduction of special forms for ordering antimicrobial prophylaxis, and use of an antibiotic prophylaxis chart in the operating theaters. Another suggestion is to give a central role to the clinical pharmacists in antimicrobial prophylaxis administration. In a descriptive study without a control group, Prado et al. (2002) showed that when pharmacists were given a central role in the administration of prophylaxis, the appropriateness of the indication increased from 56% to 100%, while the costs decreased by 40%.

Moreover, in a study of an intervention to reduce the prescribing of antibiotics for upper respiratory infections by general practitioners in Australia, Zwar et al. (2002) found that giving feedback on prescription behavior increased the appropriateness of the prescriptions.

The present study also demonstrated that, although adherence to all guidelines was not achieved for any study patients, adherence was better for some specific guidelines than for others. For example, the decision to use antimicrobial prophylaxis (indication) and the timing of antimicrobial prophylaxis before incision showed high rates of adherence (100.0% and 99.1%, respectively), indicating that the surgical teams were aware of the importance of giving antimicrobial prophylaxis within 30-60 minutes prior to skin incision to prevent SSI in cardiac surgeries. The importance of the timely administration of pre-operative antibiotics is well established and is broadly applicable to all procedures for which prophylactic antibiotics are administered. It has been suggested that antimicrobial selection is a moot point if the agent is not delivered during the optimal 30-60 minute window just before incision and that the beneficial effect is negated if the drug is given after incision.

Investigation of the reasons for adherence to timing guidelines revealed that anesthesiologists were responsible for giving the intra-operative antimicrobial prophylaxis doses, providing further support for the suggestion to improve adherence by specifying tasks and distributing responsibilities among members of the surgical team.

Use of antibiotics for longer than the recommended period, especially in the absence of any evidence of secondary infection or SSI until the day of discharge in an attempt to prevent infection while patients were hospitalized, was observed in 58% of our study patients and has also been reported by some other researchers. Prolonged antibiotic prophylaxis is, at best, of no benefit and, at worst, potentially harmful to patients because of drug toxicity, the risk of super-infection, and the risk of inducing more bacterial resistance, both in surgical patients and throughout the hospital.

Doses and dosing intervals were discordant in 72% and 88% of patients, respectively. That is, no dose adjustment was done when it was needed and doses were not repeated intra-operatively in long-duration procedures. These findings are consistent with the work of Gupta et al. (2003), who found that prophylactic antibiotic administration in procedures lasting more than 4 hours was repeated in only 9 patients (3%) in 300 cases at the correct time for the entire duration of the surgery in complete compliance with the published guidelines.

Limitations
First, the exact timing of the intra-operative antimicrobial prophylaxis dose was assessed based on the anesthesiologists’ notes on the anesthesia chart, and it was recorded always at induction. However, we cannot guarantee the accuracy of recorded notes. In the future, one could consider a method to record the time of dose administration more precisely. Second, although anecdotal information suggests that most hospitals in Jordan share similar standards, our results may not be entirely applicable to other countries. However, our results can be generalized to hospitals in other developing countries, where not much attention is paid to international practice guidelines. Additionally, previous research has documented widespread nonadherence to antimicrobial practice guidelines in many countries, including the United States and Canada.

Conclusion
We found that adherence to international antimicrobial prophylaxis guidelines for cardiac surgery is far from optimal in the QAHI, which led to the inappropriate administration of many antibiotics. This pattern unnecessarily increases expenditures and likely plays a major role in the growing prevalence of antibiotic-resistant microbial strains. Strategies such as the development of local hospital guidelines may improve current antimicrobial prophylaxis practice in QAHI specifically and in other hospitals in general. There is a need to increase adherence to clinical guidelines for antimicrobial prophylaxis in cardiac surgery patients in QAHI, and other research has shown quality improvement using clinical pharmacists in a central role in the administration, monitoring, and intervention of antimicrobial prophylaxis. Additional effort should also be directed towards increasing the awareness of practitioners about the dangers of inappropriate use of antimicrobials before, during, and after surgeries.
Adherence to International Antimicrobial Prophylaxis Guidelines in Cardiac Surgery: A Jordanian Study Demonstrates Need for Quality Improvement

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REFERENCES


Pharmacists have been splitting scored tablets to individualize and titrate dosages since the end of the pill-rolling era. We have generally accepted that scored tablets may be evenly divided, resulting in 2 half-tablets containing one-half of the whole tablet strength. Slight powdering is unavoidable, but it is generally accepted that loss of a few molecules of active drug is not likely to be clinically significant. However, even when tablets are split by pharmacists, 1 study found significant weight deviations in almost 10% of half-tablets. We do not know if this weight variation correlates with active drug in each tablet half, or more importantly, if this variation will jeopardize clinical outcomes or safety.

In some instances, there may be no other way to satisfy the prescribed dose other than tablet splitting. In any case, we rationalize that the patient receives the necessary dose during the course of chronic therapy because the patient eventually consumes all tablet halves as prescribed—1 half-tablet at a time. Assuming a 10% weight deviation, if one half-tablet provides 90%, and the next contributes 110%, on average, the patient receives 100% of the dose over 2 doses. Presumably pharmacists rely on pharmacokinetics and pharmacodynamics when selecting opportunities for tablet splitting and pass on those drugs for which fluctuations may be a concern; one wonders if physicians share such concerns when nonstandard doses are prescribed. Pharmacists must be involved and vigilant when advising individual patients and participating in population-based tablet-splitting programs.

We have made assumptions and selected appropriate drugs to be halved based on our understanding of pathophysiology, pharmacology, and pharmacodynamics. We assume homogenous distribution of active drug in whole tablets, and thus, an equal distribution of active drug in the half-tablets. Some variation is expected, and the U.S. Food and Drug Administration (FDA) bioequivalence standards permit variance of plus or minus 20%. So, even with whole tablets, the actual dose ingested may fluctuate from whole tablet to whole tablet.

Past tablet-splitting research has assessed the half-tablet weight, uniformity, and even the clinical outcome of split tablets, including the work of Gee et al. (2002), which assessed clinical, service, and cost outcomes associated with tablet splitting. In this issue of JMCP, Hill et al. offer an unprecedented analysis of the accuracy and precision of tablet splitting by measuring the active drug component in tablet halves. This use of assay is an important step in assessing half-tablet weight variations.

Half-Tablet Variations—Do They Have Clinical or Practical Meaning?

As pharmacists, we presume that if the dose of an angiotensin-converting enzyme (ACE) inhibitor, statin, analgesic, or anti-de pressant fluctuates by a few molecules more or less than the prescribed dose, surely this fluctuation would not jeopardize effectiveness or safety, as these drugs are titrated in approximate milligram increments even with whole tablets. However, warfarin is typically not included in half-tablet programs. Controversy surrounding the narrow therapeutic index of this drug, its relatively low cost, and the often short-term nature of dosing associated with acute events such as orthopedic surgery for hip or knee replacement probably contribute to the absence of warfarin from formal tablet-splitting programs. For example, UnitedHealthcare’s Half Tablet Program in June 2007 listed only 15 drugs in 4 categories: 3 ACE inhibitors, 5 angiotensin receptor blockers (ARBs), 4 antidepressants, and 4 statins.

While most health plans do not promote splitting of warfarin tablets, Hill et al. included warfarin in their research because it was among the drugs “commonly split” in 1 Department of Veterans Affairs (VA) health care system. It is important to note that Hill et al. used an arbitrary standard for warfarin individual tablet variation (95%-105%), which is more narrow than the variation standard that they used for other drugs (90%-110%) and more narrow than the standard used by the United States Pharmacopeia (USP; 85%-115%) for weight and content uniformity of individual tablets. The standards used by Hill et al. are “typically applied to samples of 20 [tablets] or greater.”

Also curious are inconsistencies in Hill et al.’s recommendations regarding splitting warfarin tablets. The authors include a warning that “caution should be taken when splitting warfarin sodium due to the potential for significant adverse events with minimal change in daily dose.” However, the authors seem to negate their concerns by stating that “daily variation of international normalized ratio (INR) values…can result from food interactions, drug interactions, and variations in daily dose. For this reason, it cannot be stated that the minor differences in warfarin sodium half-tablet drug content will predict clinical outcomes.”

While splitting of warfarin tablets presents a theoretically realistic concern in a population-based program, apparently the VA, the setting for the Hill et al. study, splits warfarin, presumably without problems.

Another point of confusion surrounds lisinopril half-tablet fluctuations. Hill et al. report that drug content variation for half-tablets “was greatest with lisinopril, which had tablet halves ranging from 81.15% to 125.72% of the target drug content for half-tablets. Thus, when tablet splitting is performed for this lot of lisinopril, patients may receive daily doses that vary by as much as 45%.” This admonition is somewhat inconsistent with Hill et al.’s later statement that “daily fluctuations in dose [of antihypertensives] would be expected to affect
blood pressure measurements and side effects and have no effect on long-term clinical end points.\textsuperscript{13}

This confusion over the clinical significance of variation in warfarin and lisinopril half-tablets creates negative sound bites that may cast an unjustified pall over tablet splitting in general for the hasty or uninformed reader who researches the topic no further.

**Tablet Splitting as a Managed Care Issue**

We acknowledge and accept that dispensing pharmacists split tablets—with fingers, a counting knife, device, or a blade—to accommodate prescribed doses not available in whole tablets. But why did tablet splitting migrate from solely a professional practice issue to a sometimes controversial managed care concern?

The reason is that tablet splitting both satisfies and challenges the \textit{raison d’être} of managed care pharmacy: to deliver a value-based pharmacy benefit. The value equation puts the drug benefit in the numerator and cost in the denominator. In this equation, value increases with a greater benefit and/or a lower cost, and decreases with a lower benefit and/or higher cost. Tablet splitting delivers the same clinical outcomes at a lower cost. From this perspective, managed care can embrace tablet splitting.

For example, the generic lisinopril 40 mg cash price is about $18.00 for 30 tablets, and lisinopril 20 mg is about $14.00 for 30 tablets.\textsuperscript{9} If a patient is prescribed 20 mg daily, and the pharmacist splits fifteen 40 mg tablets to dispense 30 half-tablets (20 mg per half-tablet), the cost would be $9.00 for a 30-day supply, rather than $13.99, a savings of 36% without jeopardizing patient care. This is a tantalizing opportunity for pharmacy benefit plans and for patients, who typically experience a copayment savings of about 50% when participating in a half-tablet program.

