Use of Fibrates in the United States and Canada

Cynthia A. Jackevicius, PharmD, MSc
Jack V. Tu, MD, PhD
Joseph S. Ross, MD, MHS
Dennis T. Ko, MD, MSc
Daniel Carreon, PharmD
Harlan M. Krumholz, MD, SM

Health care reform has generated interest in identifying strategies to decrease health care costs without depriving patients of the health benefits of evidence-based therapies and generic formulations of drugs. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial recently showed that fenofibrate plus statins in patients with type 2 diabetes did not reduce cardiovascular events more than use of statins alone. The only other fenofibrate study, Fibrate Intervention and Event Lowering in Diabetes (FIELD), also failed to show reduced cardiovascular morbidity and mortality. These negative studies raise questions about a medication with more than $1 billion in sales in the United States.

Evidence that fibrates have clinical benefit is mixed, with most studies focusing on lipid effects. Fibrates primarily reduce levels of triglycerides with only modest effects on levels of low-density and high-density lipoprotein cholesterol. The main evidence for clinical benefit comes from placebo-controlled trials with the older fibrates such as gemfibrozil (for which some safety concerns were raised primarily when used with cerivastatin) and clofibrate (which is no longer available due to safety concerns). These trials exert substantial influence in meta-analyses that show that fibrates in aggregate significantly reduce cardiac events but not overall mortality.

Context Interest in the role of fibrates intensified after the publication of the negative results from the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, which assessed therapy with fenofibrate plus statins. The evidence for clinical benefit in outcomes with the use of fibrates is heavily weighted on the use of the older fibrates such as gemfibrozil and clofibrate.

Objectives To examine trends in the current use of fibrates and to examine the relationship between differences in the availability and use of brand-name vs generic formulations of fenofibrate and the economic implications in the United States compared with Canada.


Main Outcome Measures Fibrate prescriptions dispensed and expenditures.

Results In the United States, fibrate prescriptions dispensed increased from 336 prescriptions/100,000 population in January 2002 to 730 prescriptions/100,000 population in December 2009, an increase of 117.1% (95% confidence interval [CI], 116.0%-117.9%), whereas in Canada, fibrate prescriptions increased from 402 prescriptions/100,000 population in January 2002 to 474 prescriptions/100,000 population in December 2009, an increase of 18.1% (95% CI, 17.9%-18.3%) (P<.001). In the United States, fenofibrate prescriptions dispensed increased from 150 prescriptions/100,000 population in January 2002 to 440 prescriptions/100,000 population in December 2009, an increase of 159.3% (95% CI, 157.7%-161.0%), comprising 47.9% of total fibrate prescriptions in 2002 and 65.2% in 2009. In Canada, fenofibrate prescriptions increased from 321 prescriptions/100,000 population in January 2002 to 429 prescriptions/100,000 population in December 2009. The annual ratio of generic to brand-name fenofibrate use in the United States ranged from 0.1 to 0.09:1 between 2002 and 2008, while the ratio in Canada steadily increased from 0.51:1 to 1.89:1 between 2005 and 2008. In the United States, crude fenofibrate expenditures increased from $11,535/100,000 population/month in 2002 to $44,975/100,000 population/month in 2009, while the rates in Canada declined from $17,695/100,000 population/month in 2002 to $16,112/100,000 population/month in 2009. Fibrate expenditures per 100,000 population were 3-fold higher in 2009 in the United States compared with Canada.

Conclusion During the past decade, prescriptions for fibrates (particularly fenofibrate) increased in the United States, while prescriptions for fibrates in Canada remained stable.

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able in Canada, and fenofibric acid (Trilipix) is only available in the United States. While generic formulations of fenofibrate have long been available in Canada, their use has lagged behind in the United States, creating market differences (eFigure at http://www.jama.com). This study seeks to examine trends in the current use of fibrates and to examine the association between differences in the availability and use of brand-name vs generic formulations of fenofibrate and the economic implications in the United States compared with Canada.

METHODS
We conducted a population-level, observational cohort study using data from 2002 through 2009 for the United States and Canada from IMS Health. This study was approved by the institutional review board of the Western University of Health Sciences (Pomona, California). Pharmacy audits were used to measure the number of dispensed prescriptions and their actual cost to the consumer (which includes product cost, markups, and pharmacist fees) in retail pharmacies in Canada (IMS Health’s CompuScript Audit) and in retail, mail order, and long-term care pharmacies in the United States (IMS Health’s National Prescription Audit). IMS Health uses similar methods for data collection and projection in the United States and Canada.

