Antidiabetic Action of Bezafibrate in a Large Observational Database

JAMES H. FLORY[1]
SUSAN ELLENBERG, PHD[1]
PHILIPPE O. SZAPARY, MD, MSCE[1,2]
BRIAN L. STROM, MD, MPH[1]
SEAN HENNESSY, PHARMD, PHD[1]

OBJECTIVE — The purpose of this study was to test the hypothesis that bezafibrate, an approved fibrate, can prevent or delay type 2 diabetes.

RESEARCH DESIGN AND METHODS — This was a retrospective cohort study using data from routine medical practice in the U.K., as captured by the General Practice Research Database (GPRD). Individuals chronically exposed to bezafibrate were compared with individuals chronically exposed to other fibrates. Hazard ratios (HRs) for incident type 2 diabetes were calculated using a Cox proportional hazards model. A post hoc analysis was used to examine the effect of bezafibrate on progression to use of oral antidiabetic medications or insulin in individuals with diabetes at baseline.

RESULTS — Bezafibrate users had a lower hazard for incident diabetes than users of other fibrates (HR 0.66 [95% CI 0.53–0.81]). This effect became stronger with increasing duration of therapy. Post hoc analysis of the effect of bezafibrate on progression of preexisting diabetes also showed a lower hazard for progression to use of antidiabetic medication (0.54 [0.38–0.76]) or progression to use of insulin (0.78 [0.55–1.10]).

CONCLUSIONS — Bezafibrate appears to have clinically important antidiabetic properties. Randomized controlled trials should be considered to assess the utility of bezafibrate in treating patients with diabetes or in preventing diabetes in high-risk patients.

Diabetes Care 32:547–551, 2009

Type 2 diabetes is a major public health threat, expected to affect more than 221 million people worldwide by 2010 (1). One key target for diabetes drug development is the peroxisome proliferator–activated receptor (PPAR) (2,3). There are three isotypes that are of specific interest in metabolic diseases: PPAR-γ, PPAR-α, and PPAR-δ. The thiazolidinediones (e.g., pioglitazone) are PPAR-γ agonists used to treat diabetes through improvement of insulin response. The fibrates are PPAR-α agonists used to treat dyslipidemia by raising HDL and lowering triglycerides. PPAR-δ remains an investigational drug target with potential uses in diabetes, dyslipidemia, and obesity (4). Because dyslipidemia and diabetes are commonly comorbid, attempts have been made to create dual PPAR-α/γ agonists or pan-PPAR agonists, although none of these has reached the market (3).

In response to efforts to develop these agents, at least one observer has pointed out that the fibrate bezafibrate actually is a pan-PPAR agonist and affects insulin resistance (5). Post hoc analyses of a placebo-controlled randomized trial showed that bezafibrate may postpone or prevent type 2 diabetes (5,6). During a mean 6 years of follow-up, hazard ratios (HRs) versus placebo for incident diabetes were 0.59 (95% CI 0.39–0.91) in obese patients (5) and 0.70 (95% CI 0.49–0.99) in prediabetic patients (6). These clinical end point data were supported by biochemical evidence showing that bezafibrate slowed progression of insulin resistance (7).

Studies of the other fibrates (gemfibrozil, fenofibrate, ciprofibrate, and clofibrate) have not shown such effects (8–14), and these drugs are far more selective for PPAR-α than bezafibrate (15). Hence, it is reasonable to hypothesize that the status of bezafibrate as a pan-PPAR agonist may give it antidiabetic properties unique among fibrates.

Although not approved in the U.S., bezafibrate has been widely prescribed for dyslipidemia in the U.K. We used observational data to examine the a priori hypothesis that bezafibrate is unique among fibrates in reducing diabetes risk.

RESEARCH DESIGN AND METHODS

— We conducted a cohort study using the General Practice Research Database (GPRD). Personal information was removed before inclusion in the database. The requirement for informed consent was waived by the University of Pennsylvania institutional review board and the GPRD Independent Scientific Advisory Committee.