In their study, Hill et al. cite other sources, including the VA, claiming success and forecasting significant cost savings from dividing certain drugs when a half-tablet of a larger strength is less expensive than a whole tablet of the half-strength.\textsuperscript{10} One source identified annual savings of approximately $342,000 through tablet-splitting in a plan with $10 million in annual pharmacy benefit expenditures.\textsuperscript{11} In 2004, the VA announced that splitting simvastatin tablets saved $46.5 million systemwide in fiscal year 2003.\textsuperscript{12} In another VA study, Gee et al. (2002) found that splitting statins produced savings of approximately $68 per patient per year without compromising lipid reduction.\textsuperscript{9}

**Concerns About Unintended Consequences Overstated?**

Detractors and concerned patient advocates have voiced concern about tablet splitting, challenging that tablet halves may not provide exactly one-half of the dose of the whole tablet; patients may be confused by one-half tablets and take an erroneous (double) dose, or splitting an extended-release tablet may jeopardize the rate of absorption; and any of these occurrences may jeopardize clinical outcomes including patient safety. For example:

• The Institute for Safe Medication Practices advises patients to split tablets “only if you ‘half’ to” although the practice may be necessary for dosage titration or to reduce drug costs; the institute also acknowledges potential risks and admonishes prescribers to select the proper patient candidate for tablet splitting.\textsuperscript{13}

• In 2004, the American Pharmacists Association stated that tablet splitting can be effective for certain drugs and certain patients but should not be automatic or mandatory.\textsuperscript{14}

• A 2006 article in the \textit{Journal of Family Practice} acknowledged the potential cost savings from tablet splitting but provided guidelines on what dosage forms or patients may or may not be appropriate candidates for tablet splitting. Also, the article pointed out that certain tablet-splitting devices may be more effective than others in creating mirror halves.\textsuperscript{15}

• Is there room for misinterpretation and a pharmaceutical misadventure if a patient is dispensed one-half tablets (split by the pharmacist) and the instructions read “take one-half tablet”? Might the patient further split the half-tablet and take one-quarter-tablet?

• Might a busy pharmacy dispense a whole tablet with the instructions reading ‘take one-half tablet’ and expect the patient to split the tablet? Can patients be expected to accurately and precisely split tablets themselves? Should they be given a tablet splitter by their managed care organization (MCO) (Some MCOs have provided splitters to patients.)

Perhaps it is not tablet splitting per se that is objectionable, but the regimented splitting that may appear forced upon patients by managed care. As a sound bite headline, a “mandatory tablet-splitting program” sounds Orwellian; without more specific definition, it may erroneously be perceived to apply to all drugs and all patients.

In reality, the pharmacy directors at the MCOs and VA centers that recommend tablet splitting for some drugs are well aware of these and other concerns and, as a result, carefully select drugs to be split without potential for hazard. They generally avoid drugs for which slightly fluctuating blood levels may compromise outcomes or safety (so-called narrow therapeutic index drugs); drugs that are frequently titrated or monitored with lab assays; and, in general, drugs requiring accurate and precise dosage adjustments on a chronic basis to maintain desired effectiveness and safety outcomes, particularly in frail or otherwise fragile patients. Similarly, patients physically unable to split tablets are excused from this requirement.

**Is Current Splitting Practice a Non-Issue?**

In preparing this commentary I spoke with pharmacy directors of several large MCOs—open-panel as well as closed-panel plans with clinic pharmacies—who had instituted mandatory tablet splitting confined to a limited number of specific brand name drugs. Most acknowledged that the tablet-splitting programs reduced drug costs. However, many have abandoned their tablet-splitting programs because the target drugs have become
available as generics—instituting a maximum allowable cost program is an easier way to achieve cost savings.

Some MCOs and VA centers, however, continue to achieve cost savings with tablet splitting for select drugs. Others may once again embrace tablet splitting as new brand tablets are launched that satisfy desired criteria, particularly flat pricing among strengths of the same drugs. For all plans that do, Hill et al. have advanced our scientific understanding by showing that drug content was uniformly distributed for all medications analyzed, and half-tablet weight seems to be directly correlated with half-tablet drug content. However, they also cautioned that a potential for half-tablet dose variation may occur with warfarin sodium, metoprolol succinate, and lisinopril. Warfarin may be a concern; lisinopril perhaps not so much, despite the varied opinions presented in Hill et al.’s paper. Pharmacy directors will use these new data to help design and execute tablet-splitting programs with value for patients and health plans.

In their penultimate paragraph, Hill et al. state that unless performed by a device, tablet splitting, even by pharmacists and especially by patients, will likely result in significant tablet weight variations, and they further opine that “therefore, equal daily doses will be determined by the ability of patients to split tablets perfectly in half.” While we all agree that certain patients with challenges in cognition or dexterity are not appropriate candidates, the authors confirm by their research that most split tablets are within accepted ranges, and even those that are not may not result in negative clinical outcomes due to the gross dosages used. Hill et al. did not measure clinical outcomes, and the takeaway message is that there is reasonable content and weight uniformity among most tablet halves that result from tablet splitting. An opportunity to improve efficiency without jeopardizing patient safety, tablet splitting has been endorsed in a professional practice advisory from the Academy of Managed Care Pharmacy. Likewise, tablet splitting may be increasingly important from the consumer’s perspective; in a February 2009 Kaiser Health Tracking Poll, 15% of respondents reported that they had either split tablets or skipped medication doses to save on prescription drug costs in the previous year. Tablet splitting may be an effective method to individualize dosages and/or reduce costs when performed under the guidance of pharmacists, for informed and competent patients, and for appropriate drugs.

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REFERENCES

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Standardizing Quality Assessment of Observational Studies for Decision Making in Health Care

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This report summarizes a roundtable discussion of managed care experts and academic pharmacoeconomists, held in March 2008 with the objective of defining action steps to overcome barriers to the incorporation of real-world data into health care decision making. The roundtable meeting was the result of an initial program in July 2007 where managed care decision makers and pharmacoeconomic experts defined these barriers. Real-world data in this context were characterized as data not routinely collected in Phase III drug registration studies, including administrative claims data, patient registries, large simple trials, resource use collection alongside clinical trials, and electronic medical records. These data are considered along with standard safety, efficacy, and pricing information. However, one conclusion from the first roundtable discussion was that concerns around the quality assessment of such data have hindered widespread use in decision making.

The Foundation of Managed Care Pharmacy (FMCP) recognized the value of real-world data in its AMCP Format for Formulary Submissions, version 2.1, a structured outline for the presentation of information by pharmaceutical companies on their products to managed care decision makers. As a sponsor and developer of this standard, FMCP has invested in the adoption of the AMCP Format by manufacturers and health plans. Following a broad communication strategy, over 50 training seminars to managed care pharmacists on using the AMCP Format have been held. The acceptance of the AMCP Format approach has improved since its inception in the year 2000; however, its impact on formulary decisions is still in its infancy. A recent survey found that approximately one-third of all pharmacy directors request information from drug manufacturers in a form that is consistent with the AMCP Format. While information delivered in the dossier concerning the safety and efficacy for labeled use was perceived by the health plans to be mostly satisfactory, the information related to off-label use, costs, and benefits was perceived as incomplete, lacking in clarity, and potentially biased. These data indicate that despite extensive efforts, the implementation process has not yet been fully effective in promoting the utilization of real-world data.

The struggle for adoption of new processes in health care delivery is not new. In the United Kingdom (UK), an initiative called PARiHS (Promoting Action on Research Implementation)

Methods
Prior to the roundtable event, participants were assigned to the following 4 workgroups: (1) Next steps for the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Task Force on Real-World Data; (2) Real-world data assessment instruments for researchers and users of research; (3) Acceptance

Note: This article is the subject of an editorial that appears on pages 294-296 of this issue.
process for an assessment instrument; and (4) Training and education on the use of an instrument. The roundtable program was structured in sequential steps, including preparatory workgroup activities, discussion and assessment at the roundtable, and work-up in the workgroups. Finally, all recommendations were collected, refined at the roundtable, and prioritized to yield an integrated action plan.

Results
The discussions are presented in the sequence of the 4 workgroups including the findings of the preparatory phase and the recommendations formed during the course of the workshop.

Workgroup 1: Continuation of the Work of the ISPOR Task Force on the Use of Real-World Data. In response to the increasing request by decision makers for real-world outcomes information,2 ISPOR created a Task Force on Real-World Data to develop a framework to assist health care decision makers in understanding real-world data in the context of application to reimbursement decisions.2 The open comment period yielded over 70 comments from ISPOR members and these comments were summarized by the workgroup. The following core needs were identified:2,10 (a) more guidance on defining a “Hierarchy of Evidence” that incorporates real-world data; and (b) guidance on how real-world data should be applied to reimbursement decisions, perhaps through guidelines or case studies. These key requests validated the overall premise of the roundtable discussion by expressing a strong need for specific guidance on interpreting real-world data.

Various systems have been suggested to grade the quality of evidence for clinical decision making.2,11-13 In a nutshell, the criteria for grading use either technical criteria to evaluate strength of research design and internal validity or the “net benefit” criterion (e.g., the magnitude of benefit compared to trade-offs). Discussion is ongoing about whether it is possible, or useful, to determine a “fixed” system for defining a hierarchy of evidence that can accommodate both criteria.13 Critics fear that hierarchies of evidence are over-simplistic, pseudo-quantitative approaches to replace informed judgment.20 Proponents state that such instruments will help producers and users of these data to orient themselves in a standard framework. The recommendation of the workgroup was that organizations vested in the creation and utilization of such evidence, such as ISPOR and AMCP, should evaluate the state of the art in developing and using “evidence hierarchies” and the feasibility of adopting a standard, more inclusive, hierarchy system.

In order to substantiate the potential for using real-world data for reimbursement decisions, the group analyzed 4 case studies where real-world data based evidence was used to make a decision involving conditional reimbursement. The first example was the conditional reimbursement for a targeted multiple sclerosis therapy of interferon and glatiramer acetate. The agreement between the UK authorities and the manufacturer was that drug costs would be reduced if a cost-effectiveness threshold of £36,000 per quality-adjusted life year over 20 years was exceeded based on an ongoing collection of real-world data.21 The second example was the reimbursement scheme for bortezomib (Velcade) in the UK. The manufacturer agreed to rebate the full cost of the drug if the patient did not achieve at least a partial response to the treatment after a maximum of 4 treatment cycles as measured by a marker protein.22 In the third case study, the reimbursement of the Oncotype Dx, a test for the identification of recurrence risk for women with early stage breast cancer, was deemed acceptable by the health insurer United Healthcare for 18 months if the test led to reduced volume of chemotherapy in those women who had been identified as low risk.23 The final example of “Coverage with Evidence Development” has been suggested by the Centers for Medicare & Medicaid Services (CMS), whereby reimbursement is given for a limited time on the condition that evidence of effectiveness and/or safety of treatment is collected, often as part of real-world trials.21,23

Agreements like the ones outlined above may allow additional data collection for new therapeutic interventions while limiting the risk for the payer. Conditions for reimbursement become linked to real-world effectiveness, as determined by the evaluation of real-world data. For such agreements it is important to use clear definitions of the type of data used, the quality of data requested, and the cut-off points for the reimbursement, and to agree on a manageable volume or length for data collection. In a subsequent step, further decisions can then be made based on improved real-world evidence on the treatment effectiveness.

