

Supplement to

Review of **ENDOCRINOLOGY**

EXAMINING THE ISSUES, TREATMENTS, AND EMERGING TRENDS IN DIABETES & ENDOCRINE DISORDERS

September 2008

Fenofibrate May Have Potential Role in Slowing the Progression of Nephropathy in Diabetes

Reviewed By Paul L. Drury, MA, MB, BChir, FRCP, FRACP

Compiled by Ryan DuBosar, Tracy DuBosar, and Conni Bergmann Koury

Emerging evidence suggests that the potential benefits of fibrates in patients with diabetes appear to extend with these new specific effects seen with fenofibrate. It is a well-tolerated medication that can be successfully used in combination with statins.

ABSTRACT

PURPOSE

The benefits of fenofibrate treatment in patients with diabetes potentially go beyond improving the dyslipidemia of diabetes. This agent appears to have several other potentially important roles, not only in reducing overall cardiovascular risk, but also in improving or preventing microvascular complications in these patients.

The following review summarizes the available data and potential benefits of treating these patients with fenofibrate, including its use in reducing the progression of microalbuminuria—a major marker of diabetic kidney damage and cardiovascular event risk—among this population. This review also examines the emerging safety profile of fenofibrate and other fibrates, particularly when used as an adjunct to statin therapy.

Jointly sponsored by The Dulaney Foundation and *Review of Endocrinology*

Jointly sponsored by The Dulaney Foundation and *Review of Endocrinology*.

Release date: September 2008. Expiration date: September 2009.

This continuing medical education activity is supported by an unrestricted educational grant from Abbott Laboratories.

STATEMENT OF NEED

Type 2 diabetes is a major independent risk factor for macrovascular disease, including ischemic heart disease, stroke, peripheral vascular disease, and heart failure. Heart disease is also a major cause of death for all people with chronic kidney disease (CKD), and diabetic nephropathy occurs in 20% to 40% of patients with diabetes. Diabetes—predominantly type 2—is the single greatest cause of end-stage renal disease (ESRD), and these patients contribute 40% to 45% of all new cases of treated ESRD in the United States and several other countries. World Health Organization statistics reveal that worldwide, 10% to 20% of people with diabetes die of kidney failure. Importantly, the combination of diabetes and nephropathy increases the risk of cardiovascular disease above that conferred by diabetes alone.¹⁻⁵

Emerging data from clinical trials appears to suggest that the current recommendations from the National Kidney Foundation with regard to treatment options among diabetes patients with CKD are probably now outdated and cannot be considered evidence based. Therefore, it is important that practitioners remain up to date on the most recent developments in this arena.

TARGET AUDIENCE

This activity is designed for endocrinologists, diabetologists, internal medicine specialists, family physicians, certified diabetes educators, and other practitioners who focus on diabetes care.

LEARNING OBJECTIVES

Upon successfully completing this learning program, participants should be able to:

- Discuss the burden of nephropathy among people with diabetes and its subsequent impact on cardiovascular disease.
- Review the mechanisms of action of fibrates.
- Cite the macrovascular findings of the FIELD study.
- Discuss the microvascular findings of FIELD, including results with regard to nephropathy and retinopathy.
- Understand the additional evidence regarding the use of fibrates among patients with diabetes.
- Discuss the safety profile of fibrates.
- Describe the use of fibrates in conjunction with statins.

METHOD OF INSTRUCTION

Participants should read the learning objectives and continuing medical education (CME) program in their entirety. After reviewing the material, please complete the self-assessment test, which consists of a series of multiple-choice questions. To answer these questions online and receive real-time results, please visit www.dulaneyfoundation.org and click "Online Courses." Upon completing the activity and achieving a passing score of over 70% on the self-assessment test, you may print out a CME credit letter awarding 1 AMA PRA Category 1 Credit.[™] The estimated time to complete this activity is 1 hour.