We had data on the numbers and costs of prescriptions dispensed but we did not have information on patient or prescriber characteristics. The pharmacy outlet population is stratified by region, type (independent, chain, etc), and size. Sample pharmacies were selected from the reporting pharmacies by applying criteria such as prescription type and volume, consistency of reporting, and payment type. Data were collected electronically each day from the sample pharmacies comprising drugstores and pharmacy outlets distributed proportionally within each stratum. The National Prescription Audit in the United States and the CompuScript Audit in Canada consist of approximately 38,000 and 5657, respectively, retail pharmacies (independent, mail order, mass merchandise, and discount houses) that are randomly sampled from the company’s database of more than 57,000 US pharmacies and 8575 Canadian pharmacies, accounting for approximately two-thirds of all retail pharmacies in the United States and Canada.

In both countries, the sample was resized as required based on quality-control measures; and major changes typically coincided with a new calendar year. Pharmacies were reimbursed for their reporting efforts. After passing through various quality-control checks and stability processes specific to the audits to ensure the consistency and accuracy of the estimates, the collected data were projected to the population in each region and region totals were summed to provide a national estimate (US data were rounded to the nearest 1000 prescriptions).

The monthly number of prescriptions and expenditures for fibrate products in the United States and Canada were the primary variables for analysis. We standardized medication use and expenditures per 100,000 population using 2001 census estimates from the United States and Canada. All expenditures are expressed in US dollars. To achieve comparable price differences between the 2 countries, the Canadian dollar costs were converted to US dollar costs using yearly purchasing power parity values from 2002 through 2009.

We calculated the rates of fibrate prescriptions dispensed overall and for each individual fibrate (bezafibrate, fenofibrate, gemfibrozil, fenofibrilic acid [the active metabolite of fenofibrate]) by country and compared the rates of change from January 2002 through December 2009. Rates of fibrate use were estimated and compared over time and by country by constructing an ordinary least-squares linear regression model using monthly use data and time variables by country. The slopes for the rates of change were compared using t tests.

For comparison purposes, the rates of change in overall statin use during the same period were calculated and compared in the same manner. In addition, the rates of change in fibrate use were compared with statin use within each country as a reference standard using the same methods. Prescriptions dispensed for all statins between January 2002 and December 2009 were included in the statin analysis.

The proportion of each individual fibrate prescription dispensed and cost compared with the total for the entire fibrate class in each country was calculated annually to determine the market share accounted for by each individual fibrate. The use ratios of generic to brand-name fibrate products were compared by country overall using the Wilcoxon signed rank test statistic W and by year using χ² statistics. All statistical analyses were performed using SPSS software version 18.0.3 (SPSS Inc, Chicago, Illinois). A 2-sided P value of less than .05 was considered statistically significant.

RESULTS
In the United States, fibrate prescriptions dispensed increased from 336 prescriptions/100,000 population in January 2002 to 730 prescriptions/100,000 population in December 2009, an increase of 117.1% (95% CI, 116.0%-117.9%), whereas statin use increased from 3388 prescriptions/100,000 population in January 2002 to 5824 prescriptions/100,000 population in December 2009, an increase of 71.9% (95% CI, 71.9%-71.9%) (P < .001). In Canada, fibrate prescriptions increased from 402 prescriptions/100,000 population in January 2002 to 474 prescriptions/100,000 population in December 2009, an increase of 18.1% (95% CI, 17.9%-18.3%), whereas statin use increased from 3104 prescriptions/100,000 population in January 2002 to 8202 prescriptions/100,000 population in December 2009, an increase of 164.1% (95% CI, 163.8%-164.4%) (P < .001). Figure 1 shows rates per country population.

Fibrate prescriptions increased in both countries over the 7-year period; however, the rate of increase was substantially higher in the United States compared with Canada (P < .001). Fibrate use overall was similar until 2006, when use in the United States began to ex-
cesed use in Canada (Figure 2). In 2002, there were 422 fibrate prescriptions/100,000 population/month dispensed in Canada compared with 356 prescriptions/100,000 population/month in the United States. In December 2009, fibrate prescriptions increased to 474 prescriptions/100,000 population in Canada and 730 prescriptions/100,000 population in the United States; therefore, the population-adjusted fibrate use in the United States had exceeded that in Canada by 50.4% (Figure 2). Conversely, the rate of increase in population-adjusted statin use

**Figure 1. Fibrate Prescriptions in the United States and Canada per 100,000 Population per Month**

A Monthly fibrate prescriptions in Canada

B Monthly fibrate prescriptions in the United States

Data are from the National Prescription Audit of IMS Health United States and the CompuScript Audit of IMS Health Canada.

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in the United States was less than half the use rate in Canada (P<.001).