To avoid biased reporting of the results of observational studies and to make sure that all existing evidence is accessible to decision makers, Workgroup 1 suggested a voluntary registry of observational studies, which should lead to increased credibility of these studies and the organizations conducting these studies. Transparency is important for models and real-world evidence. However, the degree of transparency depends, among other factors, on the level of expertise of the user of this information. To allow more standardized qualifications of models or real-world data studies, Workgroup 1 proposed the establishment of an independent body or review process, which could be formed as a consortium of experts giving access to a broad range of resources and expertise for an audit, review or quality certification process. Such a body could, for example, be associated with an organization like FMCP as a service to the AMCP membership.

Workgroup 2: Assessment Tool for Researchers and Users of Research. The 4 managed care organization participants reviewed how instruments for assessing the quality of real-world data studies have been used in their organizations. Among them, none used a published instrument for assessment of the quality of real-world data studies currently, or had done so in the past. In order to consider such a tool, the instrument
### TABLE 1

**Summary of Checklists Evaluated as Basis for the Roundtable Discussions**

<table>
<thead>
<tr>
<th>Year</th>
<th>Authors and Source</th>
<th>Country</th>
<th>Title</th>
<th>Objectives</th>
<th>Number of Criteria</th>
</tr>
</thead>
</table>
| 2004 | Philips, Ginnelly, Sculpher, et al. | UK      | Review of guidelines for good practice in decision-analytic modeling in health technology assessment | • To summarize published guidelines for assessing the quality of decision-analytic models in HTA  
• To develop a synthesized guideline and accompanying checklist using available good practice guidelines.  
• To provide guidance on key issues not yet covered in published guidelines.  
• To consider expectations of future decision-analytic models for NICE technology appraisal process and HTA. | 69                |
| 1996 | Drummond, Jefferson | UK      | Guidelines for authors and peer reviewers of economic submissions to the BMJ | To improve the quality of submitted and published economic evaluations by agreeing on acceptable methods and their systematic application before, during, and after peer review. Includes:  
• Easy guidelines for economic evaluation  
• A checklist for use by referees and authors  
• A checklist for use by editors | 35                |
| 2007 | von Elm, Altman, Egger, et al. | International | The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies | To develop recommendations on what should be included in an accurate and complete report of an observational study. The scope of the recommendations was to cover 3 main study designs:  
• cohort  
• case–control  
• cross-sectional studies. | 22                |
| 2007 | Peterson, Nau, Cramer, et al. | International | A checklist for medication compliance and persistence studies using retrospective databases | To develop a checklist of items that should be either included, or at least considered, when a retrospective database analysis of medication compliance or persistence is undertaken. | 20                |
| 2003 | Mohterlal, Brooks, Clark, et al. | US | A checklist for retrospective database studies—report of the ISPOR Task Force on Retrospective Databases | To develop a checklist supporting decision makers in evaluating the quality of published studies that use health-related retrospective databases. | 27                |
| 1998 | Halpern, Luce, Brown, Geneste | International | Health and economic outcomes modeling practices: a suggested framework | To improve the development and review of models by defining recommendations and a quality control checklist | 26                |
To develop a format for presenting the results | 29                |
| 2003 | Collège des Economistes de la Santé | France | Guide méthodologique pour l’évaluation économique des stratégies de santé | To improve the quality of health-economic studies in France | 22                |
| 2000 | Hannover Consensus Group | Germany | Deutsche Empfehlungen zur gesundheitsökonomischen Evaluation (German recommendations for health care economic evaluation studies) | To define the minimum requirements for methodology and transparency | 10                |
| 2004 | Des Jarlais, Lyles, Crepaz, et al. | International | Improving the Reporting Quality of Nonrandomized Evaluations of Behavioral and Public Health Interventions: The TREND Statement | The main goals of the meeting were to:  
(1) communicate the usefulness and importance of adequate reporting standards,  
(2) reach consensus on reporting standards for behavioral interventions,  
(3) develop a checklist of reporting standards to guide authors and journal reviewers, and  
(4) Develop strategies to disseminate the resulting reporting standards. | 46                |
| 2003 | Ofman, Sullivan, Neumann, et al. | International | Examining the value and quality of health economic analyses: implications of utilizing the QHES | To create a quantitative approach to the appraisal of health economic studies | 16                |
Table 1: Summary of Checklists Evaluated as Basis for the Roundtable Discussions
(continued from previous page)

<table>
<thead>
<tr>
<th>Year</th>
<th>Checklist</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1998</td>
<td>Downs, Black</td>
<td>The feasibility of creating a checklist for the assessment of the methodological quality both of randomized and non-randomized studies of health care interventions.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>To test the feasibility of creating a valid and reliable checklist with the following features: appropriate for assessing both randomized and non-randomized studies; providing both an overall score for study quality and a profile of scores not only for the quality of reporting, internal validity (bias and confounding) and power, but also for external validity.</td>
</tr>
</tbody>
</table>

HtA = health technology assessment; ISPOR = International Society for Pharmacoeconomic and Outcomes Research; NICE = National Institute for Clinical Excellence; QHES = Quality of Health Economic Studies; TREND = Transparent Reporting of Evaluations with Non-randomized Designs; UK = United Kingdom; US = United States.

would need to be short, simple to use, concise, and validated. In addition, recommendation by a national organization would be seen as a positive factor.

With these objectives in mind, Workgroup 2 evaluated existing instruments for application towards the assessment of real-world data studies. The goal would be to consolidate these instruments into a useful tool for decision makers to evaluate real-world data.

Individual members of the workgroup nominated various instruments for inclusion in the evaluation. The resulting 13 published assessment tools were reviewed for suitability to critique real-world data studies. Table 1 summarizes the evaluation tools included in this work. Prior to the meeting, members of the workgroup assessed the tools according to (a) target user (researcher, journal reviewer, systematic reviewer, decision maker); (b) study type (prospective, retrospective, modeling); (c) phase of research (planning, publishing, using); (d) type and number of domains used in the assessment tool; (e) grading system used; (f) strengths and weaknesses; and (g) geographic transferability. The perspectives of evaluation tools can be either from the viewpoint of the researcher (assurance of research quality), of the reviewer (assurance of research and publication quality), or of the decision maker (assurance of evidence quality and relevance). The instruments evaluated had been developed for a variety of study types, including modeling, non-randomized studies, budget impact analysis, retrospective studies, or studies of compliance and persistence.

The number of questions or criteria assessed varied considerably across the instruments. The mean number of criteria was 30.5 with a range of 10 to 69 questions. The structure of the questions was either by publication outline (objectives, background, methods, results, discussion, and limitations) or by methods (comparators, bias, and sensitivity analysis). Only 2 of the instruments indicated that they had been validated, whereby a validation process involves determination of the congruency of independent assessments of the same research report by several evaluators using the instrument to be validated. For the majority of instruments, no updates were available. In general, yes-or-no questions were used in the evaluation as opposed to a scale. Although our review was not intended to be comprehensive of every real-world data assessment tool available, this evaluation of a selection of 13 assessment tools confirms the findings of a previous study performed by the Agency for Healthcare Research and Quality (AHRQ) in 2002. There are a variety of checklists, which may lead to different assessment results, and it is up to the user to select the most suitable tool.

This workgroup recommended the collection of all instruments available and classification according to their usefulness and impact on decisions from the viewpoint of a decision maker. The overriding objective of this work would be the development of 1 consolidated instrument in the form of a modular assessment tool with different axes by (a) study objective: economic impact or cost-effectiveness, health outcomes, patient reported outcomes; and (b) study type: model, clinical prospective study, or retrospective data analysis. Workgroup 2 also acknowledged the importance of validating a consolidated instrument for quality assessment of real-world data by a broader group of users.

Consolidation does not necessarily mean the creation of a new additional instrument. Instead, it involves a thorough comparison of the existing instruments and selection of those criteria that are recognized as key indicators of the required quality assessment. In the September 2008 issue of JMCP, Fairman and Curtiss reported a comparison of a range of research and publication guidelines. A similar comparison, with a focus on real-world database research, would form the foundation of a consolidated tool to quickly link assessment to the quality evaluation at hand. Consequently, the first step for a consolidated tool would be the development of a comprehensive list of criteria, which define the quality standard expectations by type of quality assessment need. However, such a comprehensive list must be balanced against a key request from the user perspective, which was to keep it short and simple. There are 2 different approaches to deal with this tension. To create a “user-friendly” tool, the items could be ranked to identify the 10 most important factors from the decision maker’s perspective. Alternatively, an independent body or review process could decrease the skepticism of decision makers towards real-world data studies, without increasing the complexity in the individual decision-making process.

Workgroup 3: Process to Achieve Dissemination and Acceptance of an Assessment Tool. One conclusion reached in the Fairman and Curtiss review of guidelines was that there is
ample guidance existing, but that the use of it is limited.40 Thus, guidelines are not widely adopted, and their existence does not guarantee a minimum quality standard of published research.

Due to the demonstrated challenges regarding the uptake of tools such as the AMCP Format for Formulary Submissions5 and implementation of evidence-based decisions in health care,6-8,41 Workgroup 3 was assigned to outline a process for high-level agreement on the acceptance of an instrument for quality assessment to ensure widespread adoption of the instrument.

The initial recommendation was to establish an expanded, multidisciplinary advisory board composed of key decision makers and academic pharmacoeconomic researchers. The primary goal of this group would be to advance the content from the 3 workgroups to present to a larger, public “user forum” including professional bodies of decision makers and researchers, clinicians, employers, patient or quality assurance organizations. Potential stakeholders represented in such a forum could be the National Committee for Quality Assurance (NCQA) or the AHRQ, CMS, Congressional Budget Office, Wellpoint, Blue Cross Blue Shield, Kaiser, state Medicaid agencies, Department of Veterans Affairs, University HealthSystem Consortium [UHC], Institute of Medicine, World Association of Medical Editors, and the recently formed Pharmacy Quality Alliance. The objective would be to increase public awareness of the need for quality assessment of observational evidence and subsequently, the acceptance of observational studies meeting defined quality standards to be used in the decision-making process.

An alternative recommendation to a grass-roots initiative was the involvement of an independent body or review process for the “Quality Assessment of Real-World Information.” Such an independent body could evaluate existing real-world data information, based on the assessment tool, and provide recommendations concerning the use of such information back to the users, such as decision makers. Such an institution could also be involved in the maintenance of the tools and in long-term studies on the accuracy of the predictions drawn from real-world data when executed within a health plan system, similar to case studies presented by Workgroup 1.

