ARE BRAND-NAME AND GENERIC WARFARIN INTERCHANGEABLE? A SURVEY OF ONTARIO PATIENTS AND PHYSICIANS

Jennifer A Pereira[1,2], Anne M Holbrook[1,2,3], Lisa Dolovich[1,4,5], Charles Goldsmith[1,6], Lehana Thabane[1,6], James D Douketis[3], Mark Crowther[3], Shannon M Bates[3], Jeffrey S Ginsberg[3]

[1]Centre for Evaluation of Medicines, St Joseph's Healthcare Hamilton, ON [2]Department of Pharmaceutical Sciences, University of Toronto, Toronto, ON, [3]Department of Medicine, McMaster University, Hamilton, ON [4]Faculty of Pharmacy, University of Toronto, Toronto, ON, [5]Department of Family Medicine, McMaster University, Hamilton, ON,[6]Department of Clinical Epidemiology and Biostatistics, McMaster University, Hamilton, ON

Corresponding Author: j.pereira@utoronto.ca

ABSTRACT

Background
The issue of therapeutic equivalence has been a source of controversy in Canada since the approval of generic warfarin products in 2000.

Objectives
We surveyed Ontario patients and physicians on perceptions of generic warfarin and brand substitution.

Methods
Self-administered questionnaires employed 7.0-point Likert scales of agreement. Patient participants were drawn from a thromboembolism clinic in Hamilton, Ontario. Physician participants were from a random sample of 375 Ontario family physicians, internists, cardiologists and hematologists.

Results
Eighty-one patients responded: 52% female, mean age 63.4 years and 63% brand-name warfarin users. Overall, 33% of respondents agreed or strongly agreed that they would feel comfortable taking generic warfarin. However, seventeen percent agreed or strongly agreed that generic warfarin was neither as safe nor as effective as brand-name warfarin, with this view more common amongst patients taking brand-name than those taking generic warfarin. One hundred and ten (29.3%) physicians returned the survey - 29% females, mean age 45.3 years, 22% family physicians. Forty-four percent agreed or strongly agreed that they would rather prescribe brand-name than generic warfarin for patients starting warfarin therapy, while 40.7% agreed or strongly agreed that they would not feel comfortable switching from brand-name to generic warfarin. However, only 19.4% of physicians who had switched patients from brand-name to generic warfarin actually reported difficulties in managing the switch.

Conclusion
While most patients and physicians appear to have accepted the principle of therapeutic equivalence of generic and brand-name warfarin, a sizable minority has concerns that could influence prescribing and compliance.

Key Words: *Warfarin, generic, bioequivalence, interchangeability, perceptions*

Warfarin is a commonly used anticoagulant with clearly documented benefits.[1-4] As a narrow therapeutic index (NTI) drug, only a small dosing range separates warfarin's therapeutic effect from toxicity in patients and appropriate dosing is critical.[5]

Since 2000, three generic brands of warfarin have been approved in Canada as bioequivalent to

Coumadin (Bristol-Myers Squibb, St. Laurent, Quebec, Canada) and generic warfarin has been added to provincial drug formularies.[6] This allows Canadian pharmacists to substitute generic warfarin for Coumadin without the prescribing physician's prior approval. This decision has generated controversy, as there is concern that generic warfarin introduces a new source of International Normalized Ratio (INR) variability to a therapy for which management is already difficult. The uncertainty stems from two sources.

First, in order for Health Canada to conclude bioequivalence between a brand-name drug and its generic version, generic products are required to meet specific standards. For most drugs, Health Canada guidelines dictate that the 90% Confidence Interval (CI) of the ratio of the overall mean area under the curve (AUC) of the generic to brand-name formulation must fall between 80% and 125 % in healthy volunteers, and the ratio for the relative mean of the maximum concentration (C_{max}) of both brands must fall between 80% and 125 %.[7] However, unlike the FDA which does not have stricter regulations for NTI drugs, for all new generic versions of a NTI drug in Canada, the 95% Confidence Interval (CI) of the relative mean AUC and C_{max} of the test to reference formulation ratio must both fall within 80-125 %.[8] Although generic warfarin products were required to meet these stricter regulations to be deemed bioequivalent to Coumadin, concern exists over whether these criteria are adequate as the testing considers only mean warfarin concentrations in a group of healthy volunteers (not patients) and does not test for subject-by-formulation interactions which occur when subjects on one formulation have consistently different values than on the other formulation.[9,10] However in 2000, a study was conducted that addressed both average and individual bioequivalence issues, comparing Coumadin to generic warfarin in healthy volunteers, finding that the individual bioequivalence assessment did not show a subject-by-formulation interaction, nor did it add value to the bioequivalence assessment of warfarin.[11]