During the study period, the estimated relative use of individual fibrates changed minimally in Canada and more apparently in the United States. Since the introduction of fenofibric acid (Trilipix) in the United States in December 2008, its use increased rapidly to 108 prescriptions/100 000 population in December 2009 (Figure 1). In the United States, fenofibrate prescriptions dispensed in-creased from 150 prescriptions/100 000 population in January 2002 to 440 prescriptions/100 000 population in December 2009. In Canada, fenofibrate prescriptions increased from 321 prescriptions/100 000 population in January 2002 to 429 prescriptions/100 000 population in December 2009. Estimated fenofibrate use was relatively constant between 2002 and 2009 in Canada, while in the United States, use increased by 159.3% (95% CI, 157.7%-161.0%), comprising 47.9% of total fibrate prescriptions in 2002 and 65.2% in 2009 (Table and Figure 1). The rate of gemfibrozil prescriptions dispensed declined from 46 prescriptions/100 000 population/month in Canada and 185 prescriptions/100 000 population/month in the United States in 2002 to 24 and 182 prescriptions/100 000 population/month, respectively, in 2009. Figure 2 summarizes yearly prescription rates. In 2009, fenofibrate and fenofibric acid products combined comprised 73.9% of

Figure 2. Standardized Annual Fibrate Prescriptions per 100 000 Population by Country

Data are from the National Prescription Audit of IMS Health United States and the CompuScript Audit of IMS Health Canada. Error bars indicate 95% confidence intervals.

Table. Estimated Annual Prescription Volume and Expenditures of Fibrates Overall and by Individual Fibrate

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aData are from the National Prescription Audit of IMS Health United States and the Canadian CompuScript Audit of IMS Health Canada.
the market share of fibrates in the United States (fenofibric acid is not available in Canada). In Canada, gemfibrozil comprised 10.9% of fibrate use in 2002 and 5.2% in 2009, whereas in the US fibrate market, it comprised 52.1% in 2002 and 26.1% in 2009. Bezafibrate (available only in Canada) comprised 7.8% of the fibrate market in 2002, decreasing to 4.6% in 2009. In the United States, fibrates accounted for 8.9% of all lipid-lowering prescriptions in 2002 and in—

Figure 3. Brand and Generic Fibrate Prescriptions in the United States and Canada per 100,000 Population per Month

Data are from the National Prescription Audit of IMS Health United States and the CompuScript Audit of IMS Health Canada. The predominant generic version of Lipidil Supra received approval for market in April 2006.
creased to 9.4% in 2009, whereas in
Canada, the fibrate market share was
10.9% in 2002 and decreased to 5.3% in
2009. The annual ratio of generic to
brand-name fenofibrate use in the
United States ranged from 0.1 to 0.09:1
between 2002 and 2008, while the
ratio in Canada steadily increased from
0.51:1 to 1.89:1 between 2005 and 2008
(\(P<.001\) for comparisons for each year
and \(P=.009\) for overall comparison; Figure 3).

The estimated crude costs associated
with fibrate use in the United States in-
creased from $17 888/100 000 populace-
month/month in 2002 to $57 172/100 000
population/month in 2009, with a no-
table increase in 2005. In Canada, the es-
timated crude costs associated with fi-
brate use decreased from $22 133/
100 000 population/month in 2002 to
$18 551/100 000 population/month in
2009, with a notable decrease after 2006.
In the United States, crude fenofibrate
costs increased from $11 535/100 000
population/month in 2002 to $44 975/
100 000 population/month in 2009, while
in Canada, the costs declined for
fenofibrate from $17 695/100 000 populace-
month/month in 2002 to $16 112/
100 000 population/month in 2009.

The decline in gemfibrozil use
was paralleled in December 2009 by a
decline in costs to $5703/100 000 populace
in the United States and $1025/100 000 populace
in Canada (Figure 4). The proportion of total fi-
brate costs accounted for by fenofi-
brate in the United States increased from
64.5% in 2002 to 78.7% in 2009, whereas
in Canada, the proportion increased from
79.9% to 86.9% (Table). Although fenofibrate accounted for only
65.2% of use in the United States in
2009, it accounted for a disproporti-
ate 78.7% of expenditures \((P<.001)\).

Adjusted estimated fibrate expendi-
tures per 100 000 populace were ap-
proximately 3-fold higher in 2009 in the
United States compared with Canada.
Despite similar numbers of populace-
standardized fenofibrate prescriptions
dispensed, expenditures associated with
this use was 2.5-fold higher in the United
States and they continued to diverge
through 2009 (Figure 4). For 2009, the
per-capita expenditure for fibrates was
$6.86 in the United States and $2.23 in
Canada; the per-capita expenditure for
fenofibrate or fenofibric acid was $6.20
and $1.93, respectively; and the per-
capita expenditure for gemfibrozil was
$0.66 and $0.12, respectively.