ACCREDITATION

This activity has been planned and implemented in accor-

dance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of The Dulaney Foundation and *Review of Endocrinology*. The Dulaney Foundation is accredited by the ACCME to provide continuing education for physicians. The Dulaney Foundation designates this educational activity for a maximum of 1 AMA PRA Category 1 Credit.[™] Physicians should only claim credit commensurate with the extent of their participation in the activity.

DISCLOSURE

In accordance with the disclosure policies of The Dulaney Foundation and to conform with ACCME and the US Food and Drug Administration guidelines, anyone in a position to affect the content of a CME activity is required to disclose to the activity's participants: (1) the existence of any financial interest or other relationships with the manufacturers of any commercial products/devices or providers of commercial services; and (2) identification of a commercial product/device that is unlabeled for use or an investigational use of a product/device not yet approved.

CONTENT VALIDATION

In compliance with ACCME standards for commercial support and The Dulaney Foundation's policy and procedure for resolving conflicts of interest, this CME activity was peer reviewed for clinical content validity to ensure the activity's materials are fair, balanced, and free of bias; the activity materials represent a standard of practice within the medical profession; and any studies cited in the materials upon which recommendations are based are scientifically objective and conform to research principles generally accepted by the scientific community.

FACULTY CREDENTIALS

Paul Drury, MA, MB, BChir, FRCP, FRACP, is Clinical Director, Auckland Diabetes Centre, New Zealand. He may be reached at PaulD@adhb.govt.nz.

Aaron I. Vinik, MD, PhD, is Director, Diabetes Research Institute, Scientific Director, Department of Medicine, Professor of Medicine, Eastern Virginia Medical School, Norfolk, Va. He may be reached at vinikai@evms.edu.

FACULTY/STAFF DISCLOSURE DECLARATIONS

Dr. Drury disclosed that he is on the speakers list for Solvay Pharmaceuticals.

Dr. Vinik disclosed that he is a consultant and a member of the speaker's bureau for Merck, Eli Lilly, Novartis Pharmaceuticals, Takeda, Astra Zeneca, Sanofi-Aventis, and Ansar. He is a consultant for Neurometrix, RW Johnson Pharmaceutical Research Institute and Mitsubishi Pharma America, Inc., and is on the speaker's bureau for Pfizer, Bristol Myers Squibb, and GlaxoSmithKline. He has received grant funding from Abbott, GlaxoSmithKline, and Eli Lilly.

Other staff involved in this review state that they have nothing to disclose.

BACKGROUND: CARDIOVASCULAR RISK AND DIABETIC NEPHROPATHY

According to the International Diabetes Federation, there were 246 million adults worldwide living with diabetes in 2007, a number which is predicted to increase to 333 million by 2025.¹ Type 2 diabetes constitutes about 85% to 95% of all diabetes cases in the developed world and may account for an even higher proportion in developing nations.

Type 2 diabetes is a major independent risk factor for macrovascular disease, including ischemic heart disease, stroke, peripheral vascular disease, and heart failure.² Heart disease is also a major cause of death for all people with chronic kidney disease (CKD),³ and diabetic nephropathy occurs in 20% to 40% of patients with diabetes (Figure 1). Diabetes—predominantly type 2—is the single greatest cause of end-stage renal disease (ESRD), and these patients contribute 40% to 45% of all new cases of treated ESRD in the United States and several other countries.⁴ World Health Organization statistics reveal that worldwide, 10% to 20% of people with diabetes die of kidney failure.⁵ Importantly, the combination of diabetes and nephropathy increases the risk of cardiovascular disease (CVD) above that conferred by diabetes alone (Table 1).