The second issue is that of tablet content uniformity. Coumadin's manufacturer has voluntarily adhered to tighter tablet content uniformity guidelines than is required by the United States Pharmacopeia (USP).[12,13] Of the three generic brands currently available in Canada, two have also adopted Coumadin's guidelines but the third generic brand only adheres to USP regulations.[14,15] When generic warfarin was approved in the United States in 1997, the American manufacturer of Coumadin, DuPont Merck, petitioned the Food and Drug Administration (FDA) and USP to establish special requirements for bioequivalence and narrower tablet content uniformity specifications for generic warfarin.[16] DuPont's arguments of an increased INR variability associated with generic brands of warfarin were judged to be unfounded given that warfarin has a long half-life of nearly two days and is generally administered daily, meaning that accumulation of warfarin is at least 3-4 fold compared to the single daily dose, minimizing the clinical impact of tablet content uniformity.[17] However, there is still uncertainty among physicians and patients regarding the safety and efficacy of generic warfarin.

Survey papers have been published describing United States physicians' and pharmacists' perceptions of the safety and efficacy of generic versions of narrow therapeutic range drugs.[18-20] Warfarin was identified in several studies as one of the few drugs for which physicians and pharmacists were reluctant to substitute a generic brand. Though the decision to add generic brands of warfarin to provincial drug formularies clearly affects Canadian warfarin users and their physicians, there is a lack of literature on their perceptions. The objective of this study was to survey Canadian physicians and patients on their attitudes towards generic drugs, the importance of bioequivalence to Coumadin and their perceptions about generic warfarin.

We hypothesized that patients and physicians would have neutral opinions on generic warfarin substitution although specific population clusters might express less confidence in generic products. The elderly have been reported to be less accepting of generic brands.[21] In separate articles, cardiologists and other specialty physicians have been reported to be both less in favour and more in favour of generic substitution, when compared to family physicians.[19,20] Varying opinions among specialties may or may not be related to the frequency with which they manage patients who require NTI drugs or their exposure to brand-name pharmaceutical advertising. Since no studies have examined opinions on generic warfarin

products based on patient gender or physician age, gender or number of years in practice, we investigated these potential predictors as well.

METHODS

We examined articles describing questionnaires on generic products[21-27] and previously published case reports[28-29] outlining problems that may be associated with generic warfarin use. A panel, including clinical pharmacologists, internists, hematologists and pharmacists also contributed to the pool of themes upon which to base the surveys. For the patient survey, respondents were required to indicate their level of agreement on a scale of 1 to 7 (1 = "strongly disagree", 7 = "strongly agree") to ten statements regarding their perceptions of generic brands, and more specifically, the safety and efficacy of the generic brands of warfarin compared to brand-name warfarin. Physician surveys also employed a 7.0-point Likert scale of agreement. The key themes of the thirteen-question survey included adequacy of bioequivalence requirements, and the safety and efficacy of generic warfarin with respect to new anticoagulant patients as well as patients who had been previously stabilized on Coumadin and were switching between brands. We tested the patient survey using the SMOG (Simple Measure of Gobbledygook) readability index[30] and found it to be at a Grade 7 reading level, which was thought to be adequate for the majority of patients taking warfarin.

The face validity of both surveys was tested by twenty-five members of the lay population, including high-school students, professionals and senior citizens to ensure that the statements were interpreted in the manner intended. The surveys were then deemed suitable for distribution.

Data Collection

Patient Surveys

Surveys were distributed to consecutive patients attending the weekly Anticoagulation Clinic at St. Joseph's Healthcare (Hamilton, Ontario) for ten weeks between Nov 19, 2001 and Feb 18, 2002. We utilized preliminary data from the first ten completed surveys to calculate sample size based on the confidence interval (CI) approach. To obtain estimates with a desired margin of error of 0.15 using a 95% CI and a standard deviation of 0.8 (based on preliminary data) on a 7.0-point Likert scale, a sample size of 109 subjects was required.

Physician Surveys

Using the College of Physicians and Surgeons of Ontario website, we retrieved demographic information and addresses for a total sample size of 375 physicians, consisting of every 50th entry for each of the following specialty groups: hematology, cardiology, internal medicine and family medicine. These were physicians groups that we expected to have patients taking warfarin. A letter describing the study's purpose was mailed along with the physician survey and a self-addressed stamped envelope, to this sample. Respondents were also asked to complete demographic information including age, gender, city of practice, specialty and number of years in practice.

Again, the confidence interval approach was used to calculate sample size based on preliminary data from the first ten completed surveys. A sample size of 84 was obtained based on desired margin of error of 0.15 at a 95% CI and a standard deviation of 0.7 using a 7.0-point Likert scale (based on preliminary data).