For either recommendation an important part of the process would be input into the dissemination and adoption of a consolidated instrument and a training platform for all stakeholders who may use the instrument.

**Workgroup 4: Training and Education.** The objective of Workgroup 4 was to outline an education process to communicate the efficient and competent use of the assessment tool to all stakeholders. The goal of this initiative was to make training available to all potential users, including researchers, evaluators, journal editors, managed care representatives, physicians, and patient organizations. The workgroup determined that any training program would have to assume that participants start from a broad range of pre-existing knowledge.

An inventory was taken of existing educational resources of related professional societies. There are several sources for education on the use of pharmacoeconomic evidence in formulary decision making provided by ISPOR and AMCP/FMCP including workshops, short courses, live seminars and program content from annual meetings, which can be retrieved through the respective internet sites (www.amcp.org and www.ispor.org). The American College of Clinical Pharmacy (ACCP) has a training module on the use of pharmacoeconomics and outcomes research in patient care,42 as well as guidelines for pharmacoeconomic fellowship training.43 Other organizations such as Health Technology Assessment international, Society for Medical Decision Making, and AcademyHealth, offer links to existing training programs, but have no internal programs of their own.

Workgroup 4 recommended the creation of a training certification program on evaluating real-world data studies. The inventory of coursework could be provided through the Web as introductory courses, and advanced courses tying this work together to the application of real-world data in formulary decision making could be conducted face-to-face. The certificate program could then be supplemented by an ongoing mentoring option. The program was envisioned as a set of sequential modules. Once all the Web-based modules have been successfully completed, the participant qualifies for an interactive live program, or advanced course, on quality assurance for real-world studies. For the face-to-face advanced programs, a “speaker’s bureau” was recommended with qualified trainers for these courses. Training could be offered from the associations to their members, or organizations or companies to train their employees could hire trainers.

After the live advanced course, the participants could then enroll into an ongoing mentoring program to facilitate the uptake of the methodology in the participant’s work routines. This mentoring program was envisioned as a “mentor’s bureau” formed by the active users of the tool in their decision-making process. The reason for suggesting such a mentoring system is the experience that it is often difficult to transfer a newly acquired process or methodology into daily practice. While the newly learned process and method may seem to be clear in the classroom situation, obstacles often appear only in the practical application. A mentoring system may be a faster way of overcoming the obstacles and avoiding frustrations in the application. Conversely, a mentoring system could also help to bring the typical problems in the application back to the development team.

The development of the program should be financed by sources independent from manufacturers of products to be decided on. The recently passed economic stimulus package may provide government-based funding options through the AHRQ. The ongoing delivery of the training should be self-sustaining and financed by fees for participation and certification. A mandatory certificate for decision makers of leading organizations would fundamentally increase the utilization and adoption of the instrument and the standardization of the process.
Integrated Results of the 4 Workgroups. Workgroup 1 defined the current status around the need for real-world evidence through examples of its use in drug reimbursement decisions. Figure 1 depicts the overall process, which was elaborated by the 4 workgroups with the goal to improve the utilization of real-world data by decision makers. The core of this approach was to create a standardized instrument for quality assessment, which was led by Workgroup 2; then to develop a process for uptake and dissemination as outlined by Workgroup 3; and finally to support the establishment of this approach with a certified training series defined by Workgroup 4. The roundtable participants could serve as a steering committee for these activities and pursue funding procurement. A larger body, to include interaction with concerned stakeholders could be considered an “Interdisciplinary Board for the Quality Assurance of Real-World Data.”

Discussion
The goal of the current roundtable discussions was to suggest processes through which to improve the quality and acceptance of studies based on real-world data to be used for decision making. The preceding event in 2007 had identified hurdles for the integration of such studies into the decision-making process and led to the need to begin formulation of a joint action plan developed by formulary decision makers from managed care and pharmaco-economic research experts on how to overcome these obstacles.1 The process recommended by the second roundtable includes: (a) the establishment of a standard quality assessment tool by consolidating previously suggested tools; (b) pilot testing and subsequent validation of the robustness of the instrument in a larger user forum; and (c) the communication of the tool through publications and workshops. In addition the creation of an oversight board for safeguarding credibility and dissemination was recommended along with a multistage training program with access to a growing pool of users of the instrument. Quality assessment using an assessment tool or process is expected to help diminish the research-to-practice gap with respect to real-world data.

The process suggested in this roundtable has been formally described as “knowledge transfer,”45 defined as the implementation of knowledge by key stakeholders with the intention of improving health outcomes and efficiencies of the health care system. Change in health care does not happen easily, even if there is hard evidence for the advantages of the new direction or intervention.6,7,44 The existence of quality processes such as the AMCP Format or quality assessment instruments as they were discussed during the roundtable event does not lead to their automatic adoption.5,40 Hurdles along the way can be located on the individual, intra-organizational, or inter-organizational level. Insufficient financial, intellectual, or structural resources can limit acceptance of the new intervention. Those who should change often fall back on the familiar way of doing things despite evidence in support of the new ways.5 Change has to be carefully planned and facilitated throughout both pre- and post implementation phases. How the intervention is packaged, training, technical assistance, and fidelity assessment are reported to be crucial to the successful implementation of effective interventions in health care.9

However, the suggested process and tool are only first steps to improve the utilization and outcomes of decision making with real-world data. An iterative improvement process is mandatory. For example, the AMCP Format, which was originally published in the year 2000, was revised in 2002 (version 2.0) and 2005 (version 2.1), and further revisions will follow.1 In addition to the expert groups helping to keep the AMCP Format up-to-date, surveys and studies have been conducted among the target audience on the utilization and usefulness of the document.5,40-48

This report only considers the validation of the instrument for consistencies of the results when used by different users. The important question, whether the inclusion of high quality
real-world data and a standardization of the process of including these data in decision making will improve the decisions and their impact on health outcomes, is not addressed.

In May 2006, an international collaborative initiative called the Enhancing the QUality and Transparency Of health Research (EQUATOR) network was launched in London. The goal of this initiative is “to enhance reliability of medical research literature by promoting transparent and accurate reporting of health research.” Assuring the quality of medical research literature will be in high synergy with the goals of the ideas discussed in the roundtable reported here. If such standards will be used more consistently, they may facilitate the task of decision makers to assess the impact of research results on the health of their membership.

Alternatives to the process suggested here were discussed throughout the roundtable session, such as the creation of a quality certification body or review process, which would as an intermediary certify the quality of real-world data and evidence and interpret the potential impact on health outcomes and budgets. The disadvantage of such an institution, in addition to the organizational and operational issues, would be that it would introduce an additional interpretation level into the process instead of increasing the general level of knowledge and experience within the organizations.

One key limitation of this discussion is the presumption that in most organizations a structured decision-making process exists and the issue is only how to incorporate assessment of real-world data into this process. This may not be the case for all health plans, pharmaceutical benefit management companies, or other organizations making decisions on drug formularies. However, following the suggested pathway will not only increase standardization of quality assessment of real-world data, but at the same time it will also direct some attention to the decision-making process in general and allow for a growing exchange among those involved in the drug formulary decision-making process.

Conclusions and Recommendations

The roundtable discussion between formulary decision makers of managed care and pharmacoconomic academic experts led to a multistep action plan to increase the utilization of real-world data in decision making (Table 2). The proposed process should involve all relevant stakeholders in the development, testing, validation, and dissemination of a consolidated quality assessment instrument. To increase the general level of qualification for users of real-world data among decision makers, a multilevel certificate-training program has been recommended. To facilitate the integration of the instrument into the user’s organizational procedures, a mentoring program for all graduates of the training was proposed.
DISCLOSURES
The roundtable meeting and this report were supported by an unrestricted educational grant from Procter and Gamble Pharmaceuticals to the Mill Creek Outcomes Group, LLC. None of Procter and Gamble’s representatives or employees was involved in the outline or conduct of the expert discussions or in writing the manuscript.

Brixner and Holtorf planned, presented and moderated this roundtable discussion, with assistance from Joseph Biskupiak, PhD, MBA. The 5 authors contributed equally to data collection and interpretation. Brixner and Holtorf wrote and revised the manuscript, with assistance from Malone, Neumann, and Watkins.

REFERENCES


Asthma is a complex disease because its presentation can vary considerably from patient to patient. The nature of asthma often requires physicians to use a multifaceted approach to ensure optimal outcomes (i.e., control of symptoms) and to prevent asthma exacerbations and increased health care utilization. Evidence-based disease management guidelines have been developed and published to aid in the diagnosis of asthma and to help guide treatment decisions. In 2007, the National Asthma Education and Prevention Program (NAEPP) released its updated guidelines for the management and treatment of asthma. National guidelines such as these generally present the evidence currently available to support best practices for managing chronic diseases.

In the January 2008 issue of JMCP, Urbano reviewed 7 changes to the NAEPP guidelines that were considered by a small expert panel to be the most important and clinically relevant messages in the updated document. The bulk of these changes address diagnosis, successful comprehensive management, assessing disease severity, monitoring disease control, and managing asthma exacerbations. Some of the changes deal directly with medication use and choice. Because there is often a lag between the release of a new guideline and implementation in clinical practice, there is an opportunity to provide education and develop strategies that incorporate new recommendations into current programs.

The management and treatment of asthma remain challenging for all health care stakeholders—patients, providers, and payers. Unlike other chronic diseases such as heart disease, which become increasingly prevalent with age, asthma affects patients across the age spectrum. Over the past 25 to 30 years, the prevalence of asthma has continued to grow at an alarming rate, with the greatest increase seen among children. Current estimates cite the overall prevalence of asthma in the United States at approximately 22 million people, or about 7.7% of the population.

Despite growing recognition of asthma as a chronic disease and strides toward improving its treatment, the financial burden of this disease is enormous. The total direct and indirect costs associated with asthma are approximately $20 billion annually, the greatest proportion of which is attributable to poorly controlled asthma. According to The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (TENOR) study, a prospective, observational, multicenter, 3-year U.S. study of 4,756 patients with severe or difficult-to-treat asthma, the highest percentage of health care utilization in the prior 3 months was linked to patients with severe asthma.

The mandate for improving the care of asthma is clear. However, the existence of guidelines does not always ensure improved patient care. In a 2-year retrospective study of claims data from more than 4 million United Healthcare enrollees nationwide, overall adherence to evidence-based practice guidelines was 59% for select chronic conditions, including coronary artery disease, congestive heart failure, hyperlipidemia, asthma, and diabetes. For adults with persistent asthma, 79% of the commercially insured population filled a prescription for inhaled corticosteroid (ICS) therapy, whereas only 58% of Medicare enrollees filled an ICS prescription. Adherence to national asthma guidelines among inner-city physicians is even poorer. In a survey of 202 primary care providers in East Harlem, New York, 62% reported adhering to the National Heart, Lung and Blood Institute (NHLBI) asthma guidelines for ICS use. However, 34% reported adherence to the NHLBI guidelines recommendations for peak flow monitoring, 10% for referrals to allergy testing, and 9% for using an asthma action plan. It was also noted that greater provider self-efficacy was associated with greater adherence to peak flow monitoring, ICS use, and use of an asthma action plan.