Data source

The GPRD contains data abstracted from a computerized medical record system used by a subset of general practices in the U.K. Ninety-eight percent of the U.K. population receives all forms of health care through their general practitioners. The database is broadly representative of the U.K. population in terms of sex, age, and geography (16). We used data from 1988 through 2002.

The information prospectively collected in the database includes demographic information, all prescriptions written by the general practitioner, clinical diagnoses, specialty consultation notes, and hospital discharge diagnoses. Medical diagnoses are classified using Read Clinical Classification and the Oxford Medical Information System codes.

Participating general practices follow prospectively designed protocols for recording computerized clinical informa-

From the [1]Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania; and [2]Centocor Research and Development, Malvern, Pennsylvania, and Preventive Cardiovascular Medicine and Lipid Clinic, Department of Medicine, University of Pennsylvania Health System, Philadelphia, Pennsylvania.
Corresponding author: James Flory, jflory@mail.med.upenn.edu.
Received 2 October and accepted 4 January 2009.
Published ahead of print at http://care.diabetesjournals.org on 8 January 2009. DOI: 10.2337/dc08-1809.
No sponsor had any role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.

tion and uploading it to the research database. Data reaching predefined quality standards are so designated. More than 400 published epidemiological studies have been performed using the GPRD (16,17).

Study cohort

From all patients being followed in the GPRD, we included only person-time from individuals who were exposed to a fibrate. Individuals were only included who had been registered and up-to-standard with the GPRD for at least 12 months before initiation of the exposure drug, making this an inception cohort.

Because the primary outcome of interest was incident diabetes, any diagnostic code for diabetes or any use of home glucose-monitoring equipment or of drugs that are only used to treat diabetes (insulin, biguanides, sulfonylureas, thiazolidinediones, or acarbose) before the first fibrate prescription or within the first 90 days of fibrate therapy excluded that individual from participation in the primary analysis. The rationale for this exclusion was to avoid including prevalent diabetic subjects in the study cohort.

Exposure definition

The study group included those with more than one prescription for bezafibrate, as a way to identify those receiving chronic treatment. Because we excluded individuals developing diabetes within the first 90 days of therapy, we began follow-up with the 91st day of fibrate therapy. The duration of each prescription was either provided in the database or, when this information was missing, estimated from the number of pills dispensed. Exposure was assumed to continue 30 days after the end of the expected duration of the last prescription. Gaps over 60 days longer than expected between prescriptions were considered to mark a last prescription, although a patient could reenter the cohort with the next prescription. Clustering methods were used to account for single patients contributing multiple blocks of time to the cohort, and sensitivity analysis was done in which patients were censored at the first gap and not allowed to reenter the cohort.

Control groups were defined using parallel criteria, with person-time for control subjects defined by exposure to other fibrates without any history of bezafibrate use. The prespecified plan for this study was to maximize power by considering all nonbezafibrate fibrates as a single exposure and only distinguishing between individual fibrates in a secondary analysis.

Any patient who switched from one study group to another was censored at the time of the switch. In a secondary analysis, each specific fibrate constituted its own exposure group, compared with bezafibrate.

Outcome definition

The outcome of interest was clinical diagnosis of or treatment for diabetes, defined by at least two codes indicative of diabetes. Such codes included any diagnostic code for diabetes, any prescription for home glucose-monitoring equipment, or any prescription for insulin or an oral antidiabetic drug.

Post hoc analysis

In a post hoc analysis, two additional cohorts were created. These consisted of individuals who would have been eligible for the primary study but were excluded because of diabetes occurring before the 91st day of fibrate treatment. These individuals with baseline diabetes were divided into two groups. The new cohort consisted of individuals who had untreated diabetes at baseline (as identified by medical codes for diabetes or use of home glucose-monitoring equipment but no use of any antidiabetic medication). For this cohort, the outcome of interest was progression to use of any antidiabetic medication. In addition, individuals who were using oral antidiabetic therapy (a biguanide, sulfonylurea, thiazolidinedione, or acarbose) at baseline were treated as a separate cohort, with progression to use of insulin as the study outcome.