Statistical Analysis

Multivariate analysis of covariance (MANCOVA) was conducted to examine whether demographic factors were significant to the overall responses to the questionnaire. This technique allows comparison of groups on multiple correlated responses simultaneously while adjusting for the effect of other covariates.[31] Univariate ANOVA was used to compare responses between groups, and if a statistically significant result was obtained ($p < 0.05$), Tukey's pairwise comparison was used to determine where the differences existed. Responses on patient questionnaires were analyzed using descriptive statistics and summarized by age and gender of the respondents as well as the brand of warfarin that the respondent was taking at the time of survey completion. For physician questionnaires, responses were evaluated based on physician specialty, age, city of practice, years of practice, and gender.

Descriptive statistics were used to describe the demographic characteristics of the

respondents, expressed as means, standard deviations (SD) or (minimum – maximum) for continuous variables and number (percentage) for categorical variables. Post-hoc analysis using Tukey's method was used. Results were expressed as estimates of differences between groups of interest, corresponding 95% confidence intervals and associated p-values. The criterion for statistical significance was set *a priori* at $\alpha = 0.05$. MINITAB Student Version 12 was used for all analyses.

The St. Joseph's Hospital Research Ethics Board, as well as the McMaster University Medical Centre Research Ethics Board granted ethics approval for this study.

RESULTS

Patient Surveys

There are approximately 500 anticoagulation clinic patients and of these, 81 patients completed questionnaires (response rate = 16.2%). The characteristics of respondents can be found in Table 1. The patient responses can be found in Table 2. Mean responses to survey statements were neutral, with the means of seven of ten statements falling between 3.0 (slightly disagree) and 5.0 (slightly agree). Approximately 17% of all individual responses were at the extremes of the scale ("strongly agree" or "strongly disagree"). Overall, respondents were familiar with generic brands and comfortable taking generic brands of drugs (42.5% and 46.9% agreed/strongly agreed respectively). Over 50% of respondents indicated that they were happy with their brand of warfarin. Of all respondents, less than 5% agreed or strongly agreed that the lower cost of generic warfarin was a good reason to take it rather than Coumadin. The mean response to statements regarding the respondent's perception of generic warfarin's safety and efficacy compared to Coumadin was neutral, although 14.2% of respondents agreed or strongly agreed that generic warfarin was neither as safe nor as effective as Coumadin. Additionally, 32.1% of respondents agreed or strongly agreed that they were aware that generic products such as warfarin must undergo bioequivalence testing with Coumadin, and the same percentage were satisfied that such testing ensured their safety. Less than 15% of all respondents indicated that they were aware of their physician's opinion of generic warfarin.

TABLE 1 Baseline Characteristics of Patient Questionnaire Responders (N = 81)

CHARACTERISTIC	Summary Measure
Age (years): mean, SD	63.4 (12.9)
Males: n (%)	42 (52%)
Responders on Coumadin: n (%)	51 (63%)
Responders on Generic Warfarin: n (%)	30 (37%)

TABLE 2 Responses to Patient Questionnaires[↑]

	Overall		Patients Taking Coumadin	Patients Taking Generic Warfarin	
Question	**D/SD***	**A/SA***	**Mean, SD (n)**	**Mean, SD (n)**	**P-value**
1) I am aware that there are many generic versions of medications available.	6.3 %	42.5 %	**4.8, 1.6 (51)**	**5.8, 1.0 (29)**	**0.01**
2) I am comfortable taking generic versions of medications generally.	7.5 %	46.9 %	**4.8, 1.7 (51)**	**5.7, 1.0 (30)**	**< 0.01**
3) I am happy with the effects I am getting from my brand of warfarin.	6.2 %	51.9 %	5.0, 1.5 (51)	5.7, 1.5 (30)	0.08
4) I would feel comfortable taking a generic brand of warfarin instead of the Coumadin brand of warfarin.	16.0 %	33.3 %	**4.1, 1.7 (51)**	**5.4, 1.4 (30)**	**< 0.01**
5) I do not think that a generic brand of warfarin would be as effective as the Coumadin brand of warfarin.	29.6 %	17.2 %	**4.2, 1.6 (51)**	**2.8, 1.6 (30)**	**< 0.01**
6) I do not think that a generic brand of warfarin would be as safe as the Coumadin brand of warfarin.	25.9 %	17.2 %	**4.3, 1.6 (51)**	**3.0, 1.6 (30)**	**< 0.01**
7) I feel that the lower cost of the generic brand is a good reason to take it instead of the Coumadin brand of warfarin.	18.5 %	4.2 %	**4.2, 1.7 (51)**	**5.9, 1.3 (30)**	**< 0.01**
8) Generic brands of warfarin must pass government testing to show that they contain the same amount of warfarin as the Coumadin brand of warfarin. I was aware of this before I took this questionnaire.	7.4 %	32.1 %	**4.2, 1.7 (51)**	**5.0, 1.4 (30)**	**0.04**
9) I am satisfied that the government testing that generic brands of warfarin must pass are enough to ensure my safety.	14.8 %	32.1 %	**4.5, 1.5 (51)**	**5.3, 1.2 (30)**	**< 0.01**
10) I am aware of my physician's opinion of generic brands of warfarin.	25.9 %	13.6 %	3.7, 1.9 (51)	3.7, 1.6 (29)	0.7