Even with various expert-derived guidelines that provide asthma treatment strategies, many patients remain symptomatic and their asthma symptoms suboptimally controlled. In the retrospective study by Thier et al., patient adherence to ICS therapy was poor, even though 78% of all adults with persistent asthma filled an ICS prescription. Among this population, 37% were nonadherent to ICS therapy. In children with persistent asthma, nonadherence to ICS medications was 42%. A retrospective cross-sectional study of nearly 12 million elderly adults showed that physicians were not adherent to asthma therapy recommendations from the NAEPP Expert Panel Report-2 guidelines. This analysis, based on data from the National Ambulatory Medical Care Survey, found that individuals aged 65 years or older were 54% as likely to be prescribed long-acting beta-2 agonists (LABAs), 49% less likely to be prescribed short-acting beta agonists (SABAs), and 49% less likely to be prescribed combination ICS and LABA...
therapy. These data point to the fact that physician and patient adherence to clinical practice guidelines and recommended therapies are often suboptimal and may be contributing to poor outcomes and increased health care utilization.

Medication management—balancing efficacy, safety, and pharmacoeconomic data—is a central component of managed care. As disease state information evolves, managed care medical and pharmacy directors must keep abreast of new information and monitor formulary management options to determine if the currently employed strategies for medication management reflect current practice guidelines. This task may be especially important for diseases that affect large numbers of individuals and are associated with significant negative economic consequences if not managed effectively.

The release of updated clinical guidelines provides an opportunity for managed care organizations (MCOs) to reassess their disease management programs. Continuous monitoring is needed to evaluate the outcomes achieved by these programs so they can be adjusted, as necessary, to optimize the overall quality of care. The inclusion of omalizumab (Xolair) in the NAEPP guidelines offers another treatment option for patients who have immunoglobulin E (IgE)-mediated asthma. Health plans, however, need to identify, through pharmacy and medical data claims, the prevalence of uncontrolled asthma in their populations and then reassess their formulary management strategies to target the appropriate use of omalizumab in select populations.

Identification of “At-Risk” Populations
Implementing strategies to identify high risk patients—those with difficult-to-treat or uncontrolled moderate-to-severe asthma—is in the best interest of MCOs. From a disease standpoint, it appears that the costs associated with moderate-to-severe asthma and the resulting morbidity and mortality are substantial. These data imply that identifying patients with poorly controlled asthma and employing implementation strategies that provide ongoing education, as well as therapeutic alternatives, to improve control are important cost-management strategies for MCOs.

Measures have been evaluated to identify at-risk patients in large patient populations. Pharmacy-driven measures that include the frequency of dispensing events for SABAs or oral corticosteroids can predict future emergency care. In a retrospective review of patients with persistent asthma in a managed care population, use of 5 to 13 canisters of a SABA in the first year was associated with an increased risk of emergency hospital utilization in the second year compared with use of only 0 to 4 canisters in the first year (odds ratio [OR] = 2.2, 95% CI = 1.2-3.8). Similarly, use of more than 2 courses of oral corticosteroids in the first year was associated with an increased risk of emergency hospital utilization in the second year compared with use of 0 to 2 courses of oral corticosteroids (OR = 2.6, 95% CI = 1.5-4.5).

In addition to clinical measures to determine asthma severity and control, the NAEPP guidelines suggest specific quality-of-life (QOL) measures, such as the Asthma Quality of Life Questionnaire (AQLQ) and the Asthma Control Test (ACT), to assess the impact of asthma on patient QOL and daily functioning. AQLQ scores were an adequate measure of control, as determined by Bateman et al. This study showed that, across a range of asthma disease severity, well-controlled asthma patients had consistently higher AQLQ scores at end point and larger AQLQ improvements from baseline than patients who were not well controlled. This correlation suggests a relationship between guideline-based asthma control and improvement in QOL.

Similarly, the ACT has been shown to be a practical and simple tool that can effectively assess the level of asthma control, with or without lung function testing. This brief 5-item questionnaire measures several different areas of asthma control, including symptoms, rescue inhaler usage, and the impact of asthma on everyday functioning. It is important to note, however, that the 2007 NAEPP guidelines state that lack of experience with QOL surveys and the time needed to administer these instruments preclude their general adoption for routine encounters. As more information becomes available, the use of QOL measures may become more commonplace. Questionnaires have been used, in some cases in addition to administrative data, to identify patients at highest risk for emergency care and may offer MCOs another means to identify at-risk patients.

The NAEPP 2007 update also addresses the role of spirometry in the evaluation of asthma control. It is recommended that the forced expiratory volume in 6 seconds (FEV6), forced vital capacity (FVC) and the FEV6/FVC ratio be done before and following the use of a short-acting bronchodilator for the initial diagnosis of asthma and should be subsequently used to assess the risk for future adverse events. While these measures are useful in the physician office, they are generally not available in administrative databases to help MCOs identify members who are at risk for future adverse events secondary to asthma so that interventions to reduce risk can be initiated. Moreover, assessments of lung function alone may not provide a clear picture of asthma control without additional information about symptoms and their effect on a patient’s QOL. Even with these additional measures for assessing control, accurate assessment can be difficult.

The Case for Omalizumab in Medication Management
The updated NAEPP guidelines (2007) include an expansion of the stepwise approach for treating asthma. Unlike previous NAEPP guidelines, which had 4 steps based on asthma severity, the current edition now uses 6 steps to better address those whose asthma remains uncontrolled with traditional therapies. According to the stepwise approach as outlined in the current update and previous (2002) NAEPP guidelines, allergen immunotherapy should be considered in Steps 2-4, regardless of age. The guidelines recommend that immunotherapy should be considered in patients whose symptoms occur year round or during a significant portion of the year and are difficult to
control pharmacologically.\textsuperscript{1} As noted by Urbano et al.,\textsuperscript{2} one significant change in the NAEPP guidelines is the inclusion of omalizumab as adjunctive therapy for youths aged 12 years or older and adults with perennial allergies and severe persistent asthma that is not adequately controlled with the combination of ICS and a LABA. Omalizumab, a recombinant deoxyribonucleic acid (DNA)-derived human monoclonal antibody, is approved by the U.S. Food and Drug Administration (FDA) for use in patients with moderate-to-severe persistent asthma.\textsuperscript{2,22} Omalizumab binds to IgE, forming complexes that inhibit the response to allergens.\textsuperscript{21,22} Sources of relevant perennial allergens include dust mites, cockroaches, cats, and dogs.

The NAEPP 2007 update reserves the use of omalizumab for Steps 5 and 6 which, by definition, are adjunctive therapy for patients aged 12 years or older who have allergies with severe persistent asthma. In such cases—patients who remain uncontrolled despite traditional therapies, especially those with IgE-mediated allergic asthma—adjunctive therapy with agents that target the underlying allergic component may be beneficial. Identification of the patient populations that could most benefit from omalizumab therapy remains a challenge, however. According to packaging labeling, omalizumab is “indicated for adults and adolescents (12 years of age and above) with moderate to severe persistent asthma who have a positive skin test or in vitro reactivity to a perennial allergen and whose symptoms are inadequately controlled with inhaled corticosteroids.”\textsuperscript{22}

The clinical benefits of omalizumab as adjunctive therapy have been detailed in the literature. Clinical studies have found that combining omalizumab with ICS reduces asthma exacerbations,\textsuperscript{23,24} improves lung function,\textsuperscript{23,24} and results in greater reductions in steroid dosing compared with placebo.\textsuperscript{23,25} Improvements in QOL have also been reported in patients receiving omalizumab compared with placebo.\textsuperscript{23,28} Unlike other adjunctive therapies that also improve outcomes and reduce steroid dosing, omalizumab has demonstrated added benefit when combined with high-dose ICS and LABA in the management of severe persistent allergic asthma.\textsuperscript{26}

The National Institute for Health and Clinical Excellence (NICE) noted in its appraisal (2007) that omalizumab may be considered as add-on therapy only to optimized, standard therapy in adults and adolescents aged 12 years or older who have severe, unstable disease.\textsuperscript{27} Use of and compliance with the standard treatments, including high-dose ICS therapy and LABAs in addition to leukotriene receptor agonists, theophylline, oral corticosteroids, and oral beta-2 agonists, are recommended before considering omalizumab as add-on therapy. In order to be considered for omalizumab therapy, the NICE guidelines define the criteria that patients must meet to establish the existence of severe, unstable allergic asthma: (a) confirmation of IgE-mediated allergic asthma by clinical history and allergy skin test; and (b) at least 2 severe exacerbations requiring hospitalization within the previous year, or at least 3 severe exacerbations within the previous year, with 1 requiring hospitalization or 2 requiring treatment or monitoring beyond the patient’s usual regimen.\textsuperscript{27} The NICE guidelines also recommend discontinuation of omalizumab after 16 weeks if there is no adequate response to therapy based on a full clinical assessment that includes degree of asthma control, QOL, control of exacerbations, avoidance of unscheduled health care utilization, spirometry and peak expiratory flow measures, and physician global assessment of treatment efficacy.\textsuperscript{27}

The NICE appraisal of omalizumab included evaluation of the results from the Investigation of Omalizumab in Severe Asthma Treatment (INNOVATE), a randomized, double-blind, multicenter study in patients with poorly controlled severe persistent asthma that measured clinically significant exacerbations and clinically significant severe exacerbations in patients receiving omalizumab as add-on therapy. The NICE committee noted that the rate of clinically significant exacerbations (the primary efficacy outcome) in the primary intention-to-treat population in INNOVATE was 0.74 for the omalizumab group versus 0.92 for the placebo group (rate ratio = 0.806, 95% CI = 0.600-1.083, \textit{P} = 0.153), which was not statistically significant until after post-hoc adjustments were made. Other INNOVATE results included statistically significant reductions in clinically significant severe asthma exacerbations and greater improvement in AQLQ scores for omalizumab compared with placebo.\textsuperscript{27}

In addition to the post hoc adjustments, NICE criticized the INNOVATE study on several points such as the exclusion of 13% of randomized patients prior to the implementation of the protocol amendments. The NICE committee wrote, “There were aspects of the INNOVATE RCT [randomized controlled trial] that led to uncertainty, including lack of detail on concealment of treatment allocation, the possibility of inadequate double blind- ing, selection bias, and exclusion of randomised patients for the intention-to-treat population.”\textsuperscript{27} These uncertainties led NICE to question “the improvement observed for the primary efficacy outcome.”\textsuperscript{27} Following testimony from both clinical specialists and patient experts, NICE concluded that “omalizumab as an add-on to optimised standard therapy is more clinically effective in particular groups of patients than optimised standard therapy alone.”\textsuperscript{27}