Statistical analysis

All exposure groups were first compared on baseline variables. For each exposure group, event rates were calculated. Next, Cox proportional hazard models were used to estimate unadjusted and adjusted HRs. Fully adjusted models were reported with all variables included in the model.

Covariates included the year that the exposure therapy was initiated. They also included a preidentified list of factors known to be associated either positively or negatively with diabetes. These included sex, age, history of stroke, history of myocardial infarction, and use of the following drugs: ACE inhibitors, calcium channel blockers, β-blockers, thiazide diuretics, loop diuretics, and corticosteroids (18). These drugs were analyzed as baseline covariates and in sensitivity analysis as time-varying covariates. BMI and smoking status were available only for a portion of the population and were included only in secondary analyses. The presence of comorbidities was determined on the basis of identification of GPRD medical diagnostic codes in the year before the first fibrate prescription.

Five secondary analyses were performed: *1*) comparison of bezafibrate users versus users of each individual fibrate; *2*) stratification by duration of therapy; *3*) stratification of bezafibrate users into approximate quartiles of average dosage (<200, 200–400, 400–600, and 600+ mg/day) with use of the low-dose category as a reference group; *4*) restriction to subjects with baseline BMI data and incorporation of BMI into multivariable modeling; and *5*) restriction to subject with baseline smoking data and incorporation of smoking into multivariable modeling.

RESULTS

— Bezafibrate was used far more commonly (12,161 users) than any other fibrate (4,191 users). Of the other fibrate users, 1,465 used ciprofibrate, 502 used clofibrate, 824 used fenofibrate, and 1,400 used gemfibrozil. Baseline characteristics of bezafibrate users and other fibrate users were consistent with previously published research (Table 1) (18). Because of the large sample size, most baseline differences were statistically significant. However, few clinically significant differences were observed. Of interest, however, the prevalence of recorded obesity was very similar (5% vs. 6%) between the two groups. However, bezafibrate users were more likely to be female than other fibrate users (48% vs. 40%).

Users of all other fibrates were less likely to have baseline diabetes than users of bezafibrate (relative risk 0.90 [95% CI 0.82–0.98] adjusted for year of the first fibrate prescription). However, bezafibrate users were less likely to have diabetes before treatment initiation compared with only one subgroup, the fenofibrate users (1.25 [1.08–1.42] adjusted for year of first fibrate prescription).

Among bezafibrate users, 272 new cases of diabetes occurred, for an incidence rate of 8.5 cases per 1,000 patient-years (95% CI 7.5–9.5). Among users of the other fibrates, 131 new cases of diabetes occurred, for an incidence rate of 14.4 cases per 1,000 patient-years (12.1–17.1).

Table 1—*Baseline characteristics and number of events in exposure groups*

	Bezafibrate	All other fibrates	*P* value for difference
n	12,161	4,191	
Person-years	32,091	9,067	
Mean duration of use (years)	2.6	2.2	<0.0001
Mode year of treatment initiation	1993	1994	<0.0001
Age (years)			
50	20	22	0.0112
50–59	33	33	0.9840
60–69	37	33	<0.0001
>69	10	12	0.0008
Male sex	52	60	<0.0001
History of myocardial infarction	1	1	0.7529
History of stroke	0	0	0.9676
History of ACE inhibitor/angiotensin receptor blocker use	5	6	0.0018
History of calcium channel blocker use	24	22	0.1756
History of β-blocker use	16	17	0.2382
History of loop diuretic use	5	5	0.2178
History of thiazide diuretic use	9	8	0.2883
History of corticosteroid use	3	3	0.6388
Never smoker	19	21	0.5114
Ever smoker	39	41	0.5114
Not reported	42	38	<0.0001
BMI			
<25 kg/m^2	9	8	0.0449
25–29.9 kg/m^2	13	13	0.6363
>29.9 kg/m^2	5	6	0.0035
Not reported	73	72	0.0523
Number of cases of incident diabetes	272	131	
Cases/1,000 person-years (95% CI)	8.5 (7.5–9.5)	14.4 (12.1–17.1)	<0.001

Data are % unless indicated otherwise. Individuals with baseline diabetes were excluded. History of cardiovascular events and drug use refer to history in the year before cohort entry. *P* values were generated using χ^2 and *t* tests.