*D/SD = Disagree or Strongly Disagree, A/SA = Agree or Strongly Agree

[↑] Response Key = Strongly Disagree, 2 = Disagree, 3 = Slightly Disagree, 4 = Neither Agree Nor Disagree, 5 = Slightly Agree, 6 = Agree, 7 = Strongly Agree

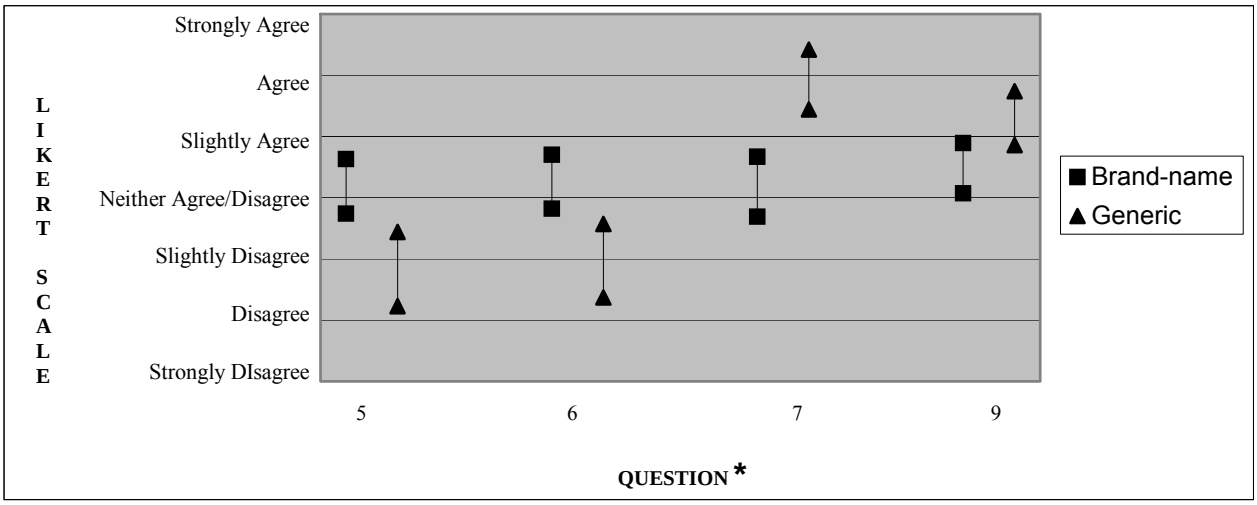
[↑]Bold, highlighted items denote a statistically significant difference ($p < 0.05$) in response between groups

Responses to patient surveys were also analyzed based on the age and gender of the respondents, as well as the brand of warfarin they were using at the time of survey completion. While age and gender of respondents were not statistically significant factors in their overall responses to the questionnaire (p = 0.269 and 0.217, respectively), the effect of respondent's brand of warfarin was significant (p=0.005). In comparison to patients taking Coumadin, a significantly larger percentage of those taking generic warfarin were aware that there are many generic versions of medications available, were comfortable taking generic brands of medications, felt that generic warfarin was as safe and effective as Coumadin and that its lower cost was a good incentive for its use, were aware that generic brands of warfarin must pass government testing to show that they compare to the Coumadin brand of warfarin, and felt that such regulations are adequate (Figure 1).

Physician Surveys

Surveys were completed by 110 physicians (29%). Respondents were classified by gender, age group, years of practice as a physician and specialty (Table 3).

FIGURE 1 Patient Questionnaires: 95% CIs of Mean Responses to Key Questions, by Brand of Warfarin Taken by Respondent



* Q5 = I think that a generic brand of warfarin would not be as effective as the Coumadin brand of warfarin.
Q6 = I think that a generic brand of warfarin would not be as safe as the Coumadin brand of warfarin.
Q7 = I feel that the lower cost of the generic brand is a good reason to take it instead of the Coumadin brand.
Q9 = I am satisfied that the government testing that generic brands of warfarin must pass are enough to ensure my safety.