In the United States, the number of people who began treatment for ESRD due to diabetes increased from about 7,000 in 1984 to more than 43,000 in 2002, according to data from the US Centers for Disease Control and Prevention.⁶ Twenty-six million Americans have CKD, and another 20 million are at increased risk—statistics which are paralleled in other countries. Medicare spends about \$19 billion annually to care for the 450,000 US patients with ESRD, accounting for about 6% of all Medicare expenditures. The potential savings to Medicare

for each patient who does not progress to dialysis is estimated to be about \$250,000 per patient.⁷

Examinations of trends in ESRD attributable to diabetes in the United States and elsewhere do, however, suggest a recent downturn in the previously increasing incidence and perhaps even a decline.^{8,9} This indicates that conventional treatment may be having some effect. According to a recent editorial,¹⁰ “Although it appears as though the tide is turning, it is too early to celebrate a victory for renoprotection.” It is also unclear as to whether this apparent “turning of the tide” is primarily due to better glycemic control in diabetes patients during recent decades, energetic antihypertensive therapy or, most likely, both.

FIBRATES: MECHANISM OF ACTION

Fibric acid derivatives or fibrates are peroxisome proliferator-activated receptor-alpha (PPAR-alpha) agonists that are hepatically metabolized and renally eliminated. Hydroxymethylglutaryl-coenzyme A reductase inhibitors (statins) predominantly lower low-density lipoprotein (LDL) cholesterol. Fibrates, however, have a completely different mechanism of action and affect different lipid components (Table 2).¹¹

Fibrates increase the size of LDL particles and at the same time, raise high-density lipoprotein (HDL). Fenofibrate also lowers triglyceride levels by reducing

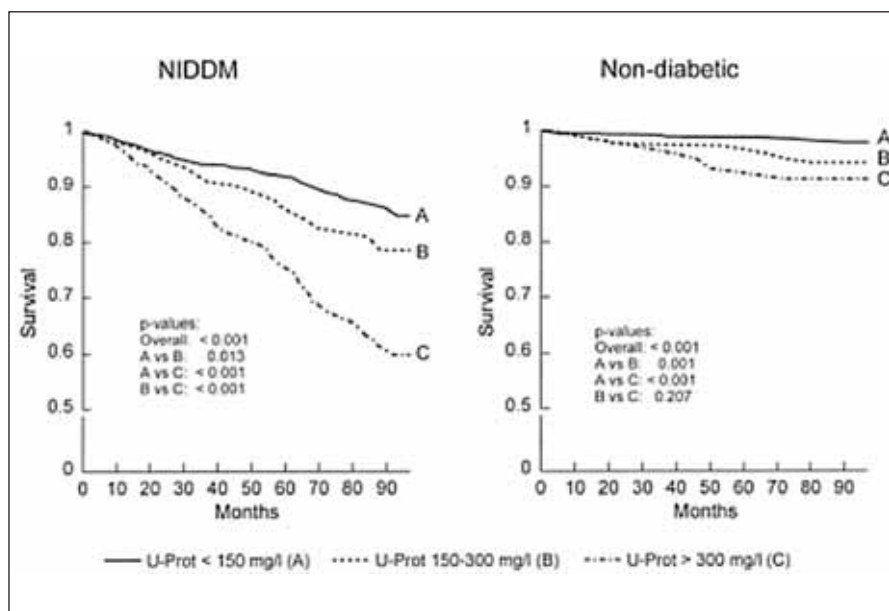


Figure 1. Survival curves for CVD mortality by urinary protein concentration (U-Protein) in noninsulin-dependent diabetes mellitus (NIDDM) and nondiabetic patients.

Figure reprinted with permission from Stroke. 1996;27:2033-2039.

TABLE 1. DIABETIC NEPHROPATHY

Kidney disease is a frequent diabetic complication

- Type 1 diabetes. Approximately 30% of patients develop clinical nephropathy according to evidence from an older 1960's cohort, the rate is progressively decreasing in more recent cohorts.
- Type 2 diabetes. Approximately 40% of patients develop clinical nephropathy according to evidence from older cohorts, this rate appears to be decreasing (data is less clear).