Cox proportional hazard regression results are shown in Table 2. The unadjusted HR for the comparison between bezafibrate and all other fibrates was 0.58 (95% CI 0.47–0.72). Adjusting for year of treatment initiation attenuated the association slightly, yielding a HR of 0.64 (0.52–0.79). No other variables modified the point estimate by as much as 10%. The fully adjusted HR for incident type 2 diabetes was 0.66 (0.53–0.81, $P = 0.0001$). Analyses were repeated with stratification by year of treatment initiation, with no substantial change in the results or evidence of heterogeneity of results by year (data not shown).

Table 2—*Prespecified secondary analyses consisting of HRs for exposure to bezafibrate*

	HRs (95% CI) for incident type 2 diabetes in individuals exposed to bezafibrate	
Reference group	Unadjusted	Fully adjusted
All fibrate users	0.58 (0.47–0.72)	0.66 (0.53–0.81)
Ciprofibrate users	0.53 (0.39–0.73)	0.72 (0.52–0.99)
Clofibrate users	1.17 (0.63–2.14)	0.78 (0.54–1.14)
Gemfibrozil users	0.30 (0.21–0.42)	0.84 (0.46–1.55)
Fenofibrate users	0.81 (0.57–1.19)	0.41 (0.29–0.58)

Fully adjusted HRs are adjusted for year of treatment initiation, age, sex, history of congestive heart failure, history of myocardial infarction, and history of use of thiazide diuretics, loop diuretics, β-blockers, calcium-channel blockers, ACE inhibitors, angiotensin receptor blockers, or steroids.

Table 2 also shows each individual fibrate treated as a distinct reference group. Bezafibrate had similar adjusted HRs compared with those for ciprofibrate, clofibrate, and gemfibrozil (Table 2). However, compared with fenofibrate, bezafibrate was associated with a particularly low hazard for diabetes (HR 0.41, 95% CI 0.29–0.58).

Table 3 shows the results of the duration-response analysis. The HR declined monotonically as duration of therapy increased.

No significant relationship with average daily dose was seen (data not shown). Neither restriction to individuals with BMI data nor adjustment for BMI substantially altered the results, although BMI of 25–30 kg/m^2 was associated with an HR of 3.72 (95% CI 1.89–7.29) and BMI >30 kg/m^2 was associated with an HR of 6.98 (95% CI 3.51–13.88), with BMI <25 kg/m^2 as a reference group. The same was true for restriction to individuals with baseline smoking data and inclusion of that information in the multivariable model (not shown).

In post hoc analysis, individuals with baseline diabetes were classified as either unmedicated (no record of use of antidiabetic medication) or receiving oral antidiabetic medication. The distribution of baseline characteristics between exposure groups was generally similar to that in the original cohort (data not shown).

Table 4 shows HRs calculated for progression from unmedicated diabetes at the time of fibrate initiation to use of any antidiabetic medication (including insulin), as well as HRs for progression from use of an oral antidiabetic drug at baseline to insulin use. Bezafibrate was associated with a lower hazard of progression to antidiabetic medication use compared with fibrates (HR 0.54, 95% CI 0.38–0.76). The HRs were not substantially altered by multivariable adjustment.

The analysis was repeated with individuals who used oral antidiabetic medications at baseline, with progression to insulin therapy as the outcome. Bezafibrate was associated with a nonsignificant trend toward a lower hazard of progression to insulin therapy (adjusted HR 0.78, 95% CI 0.55–1.10).

No significant differences in HRs were observed for sex. Data on ethnicity were not available for this study.