TABLE 3 Baseline Characteristics of Physician Questionnaire Responders and Non-Responders

CHARACTERISTIC	Responders (110)	Non-responders (265)	P-value
Age (years): mean (SD)	45.4 (9.5)	48.2 (10.7)	0.02
Males: n (%)	78 (71)	188 (71)	0.90
Cardiologists: n (%)	29 (25)	65 (25)	0.45
Hematologists: n (%)	32 (28)	61 (23)	0.46
Internists: (%)	18 (16)	44 (17)	0.66
Family Physicians: n (%)	25 (22)	95 (36)	< 0.01
Other: (%)	6 (5)		
Years of Practice (years): mean (SD)	16.5 (9.8)	22.2 (10.7)	< 0.01

TABLE 4 Percentage of Agree and Strongly Agree Responses to Physician Questionnaire[↑]

Question	Overall A/SA* (n)	Hematologists A/SA* (n)	Cardiologists A/SA* (n)	Internists A/SA* (n)	Family Physicians A/SA* (n)	Other A/SA* (n)
1) All products rated by Health Canada as generic bioequivalents can be used interchangeably with the brand product	40.0 % (110)	40.6% (32)	31.0% (29)	33.3% (18)	20.0% (25)	55.6% (6)
2) I willingly support generic substitutions for brand-name products in general.	65.5 % (110)	62.5% (32)	37.9% (29)	38.9% (18)	44.0% (25)	88.9% (6)
3) Therapeutic failure is a common result from switching to generic drugs in general.	6.3 % (110)	6.3% (32)	3.5% (29)	11.1% (18)	0.0% (25)	0.0% (6)
4) Generic equivalents of narrow therapeutic index drugs should never be substituted for brand-name products.	43.6 % (109)	28.1% (32)	24.1% (29)	38.9% (18)	48.0% (25)	0.0% (5)
5) I am familiar with the specific bioequivalence requirements that apply to generic warfarin in Canada.	14.5 % (110)	**28.1%** (32)	10.3% (29)	11.1% (18)	**4.0%** (25)	11.1% (9)
6) INR changes primarily stem from differences in content uniformity between warfarin tablets.	11.0 % (109)	9.4% (32)	6.9% (29)	11.1% (18)	16.0% (25)	0.0% (5)
7) Bioequivalent regulations set by Health Canada are appropriate for narrow therapeutic range drugs such as warfarin.	26.5 % (109)	29.0% (32)	13.8% (29)	11.1% (18)	16.0% (25)	44.4% (5)
8) I am more comfortable prescribing Coumadin than generic warfarin to a new anticoagulant patient.	44.0 % (109)	25.0% (32)	44.8% (29)	38.9% (18)	44.0% (25)	11.1% (5)
9) I would not feel comfortable substituting generic warfarin for Coumadin in a patient who had been stabilized on Coumadin.	40.7 % (109)	25.0% (32)	48.2% (29)	38.9% (18)	44.0% (25)	11.1% (5)
10) I have had difficulties managing patients on generic warfarin, who were managed quite easily on Coumadin.[♦]	19.4 % (35)	16.7% (12)	**42.9%** (7)	**50.0%** (6)	**0.0%** (10)	N/A (0)
11) I have had difficulties managing new anticoagulant patients on generic warfarin[■].	9.5 % (42)	**0.0%** (13)	**0.0%** (7)	**60.0%** (5)	**0.0%** (13)	0.0% (4)
12) Additional laboratory testing and INR monitoring is required for patients using generic warfarin.	15.7 % (109)	9.4% (32)	17.2% (29)	27.8% (18)	20.8% (24)	0.0% (5)
13) The costs of additional laboratory testing and INR monitoring that I would do, would negate the savings of generic warfarin.[×]	15.6 % (45)	23.1% (13)	10.0% (10)	10.0% (10)	22.2% (9)	0.0% (3)

* A/SA = Agree or Strongly Agree [↑] 1= Strongly Disagree, 2 = Disagree, 3 = Slightly Disagree, 4 = Neither Agree Nor Disagree, 5 = Slightly Agree, 6 = Agree, 7 = Strongly Agree

[↑]Bold, highlighted items denote a statistically significant difference ($p < 0.05$) in response between groups

[♦]Only physicians who had managed former Coumadin patients on generic warfarin were requested to respond

[■] Only physicians who had managed new anticoagulant patients on generic warfarin were requested to respond [×] Only physicians who had responded with 5, 6 or 7 to Q12 were requested to respond