Diabetes is common in ESRD

- Among patients with diabetes the rate of diabetic kidney disease: is approximately 45% in countries including the United States, Mexico, Taiwan and New Zealand; it is the most common cause of ESRD in these countries.
- Diabetic nephropathy progressively amplifies CVD risk.
 - microalbuminuria increased cardiovascular risk substantially compared with normoalbuminuria
 - macroalbuminuria and clinical nephropathy increase cardiovascular risk massively

the creation of lipid in the liver and by stimulating reverse cholesterol transport.¹¹ Apart from lipid effects, fibrates also affect the microvasculature in some ways that statins do not.

**FENOFIBRATE:
CLINICAL TRIAL FINDINGS**

FIELD (Fenofibrate in Intervention and Event Lowering in Diabetes)

FIELD¹² sought to investigate whether long-term lipid-lowering therapy with fenofibrate would reduce macro- and microvascular complications among patients with type 2 diabetes.

FIELD was a multinational, randomized, placebo-controlled clinical trial of 9,795 patients aged 50 to 75 years. After a placebo and a fenofibrate run-in phase, patients were randomized to 200 mg/day fenofibrate (n = 4,895) or placebo (n = 4,900). At baseline, patients had total cholesterol levels of 3.0 to 6.5 mmol/L (117–254 mg/dL), a ratio of total cholesterol to HDL of ≥ 4 mmol/L (156 mg/dL), or triglyceride concentrations of 1.0 to 5 mmol/L (88.6–443 mg/dL). Exclusion criteria included renal impairment indicated by plasma creatinine $> 130 \mu\text{mol/L}$ (1.47 mg/dL), known chronic liver disease or symptomatic gallbladder disease, or a cardiovascular event within 3 months of enrollment.

Postrandomization fasting blood samples were taken at baseline, 4, 8, and 12 months, and then annually until the end of the study. Plasma lipids, including apolipoproteins A1, A2, and B, lipoprotein A, creatinine clearance, and alanine aminotransferase were all measured. Plasma glucose, A1C,

insulin, C-peptide, fibrinogen and homocysteine, urine albumin and urine creatinine were also measured periodically. Baseline albumin/creatinine ratios were calculated as the mean of two measurements from spot morning urine samples and then remeasured at year 2 and study close.

Treating physicians were informed when serum creatinine rose by $> 30 \mu\text{mol/L}$ (0.34 mg/dL) or exceeded $150 \mu\text{mol/L}$ (1.70 mg/dL), when alanine aminotransferase exceeded three times the normal limit, or when creatinine phosphokinase exceeded twice the upper limit of normal.

Progression of renal disease, both clinically and in terms of albuminuria, was recorded as a previously specified tertiary outcome.

Lipid outcomes. Fenofibrate reduced total cholesterol concentrations, LDL, and triglyceride levels, and increased HDL. The researchers also found that apolipoprotein A1 concentrations increased by 3.9% and apolipoprotein A2 by 28%. Apolipoprotein B levels fell by 13.6% at 4 months. By the end of the study, the percentages were 1.8%, 23.7%, and -7.5%, respectively. In a subset of patients who had not undergone any other lipid-lowering treatment, changes included a lasting 24.5% effect on apolipoprotein A2, a 15.7% lasting effect on apolipoprotein B, and a 2% reduction of apolipoprotein A1.

Microvascular outcomes. In FIELD, fenofibrate was associated with less albuminuria progression ($P=.002$). In terms of albuminuria by category, in the placebo group, 539 patients (11%) progressed from normal albuminuria to macroalbuminuria, compared with 466 patients (10%) assigned to fenofi-

brate therapy. Another 400 (8%) in the placebo group regressed, as did 462 (9%) in the fenofibrate group. This represents 2.6% more patients taking fenofibrate regressing or not progressing compared with placebo ($P=.002$).

Although researchers have reported this reduction with other antihypertensive and antidiabetic therapies, there was no association between the lipid or uric acid changes and a reduction in urinary albumin excretion.¹³ Fenofibrate thus significantly reduced the rate of progression to albuminuria. A similar effect was apparent for urinary albumin concentration unadjusted for urinary creatinine ($P=.001$). Few patients from this selected group of nearly 10,000 patients reached ESRD over the median 5 years of the study. In the placebo group, 21 patients needed dialysis compared with 16 in the fenofibrate group. The numbers are understandably small, as people with significant renal impairment at baseline were excluded, but these results are very reassuring in terms of the renal safety of fenofibrate.