In clinical studies, omalizumab has been shown to reduce asthma-related hospitalizations and emergency room visits.\textsuperscript{26,28} Ayres et al. compared the safety and efficacy of omalizumab versus best standard care in patients with moderate-to-severe asthma in a randomized, open-label, multicenter study.\textsuperscript{28} The primary efficacy measure (annualized asthma deterioration-related incidents defined as asthma-related need for systemic antibiotics or corticosteroids, missed school or work, unscheduled physician office visits or hospitalization or emergency room visits) was 9.76 with best standard care alone (\textit{n} = 106) versus 4.92 (\textit{n} = 206) per patient-year with omalizumab (\textit{P} < 0.001).\textsuperscript{28} In the INNOVATE study, the addition of omalizumab to high-dose ICS and LABA...
during the 28-week study period resulted in fewer total emergency visits compared with placebo added to high-dose ICS and LABA (50 vs. 93, \(P=0.038\)). The omalizumab group also had nonsignificantly lower rates of hospital admissions (13 vs. 25 for placebo, \(P=0.117\)) and unscheduled doctor visits (28 vs. 54 for placebo, \(P=0.090\)).²⁶

Administration of omalizumab is not without risks.¹ Pain and bruising can occur in 5%-20% of patients following administration and malignant neoplasms were reported in 0.5% of patients compared with 0.2% in those treated with placebo. Anaphylaxis has also been reported in 0.2% of patients. Because of the risk of anaphylaxis, clinicians that decide to administer omalizumab must be prepared and equipped to identify and treat anaphylaxis should it occur.¹ Additionally, the manufacturers of omalizumab added a black-box warning in 2007 to highlight the possibility of anaphylaxis, which includes bronchospasm, hypotension, syncope, urticaria, and/or angioedema of the throat or tongue.²² The warning also notes that anaphylaxis has been reported from the time of the first dose and beyond 1 year of treatment.²² Physicians are also advised to be prepared to manage life-threatening anaphylaxis if it occurs, inform patients of the signs/symptoms of anaphylaxis, and instruct patients to seek medical care if any symptoms occur.²² The NAEPP guidelines suggest referral to an asthma specialist for consultation or comanagement if the patient is not well controlled, if the patient requires Step 4 therapy or asthma specialist for consultation or comanagement if the patient needs it.²³ Physicians also have to be prepared and equipped to identify and treat anaphylaxis should it occur.¹ Additionally, the manufacturers of omalizumab added a black-box warning in 2007 to highlight the possibility of anaphylaxis, which includes bronchospasm, hypotension, syncope, urticaria, and/or angioedema of the throat or tongue.²² The warning also notes that anaphylaxis has been reported from the time of the first dose and beyond 1 year of treatment.²² Physicians are also advised to be prepared to manage life-threatening anaphylaxis if it occurs, inform patients of the signs/symptoms of anaphylaxis, and instruct patients to seek medical care if any symptoms occur.²² The NAEPP guidelines suggest referral to an asthma specialist for consultation or comanagement if the patient is not well controlled, if the patient requires Step 4 therapy or higher, if immunotherapy or omalizumab are considered, or if the patient has had an exacerbation requiring a hospitalization.¹

As with the identification of the at-risk patient with asthma, the optimal method of identifying the patient who is a candidate for omalizumab is complicated. Belliveau et al. noted in their review in JMCP (2005) that appropriate screening is needed to determine which patients would respond most favorably to omalizumab treatment, and that when this subset of patients is targeted, the reduction of medical resources could potentially offset the drug’s high acquisition cost.²⁹ In an accompanying editorial, Curtiss commented that based on the evidence to date, the efficacy of omalizumab beyond 7 months is unknown and the key to cost-effective use lies in selective and specific use.³⁰

Currently, most health plans have placed prior authorization (PA) restrictions on omalizumab due to its high cost, the availability of other agents, and concerns regarding its safety, including the potential for anaphylaxis and lack of safety data beyond 1 year of treatment.

Since its approval by the FDA in 2003, the safety and efficacy of omalizumab and its appropriate use in asthma patients have been debated in the clinical literature. The release of the 2007 NAEPP update provides an opportunity to re-evaluate the place in therapy of omalizumab. At this point, the definition of the ideal candidate most likely to respond favorably to omalizumab therapy is not clear. Continued monitoring of outcomes for patients who receive omalizumab, however, will be essential and perhaps, with continued use, a pattern will evolve that better defines those who best respond to this therapy.

Conclusion

As noted previously by Urbano,² currently available clinical guidelines serve as an ideal starting point for improving the quality of care for the asthma disease state. The NAEPP guideline update in August 2007 should help clinicians in assessing and monitoring asthma. With a shift in focus to measuring control with a combination of outcomes tools, the identification and treatment of patients with poorly controlled asthma may be improved. The integration of various outcomes measures will be required and should include clinical assessments, physician and patient-reported measures of productivity/avoidance of activity, and burden to society and the workplace. In certain high-risk patients with severe persistent asthma, omalizumab may be considered as a treatment option. The ideal candidate for omalizumab therapy is as of yet unknown. Therefore, continued evaluation of this treatment is needed to refine the parameters for targeting patients who may benefit most from omalizumab.

REFERENCES


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30. Curtiss FR. Selectivity and specificity are the keys to cost-effective use of omalizumab for allergic asthma. J Manag Care Pharm. 2005;11(9):774-76. Available at: http://www.amcp.org/data/jmcp/editorial_774-776.pdf.
Omalizumab and Other New Drug Therapies Occupy a Small Space in Asthma Disease Management

Frederic R. Curtiss, PhD, RPh, CEBS

Asthma disease management can be a frustrating experience for clinician and patient, and it seems what we don’t know about the subject is about as much as what we do know. Asthma is a stubborn disease to manage due to variability in patient response to treatment and difficulty in identifying (targeting) the patients at risk of exacerbation sufficient to precipitate urgent care in the form of hospitalization or emergency room visits. Nonetheless, despite the increasing prevalence of asthma in the United States, hospital discharge rates for asthma decreased 16.2% between 2003 and 2005.1

The patient variability in response to pharmacotherapy suggests that there may be a strong pharmacogenetic influence. For example, the long-acting beta-2 agonists (LABAs) have a black-box warning of increased risk of exacerbation of asthma and death, but the results of the Salmeterol Multicenter Asthma Research Trial (SMART) suggest that the risk associated with LABAs seems significant primarily in certain subgroups of patients.4 For example, retrospective analysis of data from 6 randomized controlled trials (RCTs) showed that persons homozygous or heterozygous for the arginine (Arg)-16 Gly polymorphism may have worse outcomes on LABAs, regardless of use of inhaled corticosteroids.5 Hall noted that 15% of the white population has this genetic characteristic, but there are not yet sufficient data to ascertain the role of Arg-16 in the variable response to the bronchodilator effects of LABAs.6

We have also recently learned more about how the effectiveness of asthma disease management is influenced by psychological factors. Negative child affect, measured by the Children’s Depression Inventory and the Revised Children’s Manifest Anxiety Scale, and negative parent affect, measured by the Center for Epidemiologic Studies Depression Scale, have been found to predict higher asthma symptom scores (a composite of self-reported wheezing, tightness of chest, shortness of breath, coughing from exercise, coughing from other causes, and nighttime symptoms).7 This new research has implications for both clinical trials and clinical practice; i.e., clinicians need to consider the emotional state of the asthma patient and of the parent of an adolescent or child patient.

Aside from the role of psychological and genetic factors in asthma disease management, from a population perspective there are 3 risk factors that appear to help explain the rising prevalence of asthma and disease severity: (a) control of infectious diseases and reduced exposure to endotoxins in the food and water supply that interfere with development of childhood antibody responses to allergens; (b) prolonged indoor exposure to allergens, particularly house mites and cockroaches; and (c) a sedentary lifestyle since there appears to be a direct relationship between physical activity and anti-inflammatory response.8 The relationship between upper airway disease and allergies has intrigued clinicians and researchers for decades, and recent research points to possible localized sensitization to immunoglobulin E (IgE).9 This evolution in research in the etiology of airway disease is logical because allergic rhinitis can occur without systemic evidence of IgE sensitization (i.e., negative skin allergy test and no specific serum IgE).

What About Omalizumab?

In this issue of JMCP, Pesko suggests that injectable omalizumab (Xolair), approved by the U.S. Food and Drug Administration (FDA) 6 years ago in June 2003, represents a promising therapeutic option for asthma disease management, citing the product labeling that includes the following indication, “For adults and adolescents 12 years of age and older with moderate to severe persistent asthma who have a positive skin test or in vitro reactivity to a perennial aeroallergen and whose symptoms are inadequately controlled with inhaled corticosteroids. Omalizumab has been shown to decrease the incidence of asthma exacerbations in these patients. Safety and efficacy have not been established in other allergic conditions.”10 Notably, the primary off-label use of omalizumab appears to be seasonal allergic rhinitis,11 despite the absence of evidence of safety or efficacy in allergic conditions other than asthma.

An underlying theme in Pesko’s suggestions that the market space for omalizumab might be larger than previously thought has to do with the number of patients who are inadequately controlled with other first-line and second-line drugs. For example, some of the results of the Gaining Optimal Asthma control (GOAL) trial might be cited as evidence that even with intervention in a clinical trial to control asthma with escalation of the dose of inhaled corticosteroid (ICS), a large proportion of patients remain uncontrolled.12 In fact, it is impressive that 59% of patients in the GOAL study with previously uncontrolled asthma were well controlled at 1 year with higher doses of fluticasone alone, and 71% of patients were well-controlled with higher doses of fluticasone plus LABA.13 However, the persistence of
symptoms in some patients with severe asthma despite treatment invites continued research on the pathophysiology of asthma.

The *raison d’être* for Pesko’s commentary is that the National Asthma Education and Prevention Program (NAEPP) guideline update (2007) should precipitate some action by health plans to reassess prior authorization (PA) criteria and utilization management of omalizumab. Two points are important with respect to this assertion. First, omalizumab was not available for consideration when the 2002 NAEPP update was written because omalizumab did not receive FDA approval until June 2003. Second, there was no sudden realization in the 2007 NAEPP update that omalizumab had an important place in therapy.

In fact, the NAEPP update in 2007 recommended use of omalizumab in a more narrow corridor than stated in the omalizumab product label approved 4 years earlier by the FDA (i.e., appropriate for use only in patients with “severe persistent asthma” versus the FDA-approved labeling that includes patients with “moderate-to-severe persistent asthma”). In the justification for this recommendation and in Figure 3-22 (long-term control medications), the NAEPP Full Report includes the warning that “Adverse effects reported from omalizumab in the trials have also included injection-site pain and bruising in up to 20 percent of patients (Holgate et al. 2004). In the trials reported to the FDA, twice as many patients receiving omalizumab had malignancies (20 of 48,127, or 0.5%) as did those receiving placebo (5 of 2,236, or 0.2%), but there were no trends for a specific tumor type.”