Overall Responses

Overall responses to the physician survey can be found in Table 4. Seventeen percent of all responses were in the "strongly agree" or "strongly disagree" categories and in general, mean responses were neutral. Of all respondents, 40% at least agreed that all generic products that what Health Canada deems bioequivalent could be used interchangeably with their brand-name versions. Over 65% of respondents indicated that they generally support generic substitutions for brand-name products though 44% of respondents agreed or strongly agreed that for narrow therapeutic index drugs, generic products should not be substituted for brand-name products. The mean response of 3.2 on our 7.0-point Likert scale to a statement on bioequivalence indicated that overall respondents slightly disagreed that they were familiar with Canada's bioequivalence regulations for narrow therapeutic index drug, while when asked whether these regulations are appropriate for drugs such as warfarin, the mean response was neutral at 4.3, indicating "neither agree nor disagree". However, 44.0% agreed or strongly agreed that they were more comfortable prescribing Coumadin than generic warfarin to a new anticoagulant patient and 40.7% agreed or strongly agreed that they would not feel comfortable switching from Coumadin to generic warfarin. Few of those who had managed newly anticoagulated patients on generic warfarin (9.5%, n = 42), or switched patients from Coumadin to generic warfarin (19.4%, n = 35) indicated difficulty managing patients on generic formulations. Age (p = 0.63), gender (p= 0.39), number of years in practice (p = 0.93) or physician specialty (p= 0.28) were not statistically significant (all p >0.28) in the overall response to the questionnaire.

Predictors of Response

Physician Specialty

When responses were examined based on physician specialty, there were no statements for which a statistically significant difference among two or more specialties was detected, though statistically significant differences in mean response between "other" respondents (consisting of nurses and pharmacists at St. Joseph's Healthcare who obtained and completed a survey or physicians whose specialty was listed incorrectly by the CPSO and were not hematologists, cardiologists, internists or family physicians) and one or more specialties could be observed. When examining differences between those who "strongly agree" or "agree" (Table 4), family physicians were significantly less likely to be aware of Canada's bioequivalence regulations for NTI drugs like warfarin than hematologists. Additionally, family physicians were significantly less likely to have had difficulties managing patients on generic warfarin, who were well-managed on Coumadin than internal medicine specialists and cardiologists, while only internal medicine specialists reported having had difficulties managing new anticoagulant patients on generic warfarin.

DISCUSSION

Despite evidence indicating the benefits of warfarin, this medication, though the most commonly used anticoagulant in North America, is still considered to be under-prescribed due to physician and patient concerns of the risk of associated complications.[32] Since generic warfarin became available in the United States in 1997, studies which have surveyed pharmacists and physicians on opinions on generic substitution of narrow therapeutic index drugs, have indicated that warfarin is a medication for which many rather prescribe the brand-name over the generic version.[18-20] The severity of the complications associated with warfarin use translate into a serious need to determine whether a specific brand, or regimen provide patients with optimal anticoagulation care, and how these brands are perceived by both patients and physicians.

Our survey results indicate that patients taking Coumadin differed significantly in their opinions of generic warfarin from those taking one of the generic versions of this anticoagulant. Patients taking Coumadin were less likely to agree that generic warfarin products are as safe and as effective as brand-name warfarin, and were less likely to feel that the lower cost of generic warfarin is a good incentive for its use. Overall, patients did not agree that they were aware of their physicians' opinions of generic warfarin making it difficult to determine who or what was influencing their opinion. However, as a large percentage of patients who completed the surveys

indicated that they were unaware that bioequivalence testing is required for generic products, it is quite likely that hesitancy to switch to generic warfarin may stem from a lack of awareness as to whether generic drugs are tested as rigorously as Coumadin. Those with reservations about taking generic warfarin may also believe that generic warfarin's cheaper price is due to its inferiority to brand-name warfarin. However, since the majority of respondents agreed that they were generally comfortable taking generic drugs, it is possible that their opinions vary depending on the severity of the indication for which they are taking the drug.

Overall responses depicted that a sizable minority of physicians have clear concerns regarding generic warfarin substitution and yet only a small number of physicians who had treated patients who switched from Coumadin to generic warfarin had experienced problems managing the switch. This indicates that a substantial proportion of physicians likely form their opinions on generic warfarin based on factors unrelated to their actual experiences with this drug in practice. Concerns may relate to lack of familiarity with bioequivalence, concern that data from healthy volunteers may not be relevant to patients, or a general distrust of brand changes in drugs. Generic drugs are only required to pass bioequivalence testing with the reference formulation,[11] and not with other generic brands, and uncertainty likely exists over whether patients who switch between generic warfarin brands are put at risk for increased INR variability. There was a significant difference between the proportion of hematologists and family physicians that agreed or strongly agreed that they were familiar with Canada's bioequivalence requirements for warfarin (Table 4). This may be reflective of the fact that the former are more specialized in dosing patients taking warfarin and therefore may be more aware of the drug regulatory process/bioequivalence.