COMMENT
Our study found that the use of fibrates
steadily increased during the last de-
cade in the United States but not in
Canada, even as evidence emerged to
question the benefit of newer fibrates in
the contemporary statin era. Increased
fibrate use in the United States appears
to be largely driven by a steady increase
in fenofibrate use of nearly 200% dur-
during the study period. In Canada, fenofi-
brate use remained stable. These rap-
idly increasing rates are more than
double the increase in statin use in the
United States during the same period.19
This pattern is paradoxical to declines
that might have been expected because
the only clinical outcomes evidence for
fenofibrate during our study period was
the FIELD trial, which failed to find a sig-
nificant reduction in the primary end
point of coronary events in a diabetic
population.5

In fact, more robust evidence regard-
regarding reducing cardiac death and nonfa-

tal myocardial infarction supports the
preferential use of gemfibrozil; how-
ever, these studies preceded the statin era
and enrolled patients with slightly worse
lipid profiles (mainly higher levels of tri-
glycerides and/or lower levels of high-
density lipoprotein cholesterol).8,13,24
Prior reports have noted increased use
of fenofibrate since 1999, which is more
than 5 years before the publication of the
FIELD trial.25 Our study shows that the
use of fenofibrate was increasing both be-
fore and after results from the FIELD
study were published, suggesting that
other factors beside clinical trial evi-
dence are influencing fibrate prescribing
patterns.

While fenofibrate use increased in the
United States, gemfibrozil use declined.
Compared with gemfibrozil, the increased use of fenofibrate may be due to its greater perceived safety.\textsuperscript{11,12,26} Fenofibrate use has been steadily increasing since 1999, which precedes the first pharmacokinetic study signaling a potential interaction between statins and gemfibrozil in 2000, and certainly prior to 2001 when the interaction between gemfibrozil and cerivastatin became apparent.\textsuperscript{27,28} Therefore, while this reasoning may account for some to switch or preferentially use fenofibrate instead of gemfibrozil, the increase in use of brand-name fenofibrate far exceeded declines in use of gemfibrozil. Additionally, subsequent research has demonstrated that gemfibrozil could be used safely in patients taking statins, such as in the Veterans Affairs study that found a rhabdomyolysis rate with combined use of only 0.16%, which is well within expected rates.\textsuperscript{11,12,29}

Our second major finding was that there was a strong preference observed for prescribing brand-name over generic fenofibrate products in the United States but not in Canada. The US pattern is unusual in that brand-name formulations typically comprise approximately 25% to 30% of the product market share for medications 12 years postmarketing launch.\textsuperscript{30} Instead, brand-name fenofibrate (mainly Tricor) was the predominant fenofibrate product used in the United States, accounting for 90% of the fenofibrate market share until recently. In Canada, the use of the comparable brand-name fenofibrate Lipidil product family (includes Lipidil, Lipidil Micro, and Lipidil Supra) declined from 66% to 35% of the fenofibrate market share during our study. To illustrate this disparate pattern between countries using population-adjusted estimates, for every 100 brand-name fenofibrate prescriptions dispensed in 2008, 166 generic fenofibrate prescriptions were dispensed in Canada and only 9 generic fenofibrate prescriptions were dispensed in the United States.

Access differences to generic fenofibrate between the United States and Canada likely contributed to the vastly different patterns of fenofibrate use, and are associated with a great economic burden for US consumers and third-party payers.\textsuperscript{9} Although both countries had similar rates of population-adjusted fenofibrate use between 2007 and 2009, the fenofibrate expenditures in the United States exceeded those in Canada by nearly 3-fold. Using 2008 population-adjusted rates of fenofibrate use, if the US market had opened access to generic fenofibrate formulations and prescribed them with a ratio of generic to brand-name formulations similar to that in Canada in which access was not limited, we would expect $364 million/year to be saved.

While Canada has benefited from access to generic fenofibrate for more than a decade, patent protections with brand-name fenofibrate products in the United States appear to have allowed these products to dominate the market, contributing to higher fibrate drug costs.\textsuperscript{31,32} The preferential use of brand-name fibrate products continues with the latest product Trilipix (which is the active metabolite of fenofibrate), showing a rate of increase in use that far exceeds even that for fenofibrate, even though this specific formulation has yet to be evaluated in clinical outcomes studies.\textsuperscript{33} Trilipix is approved for use with statins, while all other fibrates have warnings against combined use with statins.\textsuperscript{9} Given that this distinctive indication simplifies concomitant therapy with fibrates and statins and may facilitate the use of Trilipix for clinicians, prompt evaluation is warranted of its efficacy and safety in reducing cardiovascular morbidity and mortality when added to statin therapy.