In essence, Pesko suggests in his commentary that we should ignore the wisdom of the experts, as reflected in the NAEPP 2007 update and the guidance (TA133) from the National Institute for Health and Clinical Evidence (NICE) released in November 2007 (Appendix), and instead rely on a product label that was developed based on data evaluated by the FDA prior to approval of the omalizumab. Pesko also fails to inform readers adequately about some important points raised by the authors of the NICE guidance. Ignored completely in this commentary are the 25 malignancies cited in the NICE guidance among 5,015 patients treated with omalizumab (0.50%) in 35 clinical trials, compared with 5 of 2,854 patients (0.18%) treated with standard therapy. Also skirted is the thrust of the summary of the NICE guidance: “The Committee concluded that it would only be clinically appropriate to consider the use of omalizumab add-on therapy once standard therapy has been optimized and that for the purposes of this guidance, optimized standard therapy is defined as a full trial of, and documented compliance with, inhaled high-dose corticosteroids and LABAs in addition to leukotriene receptor antagonists, theophyllines, oral corticosteroids and beta-2 agonist tablets and smoking cessation where clinically appropriate.”

Unfortunately, omalizumab falls short of being a “magic bullet” for allergic asthma. Among the outcomes that under-perform the expectations for this drug, the NAEPP 2007 update referred to the steroid-sparing effect of omalizumab as “modest” (median 25% reduction), and the NICE guidance noted the evidence that “asthmatic patients who are known to be refractory to high-dose oral corticosteroids may be less likely to respond to omalizumab treatment, whereas omalizumab may provide steroid-sparing benefits on lower doses of oral steroids.”

Omalizumab is administered by subcutaneous injection, and it is expensive. It should be dosed by body weight and baseline serum IgE level, and the drug cost alone is $4,000 to $30,000 per year of therapy, with an average drug cost of about $1,000 per month. Actual claims analysis for calendar year 2008 in 1 employer health plan showed that omalizumab had an average cost of about $20 per day of therapy at its lowest dose (150 mg every 4 weeks). The key to cost-effective use of omalizumab depends on selectivity and specificity in the asthma population, but the clinical characteristics that predict individual patient response to therapy are unreliable.

There is also a sizable safety risk associated with the use of omalizumab beyond the aforementioned increased risk of malignancies. Four years after approval of omalizumab by the FDA on June 20, 2003, a black-box warning was added in July 2007. The black-box warning followed an FDA alert released 5 months earlier, in February 2007, regarding possible anaphylaxis after any dose of omalizumab, up to 24 hours after the dose is administered, and even if there was no reaction to the first dose.

**Narrowing the Target Space for Omalizumab**

The size of the space that omalizumab might occupy in asthma management is small, but the precise size is unknown. We know that severe persistent asthma accounts for less than 20% of the asthma population. For example, of the adults in Michigan who took asthma medication in the past 30 days, 16.1% were categorized as severe persistent, and about 1 in 5 of all adult asthma patients report daily symptoms.

In an attempt to precisely identify the target population of asthma patients most likely to benefit from omalizumab, it is helpful to recall that the clinical trials of omalizumab enrolled patients who had demonstrated sensitivity by positive skin test to specific perennial allergens (specifically, dust mites, cockroaches, dog or cat dander) and baseline serum IgE levels in the range of 30 to 700 international units (IU) per milliliter for patients 12 to 75 years of age. Bousquet et al. (2004) found that 3 factors predicted response to omalizumab, although the absolute differences compared with placebo are small and statistically insignificant for forced expiratory volume: high dose of the ICS beclomethasone (800 mcg or more per day; 65% for omalizumab vs. 40% for placebo, P = 0.037), a history of emergency treatment for asthma in the past year (67% for omalizumab vs. 40% for placebo, P = 0.015), and poor lung function (forced expiratory volume in 1 second [FEV1] ≤ 65% predicted; 67% for omalizumab vs. 40% for placebo, P = 0.015).
Currie et al. (2009) reviewed the characteristics of the difficult-to-treat adult asthma patient. This category of patient represents about 5%–10% of adults with asthma but accounts for disproportionately high morbidity, medical costs, and fatal and near-fatal exacerbations. There are few new approaches to better manage this difficult population, and the clinical results are not encouraging. The tumor necrosis factor (TNF) antagonist etanercept showed initial promise, but a double-blind RCT over 24 weeks found no significant improvement in patients with steroid-dependent asthma. And, a 24-week trial with the human anti-TNF monoclonal antibody golimumab showed not only no improvement in efficacy but significantly increased risk of infection and malignancies. A number of older drugs such as cyclosporine, methotrexate, gold, and subcutaneous terbutaline have been tried with apparent efficacy in difficult-to-treat adult asthma patients (e.g., Nair et al. screened hundreds of severe asthma patients to obtain the 20 patients in their study); and (d) the subjects recruited in the 2 recent studies were extraordinary asthma patients (e.g., Nair et al. screened hundreds of severe asthma patients to obtain the 20 patients in their study); and (d) the eosinophilic form of asthma accounts for about 5% of the total number of cases of adult-onset asthma, the more likely target group compared with childhood-onset asthma.

Therefore, the newest light on biologic factors in asthma appears to illuminate better the path to further research rather than provide solutions to the challenge of improving outcomes in patients with difficult-to-treat asthma.

## Confining the Space for Omalizumab

In the category of drugs to suppress IgE, the biological omalizumab should be effective, but (a) Currie et al. remind us that the Scottish Medicines Consortium advises the use of omalizumab only in patients who require maintenance oral steroids when all other treatments have failed, and (b) NICE advises its use only in patients with severe unstable allergic asthma who have had at least 2 severe exacerbations requiring hospital admission within the previous year. The important takeaway message from the collective evidence is that the therapeutic space for omalizumab is small. NAEPP 2007 makes this very clear: omalizumab is considered add-on treatment at the end steps of management of persistent asthma in patients who have allergies and continue to have symptoms uncontrolled with high-dose ICS and LABA (step 5) and with oral corticosteroid (step 6), and administered by clinicians who are “prepared and
Omalizumab and Other New Drug Therapies Occupy a Small Space in Asthma Disease Management

NICE is somewhat less nice to omalizumab, restricting its recommended use to add-on therapy in patients with:
• confirmation by clinical history and skin test of IgE-mediated allergy to a perennial allergen;
• evidence of severe exacerbations of asthma in the last year, defined as (a) at least 2 exacerbations that required hospital admission, or (b) 3 or more exacerbations that included at least 1 hospital admission and 2 emergency room visits;
• discontinuation of omalizumab at 16 weeks in the absence of response to therapy (Appendix).

Despite ostensible promise in patients with allergic asthma, omalizumab is appropriate in only a small proportion of asthma patients.

APPENDIX  NAEPP 2007 and NICE Recommendations (2007) for Appropriate Use of Omalizumab

NAEPP 2007 Guidelines

“The Expert Panel recommends that omalizumab may be considered as adjunctive therapy in step 5 or 6 care for patients who have allergies and severe persistent asthma that is inadequately controlled with the combination of high-dose ICS and LABA (Evidence B).”

NICE Technology Appraisal Guidance 133 – Omalizumab for Severe Persistent Allergic Asthma

1.1 Omalizumab is recommended, within its licensed indication, as an option for the treatment of severe persistent allergic (IgE mediated) asthma as add-on therapy to optimized standard therapy, only in adults and adolescents (12 years and older) who have been identified as having severe unstable disease.

1.2 For the purposes of this guidance, optimized standard therapy is defined as a full trial of, and documented compliance with, inhaled high-dose corticosteroids and long-acting beta-2 agonists in addition to leukotriene receptor antagonists, theophyllines, oral corticosteroids and beta-2 agonist tablets and smoking cessation where clinically appropriate.

1.3 Omalizumab add-on therapy should only be initiated if the patient fulfills the following criteria of severe unstable allergic asthma: (a) confirmation of IgE mediated allergy to a perennial allergen by clinical history and allergy skin testing, and (b) either 2 or more severe exacerbations of asthma requiring hospital admission within the previous year, or 3 or more severe exacerbations of asthma within the previous year, at least one of which required admission to hospital, and a further two which required treatment or monitoring in excess of the patient’s usual regimen, in an accident and emergency unit.

1.4 Omalizumab add-on therapy should be initiated and monitored by a physician experienced in both allergy and respiratory medicine in a specialist centre.

1.5 Omalizumab add-on therapy should be discontinued at 16 weeks in patients who have not shown an adequate response to therapy.

Response to treatment should be defined on the basis of a full clinical assessment comprising: degree of asthma control, quality of life, control of exacerbations, avoidance of unscheduled healthcare utilization; spirometry and peak expiratory flow measures and a global evaluation of treatment effectiveness, as assessed by the physician.”

The NICE TA133 Guidance includes some particularly succinct points regarding cost-effectiveness:
“Overall, therefore, the Committee concluded that there were a number of considerations which meant the ICER was higher than acceptable for patients with severe persistent allergic asthma. However, the Committee was persuaded that for a narrowly defined severely affected group of asthma patients, at an elevated risk of asthma-related mortality, cost-effective treatment with omalizumab was possible, if therapy was discontinued in non-responders at 16 weeks and if vial wastage could be minimized to reduce costs. The Committee concluded that omalizumab add-on therapy is recommended as an option for the treatment of asthma in patients with severe unstable disease (that is, those who have had either two or more severe exacerbations of asthma requiring hospital admission within the previous year, or three or more severe exacerbations of asthma within the previous year, at least one of which required admission to hospital, and a further two which required treatment or monitoring in excess of the patient’s usual regimen, in an accident and emergency unit), who have clinical confirmation of IgE mediation of asthma exacerbations and have had a full trial of, and documented compliance with all standard asthma medication (see 4.4). It also concluded that omalizumab treatment should only be initiated and monitored by physicians experienced in both allergy and chest medicine in a specialist centre.”

REFERENCES


20. Curtiss FR. Selectivity and specificity are the keys to cost-effective use of omalizumab for allergic asthma. J Manag Care Pharm. 2005;11(9):774-76. Available at: www.amcp.org/data/jmcp/editorial_774-776.pdf.


Selling Real-World Health Care Research to Reluctant Buyers—Evidence-Based Education or Marketing a Defective Product?