While more than a quarter of physician respondents agreed or strongly agreed that Canada's bioequivalent regulations for narrow therapeutic range drugs are appropriate, only 14% agreed that they were familiar with the specific requirements of the regulations. It is apparent that the mixed responses to generic warfarin might stem from a lack of knowledge of the testing that generic warfarin products are required to pass to be considered bioequivalent to Coumadin or a belief that present regulations are inadequate. It is important to note that differences in bioavailability do not necessarily transfer into differences in therapeutic effect.[10] Differences in the rate and extent of warfarin's absorption may not have a significant bearing on the INR, which is ultimately used to monitor patients taking warfarin. Likewise, a statistically significant difference in clinical endpoints does not necessarily imply that the difference is clinically important.[10] As patients taking warfarin can have erratic INRs that are not accounted for by common factors such as diet, concomitant medications or comorbidities,[33-35] it is important to determine whether patients are actually experiencing less variation with one brand over another or whether they are simply part of the population who have unexplainable highly variable INRs. This has been addressed in a related study.[36]

Our study has a number of limitations. Response rate, particularly for the patient surveys, was fairly low (16.2%), with the most frequent reasons for not completing the survey including patient's lack of time and language barriers. Additionally, it is very conceivable that not all of the 500 anticoagulation patients registered with the hospital's outpatient clinic came in for their PT test within the ten weeks in which we were recruiting for the survey, and consequently were not approached to complete a survey. Therefore, the response rate may actually be somewhat higher. Sampling bias may also be a limitation of the responses to both the patient and physician questionnaires. Those patients and physicians who have a particular interest in the overall topic (more likely to be concerned about generic substitution) were likely to have responded. The results may not provide a true representation of the opinions of all physician specialty groups. In the case of patient questionnaires, a wider selection of patients in terms of geography as well as source may have been advisable. For example, patients cared for by their family physicians are likely to be more representative than those in specialty clinics. Open-ended questionnaire items might have helped determine specific factors influencing the opinions.

Additionally, while sample size calculations were based on standard deviations of less than 1.0 unit on a 7.0-point Likert scale which were calculated in our ten patient pilot study, standard deviations in our respondents were typically between 1.0 and 2.0 units as indicated in Table 2. This can likely explain why seemingly notable differences in response did not reach statistical significance.

CONCLUSION

The results of our perception surveys indicate that both physicians and patients primarily have neutral views on generic warfarin, though a minority has concerns regarding generic warfarin substitution. There is an obvious lack of awareness of Canada's bioequivalence regulations as they pertain to warfarin, and increased knowledge on this issue may help patients and physicians to make more informed decisions on warfarin substitution.

Acknowledgements

We acknowledge the Father Sean O'Sullivan Research Centre of St Joseph's Healthcare, Hamilton, Ontario, Canada for financial support received.

REFERENCES

1. Gullov AL, Koefoed BG, Petersen P. Fixed minidose warfarin and aspirin alone and in combination versus adjusted-dose warfarin for stroke prevention in atrial fibrillation: second Copenhagen atrial fibrillation, aspirin, and anticoagulation study. Arch Intern Med 1998; 158:1513-1521.
2. Atrial Fibrillation Investigators. Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation: analysis of pooled data from five randomized controlled trials. Arch Intern Med 1994; 154:1449-1457.
3. Segal JB, McNamara RL, Miller MR. Prevention of thromboembolism in atrial fibrillation: a meta analysis of trials of anticoagulants and antiplatelet drugs. J Gen Intern Med 2000; 15:56-97.
4. Ezekowitz MD, Levine JA. Preventing stroke in patients with atrial fibrillation. JAMA 1999; 281:1830-1835.
5. Hirsh J, Dalen J, Anderson DR et al. Oral anticoagulants: mechanism of action, clinical effectiveness, and optimal therapeutic range. Chest 2001; 119(Suppl 1):8S-21S.
6. DQTC Drug Reviews (2001, June). Drug Program Branch Bulletin. Retrieved August 7, 2002 from http://www.gov.on.ca/health/english/program/drugs/odbf/bulletin/bul_0601.pdf
7. Midha KK, Nagai T. Bioavailability, bioequivalence and pharmacokinetic studies: F.I.P. Bio international '96: Internal conference of F.I.P. "Bio-International '96", Tokyo, Japan, April 22-24, 1996. Tokyo: Business Center for Academic Studies, 1996.
8. Palylyk-Colwell E, Jamali F, Dryden W et al. Bioequivalence and interchangeability of narrow therapeutic range drugs. J Pharm Pharm Sci 1998; 1(1):2-7.
9. Chow S, Liu J. Design and analysis of bioavailability and bioequivalence studies. 2nd ed. New York: M. Dekker, 2000.
10. Friesen MH, Walker SE. Are the current bioequivalence standards sufficient for the acceptance of narrow therapeutic index drugs? Utilization of a computer simulated warfarin bioequivalence model. J Pharm Pharm Sci 1999; 2(1):15-22.
11. Yacobi A, Masson E, Moros D. Who needs individual bioequivalence studies for narrow therapeutic index drugs? A case for warfarin. J Clin Pharmacol. 2000 Aug;40(8):826-35.
12. The United States Pharmacopeia 23 / The National Formulary 18. Taunton: Rand McNally, 2003.
13. Wittkowsky AK. Generic warfarin: implications for patient care. Pharmacotherapy 1997;17:640-643.
14. Apotex Canada. Prescribing information - Apo-warfarin. Retrieved March 8, 2003 from http://www.apotex.ca/En/Products/PrescribingInfo/WARFARIN-PR.pdf .
15. The Alberta Health Drug Benefit List Update. Interchangeability of warfarin sodium preparations. 2003 Retrieved June 7, 2003 from http://www.ab.bluecross.ca/dbl/pdfs/dblreportdec00update.pdf.
16. Lawrence J. (1998, January 12). State by state - DuPont-Merck battles to limit NTI substitution. Drug Store News. Retrieved March 3, 2003, from http://www.findarticles.com/p/articles/mi_m3374/is_n1_v20/ai_20801949.
17. Barlas S. (1998, March 2). FDA chastises DuPont-Merck on Coumadin campaign. Drug Store News. Retrieved March 4, 2003 from http://www.findarticles.com/p/articles/mi_m3374/is_4_20/ai_56202109.
18. Snyder K. Brands losing physician, pharmacist loyalty. Drug Topics 1995; Suppl:26S-28S.
19. Banahan BF, Kolassa EM. A physician survey on generic drugs and substitution of critical dose