Macrovascular outcomes. Fenofibrate treatment in FIELD¹² did not reduce the primary composite endpoint of coronary heart disease (CHD), death, or nonfatal myocardial infarction (MI): 5.9% of patients

assigned placebo and 5.3% ($n = 256$) of those assigned fenofibrate had a coronary event (hazard ratio [HR], 0.89; 95% confidence interval [CI], 0.75–1.05; $P=.16$). The agent did, however, reduce nonfatal MI by 24% (HR, 0.76; CI, 0.62–0.94; $P=.010$), a finding that included a 21% reduction in coronary revascularization (HR, 0.79; CI, 0.68–0.93; $P=.003$). There was a nonsignificant increase in CHD mortality (HR, 1.19; CI, 0.90–1.57; $P=.22$). Total CVD events were significantly reduced from 13.9% to 12.5% (HR, 0.89; CI, 0.80–0.99; $P=.035$).

By the study's end, twice as many patients in the placebo arm had received statin "drop-in" therapy compared with the fenofibrate group (32% vs 16%, $P<.0001$). The FIELD authors noted that the higher rate of statin therapy in patients allocated to the placebo group might have masked a moderately larger treatment benefit.

DAIS (Diabetes Atherosclerosis Intervention Study)

DAIS¹⁴ was specifically designed to assess the effects of correcting lipoprotein abnormalities on coronary atherosclerosis in type 2 diabetes patients. DAIS examined 314 patients with type 2 diabetes

TABLE 2. CURRENTLY AVAILABLE LIPID-LOWERING AGENTS

Agent	Mechanisms of Action	Examples
HMG CoA reductase inhibitors (statins)	Reduces hepatic cholesterol synthesis, lowering intracellular cholesterol, which stimulates upregulation of LDL receptors and increase the uptake of non-HDL particles from systemic circulation.	Lovastatin, pravastatin, simvastatin, fluvastatin, atorvastatin
Bile acid sequestrants	Binds bile acids in the intestine, which reduces the enterohepatic recirculation of bile acids. Net effect is lowering of LDL.	Cholestyramine, colestipol
Nicotinic acid	Decreases hepatic production of VLDL and apo B.	Niacin, vitamin B derivative
Fibric acid derivative	Increases peripheral lipolysis and decreases hepatic triglyceride production. Increased synthesis of apo A-I tends to raise HDL-C levels.	Gemfibrozil, fenofibrate, clofibrate

Source: *Lipids Online* (lipidsonline.org, *Selecting Successful Lipid-Lowering Treatments* by James M. McKenney, PharmD).

aged an average age of 56 years. Patients were taking micronized fenofibrate for an average of 38 months compared with placebo, and investigators also examined the influence of treatment on changes to urinary albumin excretion.

Microalbuminuria was also measured on two or three occasions using timed overnight samples at baseline and annually thereafter for 3 years. Researchers compared tabulated shifts between normal, microalbuminuria, and macroalbuminuria from baseline to last observed values between treatment groups by chi-square or Fisher's exact test.

A surprising incidental finding of DAIS was that fenofibrate significantly reduced worsening of albumin excretion by 8%, compared with 18% for placebo.

Findings. As the main outcome, researchers reported a reduced progression of angiographically evaluated coronary artery disease and improved lipoprotein level abnormalities. The fenofibrate group showed a significantly smaller increase in percentage diameter stenosis than the placebo group (mean, 2.11 [standard error {SE}, 0.594] vs 3.65; [SE, 0.608]%, $P=.02$), a significantly smaller decrease in minimum lumen diameter (-0.06 [SE, 0.016] vs -0.10 [SE, 0.016] mm; $P=.029$), and a nonsignificantly smaller decrease in mean segment diameter (-0.06 [SE, 0.017] vs -0.08 [SE, 0.018] mm; $P=.171$).