CONCLUSIONS — This study provides strong evidence that bezafibrate has antidiabetic properties, supporting both

Table 3—*HRs stratified by years of cumulative use*

	Fully adjusted HRs (95% CI) stratified by years of cumulative exposure		
Reference group	Year 1	Years 2–3	Years 4–5
All fibrate users	0.74 (0.52–1.05)	0.62 (0.44–0.89)	0.57 (0.35–0.93)

Fully adjusted HRs are adjusted for year of treatment initiation, age, sex, history of congestive heart failure, history of myocardial infarction, and history of use of thiazide diuretics, loop diuretics, β-blockers, calcium-channel blockers, ACE inhibitors, angiotensin receptor blockers, or steroids.

in vitro data and earlier post hoc analyses suggesting that bezafibrate can prevent or delay the onset of type 2 diabetes (5–7). It further indicates that this effect is unique to bezafibrate among the fibrates. These findings have important implications for research. Our findings are bolstered by the similarity of subjects in exposure groups on clinically relevant characteristics, the fact that the finding of a protective effect is of a clinically relevant magnitude, statistically significant, and robust to sensitivity analyses including adjustment for BMI, and the monotonic duration-response relationship.

The results of the post hoc analysis are reassuring. It was reasonable to worry that fenofibrate was more likely to be prescribed to individuals with a high risk for diabetes or unrecorded diabetes, creating a falsely elevated hazard for development of diabetes during fenofibrate treatment compared with bezafibrate treatment. It was hence useful to do a post hoc analysis confined to individuals who already had diabetes. In this post hoc analysis, bezafibrate also appeared to have antidiabetic properties.

Taken together, these findings support and complement previous observations. Post hoc analyses of the Bezafibrate Infarction Prevention (BIP) Study have suggested that bezafibrate may reduce the hazard for incident diabetes, with point estimates for the HR of 0.59 and 0.70 (5,6). The fully adjusted point estimate from our study (0.66, 95% CI 0.3–0.81) is very consistent with those earlier results. These additional results are important because they confirm a post hoc analysis in a new study with this as a prespecified hypothesis, they generalize the results to a broader population than the original post hoc analysis did, and they provide considerably more precise point estimates.

Another publication from the BIP showed that bezafibrate attenuated progression of the homeostasis model assessment of insulin resistance marker for insulin resistance in all patients, suggesting that bezafibrate might also slow progression of diabetes (7). Our results were consistent with that hypothesis as well, both for progression from diagnosis to any use of antidiabetic drugs (HR 0.54, 95% CI 0.38–0.76) and for progression from use of oral antidiabetics to insulin (0.78, 0.55–1.10). The finding for progression to insulin was a trend but was not statistically significant. In addition, the findings on diabetes progression should be noted to be post hoc and are not adjusted for multiple comparisons.

The major limitation of this study was the potential for unadjusted confounding, a problem in any observational study. Despite the similar indications for the fibrates, the drugs are clearly not identically prescribed. Most strikingly, bezafibrate was by far the most commonly used fibrate in the U.K. and had the highest proportion of female users. Of most concern, rates of baseline diabetes differed by exposure group. Adjusting for these baseline differences did not change our results. Further, it is reassuring that bezafibrate still appeared to be protective even when compared with ciprofibrate, clofibrate, or gemfibrozil (which were not preferentially prescribed to diabetic subjects compared with bezafibrate). It is especially reassuring that a post hoc analysis of diabetes progression that could not have been confounded by preferential prescribing to diabetic subjects still showed a protective effect from bezafibrate. We in turn note that this post hoc analysis was not part of the original study design, was subject to false-positive results due to multiple comparisons, and used rough proxies for diabetes progression (progression to oral or insulin therapy). No observational study can completely exclude the possibility of confounding by indication, and the results of this study need to be confirmed in a subsequent randomized study. Another potential limitation of this study is the likelihood that some incident cases of diabetes were not captured by the database; however, such misclassification would most likely be nondifferential and would bias any finding toward the null.