During the period in which there was escalating use of fibrates (particularly fenofibrate), new clinical outcomes evidence should have steered clinicians away from prescribing fenofibrate. Clinicians may have been reluctant to initially accept the negative findings from the FIELD study in 2004. In 2010, the ACCORD trial was published and it has been the only fibrate study to use a statin-treated comparison group. The ACCORD trial did not find clinical benefit in outcomes with fenofibrate plus a statin compared with a statin alone, reiterating the negative findings from the FIELD trial.\textsuperscript{7} At a time when a less-is-more approach is being embraced by the medical community, this ever-increasing pattern of prescribing brand-name medications without evidence of clinical benefit warrants attention and close scrutiny to ensure that such medication use is optimized for clinical benefit, while avoiding unwarranted costs.\textsuperscript{23,33} Current US guidelines recommend that fibrates without regard to type should only be considered for reducing very high levels of triglycerides to prevent pancreatitis, for treatment of dysbetalipoproteinemia, and as supplemental therapy to statins in patients with diabetes and high non–high-density lipoprotein cholesterol.\textsuperscript{34,35} The 2006 revision of the Canadian guidelines now more cautiously reserves treatment with fibrates for severe hypertriglyceridemia. Continued caution is warranted in guideline recommendations for fibrates as we await evidence of clinical benefits.

Our study has some limitations. IMS Health uses data collected from audits of prescriptions dispensed to describe general trends in drug use. These data trends do not provide exact drug use data by the individual patients or data by the individual prescribers to determine the appropriateness of prescribing the medication. Although IMS Health uses similar processes in both countries for data collection and projection, it is possible that slight differences may exist. Therefore, we have developed population-adjusted and relative estimates for comparison purposes. We did not have access to state-level data, patient or prescriber characteristics, or clinical data such as medical conditions or lipid profile to determine whether fibrate prescribing was clinically appropriate. Although increased fibrate use was demonstrated, its relationship to patient outcomes could not be evaluated.

CONCLUSION

Fibrates are used commonly in the United States and Canada. Use has increased steadily in the United States over the last decade despite published negative results from fibrate trials in pa-
ties with diabetes who were also taking statins; however, fibrate use in Canada has remained stable. Fenofibrate dominates the market despite it having the least supportive clinical outcomes evidence. While this growth in the setting of a strong preference for brand-name over generic fenofibrate in the United States has been associated with higher medication costs, improvement in clinical outcomes is uncertain.

Author Affiliations: Department of Pharmacy Practice and Administration, College of Pharmacy, Western University of Health Sciences, Pomona, California (Dr Jackevicius and Carreon); Institute for Clinical Evaluative Sciences, Toronto, Ontario, Canada (Dr Jackevicius, Tu, and Ko); Department of Health Policy, Management, and Evaluation, Faculty of Medicine (Dr’s Jackevicius and Tu) and Division of Cardiology, Schulich Heart Centre, Sunnybrook Health Sciences Centre (Dr’s Tu and Ko), University of Toronto, Toronto, Ontario, Canada; Veterans Affairs Greater Los Angeles Healthcare System, Los Angeles, California (Dr Jackevicius); University Health Network, Toronto, Ontario, Canada (Dr Jackevicius); Department of Epidemiology and Public Health, Section of Cardiovascular Medicine (Dr Krumholz), Yale University School of Medicine, Center for Outcomes Research and Evaluation, Yale New Haven Hospital, New Haven, Connecticut (Dr’s Ross and Krumholz); and Robert Wood Johnson Clinical Scholars Program, New Jersey, New Jersey, Connecticut (Dr Krumholz). 

Author Contributions: Dr Jackevicius had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Jackevicius, Krumholz.

Acquisition of data: Jackevicius, Carreon, Krumholz.

Analysis and interpretation of data: Jackevicius, Tu, Ross, Ko, Carreon, Krumholz.

Drafting of the manuscript: Jackevicius.

Critical revision of the manuscript for important intellectual content: Jackevicius, Tu, Ross, Ko, Carreon, Krumholz.

Statistical analysis: Jackevicius, Carreon.

Obtained funding: Jackevicius, Krumholz.

Study supervision: Jackevicius.

Potential Conflict of Interest: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Krumholz reported being the chair of the cardiac scientific advisory board for UnitedHealthCare and is under contract to develop performance measures for the Centers for Medicare & Medicaid Services. None of the other authors reported disclosures.

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