medications. Arch Intern Med 1997; 157(18):2080-2088.
20. Vasquez EM, Min DI. Transplant pharmacists' opinions of generic product selection of critical-dose drugs. Am J Health-Syst Pharm 1999; 56(7):615-621.
21. Kendall KW, Ng S, Schoner B. Consumer response to generic/chemically equivalent drugs. Journal of Public Policy and Marketing 1991; 10:182-201.
22. Lamert ZV, Doering PL, Golstein E, McCormack WC. Predispositions toward generic drug substitution. J Consumer Res 1980; 14:23.
23. Bearden W, Mason JB, Smith E. Perceived risk and elderly perceptions on generic drug prescribing. Gerontologist 1979; 19:191-195.
24. Anonymous. Consumer drug purchases are based on perceptions of quality, survey on generic finds. Am J Hosp Pharm 1988; 45:1245.
25. Carroll NV, Wolfgang AP, Kotzan JA, Perri M. Consumer attitudes and actions towards generic drugs. J Pharm Mark Manage 1988; 2(4):87-89.
26. Tootelian DH, Gaedeke RM, Schlacter J. Branded versus generic prescription drugs: perceptions of risk, efficacy, safety and value. J Health Care Mark 1988; 8(3):26-29.
27. Carroll NV, Jang R. Consumer awareness of generic drugs. Contemporary Pharmacy Practice 1981; 4(3):155-159.
28. Wagner JL, Dent LA. Epistaxis associated with elevation of INR in a patient switched to generic warfarin. Pharmacother 2000; 20(2):240-243.
29. Hope KA, Havrda DE. Subtherapeutic INR values association with a switch to generic warfarin. Ann Pharmacother 2001; 35:183-187.
30. McCallum D, Peterson J. Computer-Based Readability Indexes.In:ACM, editor. Proceedings of the ACM '82 conference. New York: ACM Press, 1982. p.44-48.
31. Tabachnick BG, Fidell LS. Using Multivariate Statistics. New York: Harper Collins College Publishers.1996.
32. Stafford RS, Singer DE. Recent national patterns of warfarin use in atrial fibrillation. Circulation 1998; 97:1231-1233.
33. Chamberlain MA, Sageser NA, Ruiz D. Comparison of anticoagulation clinic patient outcomes with outcomes from traditional care in a family medicine clinic. J Am Board Fam Pract 2001;14:16-21.
34. Samsa GP, Matchar DB, Goldstein LB, et al. Quality of anticoagulation management among patients with atrial fibrillation: results of a review of medical records from 2 communities. Arch Intern Med 2000;160:967-973.
35. Chiquette E, Amato MG, Bussey HI. Comparison of an anticoagulation clinic with usual medical care, anticoagulation control, patient outcomes, and health care costs. Arch Intern Med 1998;158:1641-1647.
36. Pereira JA, Holbrook AM, Dolovich L et al. Are brand-name and generic warfarin interchangeable? Can J Clin Pharmacol. 2004;75(2):27.