Kathleen A. Fairman MA, and Frederic R. Curtiss, PhD, RPh, CEBS

In December 2004, the editors of BMJ announced a new policy requiring submission of *a priori* research protocols with manuscripts reporting the results of randomized controlled trials (RCTs). Under the new policy, RCTs would have to be registered at their outset with “a suitable trial registry,” and manuscripts lacking a registered protocol would no longer be sent to peer review. The editors explained that this decision had been made because their “experience of chasing authors for trial protocols, when we have suspected deviation in the protocol or found it hard to fathom what the authors set out to do,” had been “miserable.”

As occasionally miserable editors, we too are familiar with the experience of seeking information from an author who is unable or unwilling to provide it; and evidence is mounting that we are not alone. As we and others have observed previously, the practices of selective reporting of study findings, publication planning, and other forms of misconduct are, sadly, reportedly endemic in health care research. Studies that use observational or “real-world” data, particularly pharmaco-economic modeling and retrospective analyses of administrative databases, are particularly vulnerable to manipulation; it is especially easy to make post hoc changes to a planned protocol behind closed doors when only claims data and hypothetical patient populations, not prospectively studied human subjects, are involved.

Thus, to the extent problem presented by Brixner et al. in their commentary on use of real-world data in this issue of *JMCP*—that decision makers are sometimes reluctant to rely on analyses of real-world data—one reasonable response is that the most reluctant “buyers” of research may well be the best informed. After all, public denunciations of the “scandal of poor epidemiological research” by von Elm and Egger in 2004, and the “scandal of poor medical research” by Altman in 1994 and again in 2002 are well-known to anyone who has been following health care research even peripherally, and have spawned dozens of publications on how to improve a demonstrably inadequate pool of knowledge about the economic and clinical outcomes of health care interventions. Yet, we also know that many—perhaps even most—researchers are “playing by the rules,” endeavoring to provide accurate information, and producing high-quality work. So for a typical decision maker, the question becomes how to distinguish between accurate and inaccurate information.

This is essentially the question raised by Brixner et al., and it is an important one. The proposals offered by the March 2008 participants in a roundtable discussion of real-world data, whose views are reported in the Brixner et al. commentary, merit consideration. Nonetheless, currently these ideas appear to generate more new questions than specific guidance. More troubling is the possibility that the effort to promote use of real-world data by decision makers may detract from ongoing efforts to improve the quality of information provided to them.

“Independent Body or Review Process”—Different From Journal Peer Review?

Among the proposals advanced by Brixner et al.’s first workgroup, which examined the “continuation of the work of the ISPOR Task Force on the Use of Real-World Data,” was the formation of an “independent body or review process.” The body would “be formed as a consortium of experts giving access to a broad range of resources and expertise for an audit, review, or quality certification process.” We wonder how such a group would differ from the available pool of journal peer reviewers who, as experts in particular topic areas, are already tasked with screening the quality of research articles. Certainly, any consortium of experts would be faced with, and challenged by, the same lack of transparency in research reporting that has by now become infamous among journal peer reviewers, editors, and methodologists. A key task of peer review—to ensure that limitations of published work are transparently disclosed in terms that are relevant to journal readers—depends in part on the cooperation of authors, and most journal editors would acknowledge that some authors are more cooperative than others.

Brixner et al. mention the efforts of the Enhancing the QUAlity and Transparency Of health Research (EQUATOR) network, formed in May 2006 to “improve the quality of scientific publications by promoting transparent and accurate reporting of health research.” They opine that the EQUATOR network’s endeavors would be synergistic with the efforts proposed by the roundtable. However, at this early stage of development, Brixner et al. offer little specific information about how the process that they propose would incorporate the EQUATOR guidelines, or how an expert consortium might be more successful in encouraging transparency than are organizations and journals that are already measuring research reports against the EQUATOR standards. Brixner et al. do raise the possibility of a voluntary registry of observational studies, similar to the registries now required by most journals for the submission of manuscripts that describe clinical trials. This idea has merit, but either voluntary or mandatory registration would pose unique challenges; voluntary registration would lack “teeth,” while journals that impose mandatory registration of observational studies would at least temporarily experience a reduction in the flow of manuscript submissions.
Public Information Campaign—How Great Is The Need?

A second key proposal advanced by the roundtable participants was a “process to achieve dissemination and acceptance of an assessment tool,” essentially a public information campaign that would “increase public awareness of the need for quality assessment of observational evidence and subsequently, the acceptance of observational studies meeting defined quality standards to be used in the decision-making process.” The window of opportunity for public dissemination of this information appears to be open—but only by the slightest crack. Deficiencies in the research literature have been publicly acknowledged for about 15 years, and EQUATOR standards have been adopted by a wide variety of journals, including Annals of Internal Medicine, BMJ, JAMA, PLoS Medicine, the Journal of Clinical Epidemiology, and others. EQUATOR standards have been endorsed by the Council of Science Editors, and guideline documents promulgated by EQUATOR are referenced by the International Committee of Medical Journal Editors in their uniform guidelines for manuscript submission. Certainly these efforts must be known among those who routinely read health care journals.

However, it is possible that many decision makers will not fall into that category. The roundtable’s work, which is in its early stages, has to date included only informal assessments of informational needs that were expressed by small numbers of meeting participants and by a convenience sample (N=70, including an unknown number of decision makers) responding to a draft ISPOR report during an open comment period. Before launching a widespread informational campaign, Brixner et al. should be encouraged to conduct a more quantitative and systematic evaluation of the informational needs of decision makers. It might even be wise to “quiz” decision makers to assess gaps in their knowledge of observational research methods and pharmacoeconomic modeling. For example, in advance of the first EQUATOR meeting, network organizers “searched literature to identify published reporting guidelines and surveyed authors to examine how the guidelines were developed and to identify problems encountered during the development” and used “the survey results and meeting discussions [to help us prioritize] main activities that were necessary for a successful start of the EQUATOR Network’s efforts to improve the quality of reporting of health research.” This kind of systematic, evidence-based approach is most likely to result in a process that will address the needs of decision makers.

An educational effort should also reflect a realistic acknowledgement of the time and resources available to a typical health care decision-maker. Although the key elements of high-quality research—such as transparency, minimization of bias, and a presentation that is sufficiently detailed to facilitate replication of study methods—are promulgated universally by guideline documents, putting these ideas into practice sometimes requires time and expertise. The expertise required for use of research guideline documents—at about the level of upperclass undergraduate or beginning graduate school research methods and statistics classes—should not exceed the ability of any researchers seeking journal publication, but could potentially be too far outside the time or expertise available to a decision maker, even after a brief educational intervention. For example, a common error seen in research reporting is the use of an underpowered sample size to compare 2 treatment approaches, followed by the assertion of a researcher that the treatments are equivalent. An author or journal peer reviewer can easily obtain the necessary power calculation tables and determine if the sample size was adequate for the task, but asking for this level of effort from a health plan executive/decision maker is probably unrealistic. However, it is realistic to train decision makers to recognize an even more common error, the description of a clinically meaningless result as important based solely on statistical significance. For example, a difference of 1 percentage point in medication possession ratio, representing only about 4 days of additional pharmacotherapy per year, is clearly unimportant whether it is statistically significant or not.

Standardized Quality Instrument—A Worthwhile Endeavor?

An additional key element in the strategy proposed by the roundtable participants in the report by Brixner et al. is a “standardized instrument for quality assessment,” which would represent “criteria that are recognized as key indicators” of quality. For the instrument to be “user-friendly,” Brixner et al. posit, it would “identify the 10 most important factors from the decision maker’s perspective.” However, they also indicate that the instrument would take “the form of a modular assessment tool with different axes by (a) study objective: economic impact or cost-effectiveness, health outcomes, patient reported outcomes; and (b) study type: model, clinical prospective study, or retrospective data analysis.” This proposal is the weakest and least evidence-based of those advanced by Brixner et al.

First, it appears that Brixner et al. may be proposing too much for just 1 document. When the Agency for Healthcare Research and Quality (AHRQ) undertook a systematic review of checklists used to rate the strength of scientific evidence in 2002, it wisely opted not to attempt a single checklist for all study types. “In the worst case,” the AHRQ observed, “combining all such systems into a single evaluation framework risked nontrivial confusion and misleading conclusions, and [we] were not willing to take the chance that users of this report would conclude that ‘a single system’ would suit all purposes. That is clearly not the case.”

Second, the most important potential need, education, does not require a new checklist. In an era of scarce resources, Brixner et al. should be mindful of the degree to which their work duplicates that already being undertaken, or already completed, by EQUATOR. For example, among the EQUATOR network’s primary objectives are the development of “a comprehensive web-based ‘Resource Centre’ providing up-to-date information, tools and other materials relating to reporting health research” and “training courses for editors, peer reviewers and researchers, and other educational activities raising awareness and importance of reporting guidelines.” A library of standards for numerous types of study reports—including RCTs, observational research,
analyses of health care interventions, meta-analyses, and more—is already available on-line, and training courses have begun. Since sensible and high-quality guideline documents already exist for nearly every conceivable major type of study, expending effort to create yet another tool seems unproductive at best, and at worst has the clear potential to become a pyrrhic attempt at an ineffective and possibly misleading “one size fits all” approach.

Our Continued Plea for Transparency

We continue to believe that the best hope for improving the quality of research evidence available to decision makers lies in a strengthened journal peer review system. Although far from perfect, the system of editorial and peer review has already been bolstered by the efforts of the EQUATOR network and others to add transparency to research reporting and by the increased “disinfectant/sunshine” that has resulted from public attention to incidents of research misconduct. Creating a new review body or expert consortium, composed of the same people who make up the current peer reviewer pool, is unlikely to be productive and at worst may divert attention from current quality improvement efforts.

The proposal from the roundtable session reported by Brixner et al. that has the most potential is the education of decision makers in the critical review of studies employing real-world data. However, such education should (a) be based on a systematic and quantitative assessment of the informational needs of decision makers; (b) openly acknowledge the scope of the problem of poor-quality research; (c) train decision makers in review methods that can be used to refute rather than accept poor quality; and (d) acknowledge the limitations of time and resources available to a typical decision maker.

Finally, the process proposed by Brixner et al. should be designed so as to minimize duplication of effort. In that regard, the clearest area for improvement in Brixner et al.’s proposals involves the standardized checklist, which is almost entirely duplicative of work already completed by others.

Brixner et al. address an issue that has become increasingly important in managed care—how to encourage decision making that is based on high-quality evidence. However, the process currently advocated by the roundtable meeting participants poses the risk of inadvertently encouraging decision makers to accept poor-quality work—providing a false sense of security about published real-world research evidence instead of facilitating a critical assessment of its strengths and weaknesses. To reduce this risk, measurement of the unmet informational needs of managed care decision makers is essential to establish a base of evidence before “promoting the utilization of real-world data.”

DISCLOSURES

The authors report no conflicts of interest related to the subjects or products discussed in this article.

REFERENCES