A surprising incidental finding of DAIS was that fenofibrate significantly reduced worsening of albumin excretion by 8%, compared with 18% for placebo ($P<.05$). This effect was attributed mostly to reduced progression from normal albumin excretion to microalbuminuria (three of 101 patients in the fenofibrate arm vs 20 of 113 in the placebo group, $P<.001$) rather than from preventing worsening excretion once microalbuminuria is already present. Changes to albumin excretion were independent of age, changes in lipid or creatinine levels, weight, or blood pressure.

FENOFIBRATE AND DIABETIC RETINOPATHY IN FIELD

Fenofibrate treatment reduced the need for laser treatment for diabetic retinopathy by 31% in FIELD

patients.¹⁵ The requirement for first laser treatment for all retinopathy was significantly lower in the fenofibrate group than in the placebo group (3.4% of fenofibrate-assigned patients vs 4.9% of placebo patients; HR, 0.69; 95% CI, 0.56–0.84; $P=.0002$; absolute risk reduction 1.5% [CI, 0.7–2.3]).

A detailed ophthalmology substudy was also undertaken and included 1,012 patients, 950 of whom were assessed at the end of the study. These patients had standardized retinal fundus photographs taken and graded according to ETDRS (Early Treatment Diabetic Retinopathy Study) criteria to determine the cumulative incidence of diabetic retinopathy and its component lesions. The full results are shown in the accompanying sidebar, *FIELD Ophthalmology Substudy*.

MICROVASCULAR DISEASE: CONCLUSIONS

Fenofibrate's effects in FIELD and DIAS suggest a beneficial impact on the kidney and/or microvasculature that cannot be explained by changes to A1C levels or a minor blood pressure reduction. In FIELD, median blood pressure in placebo-assigned patients was 140/82 mm Hg at baseline and 138/78 mm Hg at study close versus 140/82 mm Hg and 136/77 mm Hg, respectively, in the fenofibrate group. Another mechanism is likely to be in effect, although a larger effect on blood pressure over a 24-hour period is still possible, as blood pressures in the trial were recorded only during daytime office visits.¹²

With the simultaneous positive retinal finding, this appears to be the first time a lipid-lowering drug has shown an effect on both the macro- and microvasculature in a large-scale study of patients with type 2 diabetes. The studies showed an impact in typical prescribing situations and in a typical group of patients with type 2 diabetes, such as when lipid-lowering agents might be added to a maintenance regimen.

STUDIES IN PROGRESS

Further results from the FIELD study and the effect of fenofibrate on renal function are awaited, as is the lipid treatment arm of the ACCORD¹⁶ (Action to Control Cardiovascular Risk in Diabetes) trial, expected to report results in 2010. ACCORD will examine as secondary outcomes, eye, kidney, and nerve complications, quality of life, and cost-

FIELD OPHTHALMOLOGY SUBSTUDY

Among patients in the FIELD study, an ophthalmology substudy included 1,012 patients, 950 of whom who had standardized retinal fundus photographs taken and graded according to ETDRS (Early Treatment Diabetic Retinopathy Study) criteria to determine the cumulative incidence of diabetic retinopathy and its component lesions. Analyses in this trial were by intention to treat. Upon each office visit, patients provided information regarding laser treatment for diabetic retinopathy, a prespecified tertiary endpoint of the main study. Ophthalmologists who were masked to treatment allocation determined instances of laser treatment for macular edema, proliferative retinopathy, or other diabetic eye disease.