In summary, this study strongly supports the idea that bezafibrate can prevent type 2 diabetes, confirming a post hoc analysis in a prior study. The effect size estimates from this study are comparable to those reported for other studies assessing the use of thiazolidinediones and metformin to prevent diabetes (19). Given concerns about cardiovascular risk with existing oral antidiabetic agents (20,21), bezafibrate may offer a unique opportunity to treat or prevent diabetes while maintaining a favorable cardiovascular risk-benefit profile. However, it would not be appropriate to establish a new indication without randomized controlled trial data to confirm these findings, similar to those recently conducted to study the antidiabetic properties of colesevelam (22). In light of the increasing population risk of diabetes, a trial that could establish the effectiveness of an inexpensive and

Table 4—*Cox proportional hazard models for ad hoc analysis*

	Fully adjusted HRs (95% CI)	
Reference group	For progression from unmedicated baseline diabetes to use of oral antidiabetic therapy	For progression from baseline use of oral antidiabetic therapy to use of insulin
All fibrate users	0.54 (0.38–0.76)	0.78 (0.55–1.10)
Ciprofibrate users	0.44 (0.28–0.69)	0.78 (0.50–1.22)
Fenofibrate users	0.57 (0.32–1.02)	0.86 (0.52–1.42)
Gemfibrozil users	0.74 (0.38–1.43)	0.57 (0.31–1.05)

All models treat bezafibrate as the exposure; reference group varies by row. Clofibrate was not used alone as a reference group because of an insufficient number of observations in the clofibrate group to support multivariable modeling. Fully adjusted models are adjusted for year of treatment initiation, age, sex, history of congestive heart failure, history of stroke, and history of drug use (ACE/angiotensin receptor blocker, calcium channel blocker, loop diuretic, thiazide diuretic, β-blocker, or steroid).

safe agent for both prophylaxis and treatment should be strongly considered for prioritization by funding agencies.

Acknowledgments— This research was supported by a National Institutes of Health T-32 and Clinical and Translation Science AWARDS (CTSA) grant, a CTSA-Automated Claims and Medical Record Databases intramural grant, and pooled pharmacoepidemiology training money that includes industry support. J.H.F. also is grateful for the support of the Center for Clinical Epidemiology and Biostatistics and the University of Pennsylvania CERT (Center for Education and Research on Therapeutics).

J.H.F. received tuition support from pharmacoepidemiology training funds, which include funding from multiple companies that manufacture fibrates. S.E. is involved in a financial, research, or advisory capacity with a number of companies that manufacture fibrates. P.O.S. is involved in a financial, research, or advisory capacity with a number of companies that manufacture fibrates. S.H. is a coinvestigator on a study sponsored by Abbott Laboratories and has served as a consultant to Wyeth and sanofi-aventis. No other potential conflicts of interest relevant to this article were reported.

Parts of this study were presented in abstract form at the 110th annual meeting of the American Society for Clinical Pharmacology and Therapeutics, Washington, DC, 18–21 March 2009.

References

1. Zimmet P, Alberti KG, Shaw J: Global and societal implications of the diabetes epidemic. *Nature* 414:782–787, 2001
2. Hansen MK, Connolly TM: Nuclear receptors as drug targets in obesity, dyslipidemia and atherosclerosis. *Curr Opin Investig Drugs* 9:247–255, 2008
3. Brophy JM: Selling safety—lessons from muraglitazar. *JAMA* 294:2633–2635, 2005
4. Narkar VA, Downes M, Yu RT, Embler E, Wang YX, Banayo E, Mihaylova MM, Nelson MC, Zou Y, Juguilon H, Kang H, Shaw RJ, Evans RM: AMPK and PPARδ agonists are exercise mimetics. *Cell* 134:405–415, 2008
5. Tenenbaum A, Motro M, Fisman EZ, Adler Y, Shemesh J, Tanne D, Leor J, Boyko V, Schwammenthal E, Behar S: Effect of bezafibrate on incidence of type 2 diabetes mellitus in obese patients. *Eur Heart J* 26:2032–2038, 2005
6. Tenenbaum A, Motro M, Fisman EZ, Schwammenthal E, Adler Y, Goldenberg I, Leor J, Boyko V, Mandelzweig L, Behar S: Peroxisome proliferator-activated receptor ligand bezafibrate for prevention of type 2 diabetes mellitus in patients with coronary artery disease. *Circulation* 109: 2197–2202, 2004
7. Tenenbaum A, Fisman EZ, Boyko V, Benderly M, Tanne D, Haim M, Matas Z, Motro M, Behar S: Attenuation of progression of insulin resistance in patients with coronary artery disease by bezafibrate. *Arch Intern Med* 166:737–741, 2006
8. Keech AC, Mitchell P, Summanen PA, O'Day J, Davis TM, Moffitt MS, Taskinen MR, Simes RJ, Tse D, Williamson E, Merrifield A, Laatikainen LT, d'Emden MC, Crimet DC, O'Connell RL, Colman PG, FIELD Study Investigators: Effect of fenofibrate on the need for laser treatment for diabetic retinopathy (FIELD study): a randomised controlled trial. *Lancet* 370: 1687–1697, 2007
9. Whitelaw DC, Smith JM, Nattrass M: Effects of gemfibrozil on insulin resistance to fat metabolism in subjects with type 2 diabetes and hypertriglyceridaemia. *Diabetes Obes Metab* 4:187–194, 2004
10. Ohrvall M, Lithell H, Johansson J, Vessby B: A comparison between the effects of gemfibrozil and simvastatin on insulin sensitivity in patients with non-insulin-dependent diabetes mellitus and hyperlipoproteinemia. *Metabolism* 44:212–217, 1995
11. Vega GL, Ma PT, Cater NB, Filipchuk N, Meguro S, Garcia-Garcia AB, Grundy SM: Effects of adding fenofibrate (200 mg/day) to simvastatin (10 mg/day) in patients with combined hyperlipidemia and metabolic syndrome. *Am J Cardiol* 91: 956–960, 2003
12. The FIELD Study Investigators: Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. *Lancet* 366: 1849–1861, 2005
13. Raslová K, Nagyová A, Dobiásová M, Ptácková K, Dusinská M: Effect of ciprofibrate on lipoprotein metabolism and oxidative stress parameters in patients with type 2 diabetes mellitus and atherogenic lipoprotein phenotype. *Acta Diabetol* 37: 131–134, 2000
14. Hernández-Mijares A, Lluch I, Vizcarra E, Martínez-Triguero ML, Ascaso JF, Carmena R: Ciprofibrate effects on carbohydrate and lipid metabolism in type 2 diabetes mellitus subjects. *Nutr Metab Cardiovasc Dis* 10:1–6, 2000
15. Willson TM, Brown PJ, Sternbach DD, Henke BR: The PPARs: from orphan receptors to drug discovery. *J Med Chem* 43: 527–550, 2000
16. Lewis JD, Brensinger C, Bilker WB, Strom BL: Validity and completeness of the General Practice Research Database for studies of inflammatory bowel disease. *Pharmacoepidemiol Drug Saf* 11:211–218, 2002
17. General Practice Research Database [online], 2002. Available from http://www.epic-uk.org/gprd.htm. Accessed 7 July 2008
18. Yang CC, Jick SS, Testa MA: Who receives lipid-lowering drugs: the effects of comorbidities and patient characteristics on treatment initiation. *Br J Clin Pharmacol* 55:288–298, 2003
19. Chiasson JL: Prevention of type 2 diabetes: fact or fiction? *Expert Opin Pharmacother* 8:3147–3158, 2007
20. Nissen SE, Wolski K: Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. *N Engl J Med* 356:2457–2471, 2007
21. Goldfine AB: Assessing the cardiovascular safety of diabetes therapies. *N Engl J Med* 359:1092–1095, 2008
22. Fonseca VA, Rosenstock J, Wang AC, Truitt KE, Jones MR: Colesevelam HCl improves glycemic control and reduces LDL cholesterol in patients with inadequately controlled type 2 diabetes on sulfonylurea-based therapy. *Diabetes Care* 31:1479–1484, 2008