Laser treatment. Laser treatment for diabetic eye disease was needed more often in participants with poor glycemic or blood pressure control than in those with good control of these factors. Laser treatment was also needed more often in those patients with a greater burden of clinical microvascular disease. The need for treatment, however, was not affected by plasma lipid concentrations. Patients assigned treatment with fenofibrate required first laser treatment for all retinopathy significantly less often than those in the placebo group (164 [3.4%] fenofibrate-assigned patients vs 238 [4.9%] placebo-assigned patients). The hazard ratio (HR) was 0.69, with a 95% confidence interval (CI), 0.56–0.84; $P=0.0002$, and there was an absolute risk reduction (RR) of 1.5% (0.7%–2.3%).

Detailed analysis of photographic substudy. In the ophthalmology substudy, the primary endpoint of a two-step progression of retinopathy grade was not significantly different between the treatment and the placebo groups overall (46 [9.6%] patients assigned fenofibrate vs 57 [12.3%] assigned placebo; $P=.19$) or in the cohort of patients who did not have preexisting diabetic retinopathy (43 [11.4%] vs 43 [11.7%]; $P=.87$). Among patients with preexisting retinopathy, however, significantly fewer who were assigned fenofibrate had a two-step progression than did those in the placebo group (three [3.1%] patients vs 14 [14.6%]; $P=.004$).

An additional, exploratory composite endpoint of two-step progression of retinopathy grade, macular edema, or laser treatments was significantly lower in the fenofibrate group versus placebo-assigned patients (HR, 0.66; 95% CI, 0.47–0.94; $P=.022$). Fenofibrate treatment among patients with type 2 diabetes reduced the need for laser treatment for diabetic eye disease. The mechanism by which this happens remains unclear, however, it does not appear to be related to plasma lipid concentrations.

effectiveness. Given that ACCORD has failed to show any significant benefit for tighter glycemic control, other means of reducing microvascular complications have become potentially more important.

RENAL IMPAIRMENT AND CARDIOVASCULAR RISK: A CLOSER LOOK

GFR. Measured glomerular filtration rate (GFR) is the best estimate of kidney function, according to the National Kidney Foundation (NKF),¹⁷ however, its use is not practical in routine clinical care. Estimated GFR (eGFR) is widely used as a surrogate, usually employing an equation from the Modification of

Diet in Renal Disease study. Studies reveal that even a modest reduction of eGFR can indicate nearly a doubled risk of cardiovascular events.¹⁸

Lowering risk. According to the American Diabetes Association's Position Statement,² in patients with type 1 diabetes, hypertension, and any degree of albuminuria, angiotensin-converting enzyme (ACE) inhibitors have been shown to delay the progression of nephropathy. In patients with type 2 diabetes, hypertension, and microalbuminuria, ACE inhibitors and angiotensin-receptor blockers (ARBs) have been shown to delay the progression to macroalbuminuria. In those patients with type 2 diabetes, hypertension, macroalbuminuria, and renal insufficiency, ARBs have been shown to

TABLE 3. CLINICAL AND LABORATORY EVIDENCE OF SAFETY OF FENOFIBRATE

	Placebo (n = 4,900)	Fenofibrate (n = 4,895)
Any serious adverse event*		
Death, other than cardiovascular causes	196 (4%)	216 (4%)
Cancer	148 (3%)	168 (3%)
Respiratory disease	16 (<1%)	19 (<1%)
Trauma	12 (<1%)	11 (<1%)
Other	20 (<1%)	18 (<1%)
Nonfatal events*	3,346 (68%)	3,361 (69%)
Gastrointestinal	927 (19%)	975 (20%)
Cardiac	807 (17%)	727 (15%)
Musculoskeletal	739 (15%)	755 (15%)
Tumor-related†	661 (14%)	643 (13%)
Genitourinary	568 (13%)	607 (12%)
Special senses‡	527 (11%)	499 (10%)
Vascular (noncardiac)	439 (9%)	418 (9%)
Respiratory	342 (7%)	384 (8%)
Newly diagnosed cancer	373 (8%)	393 (8%)
Colorectal	60 (1%)	67 (1%)
Prostate	59 (1%)	65 (1%)
Other gastrointestinal	49 (1%)	47 (1%)
Respiratory	41 (<1%)	45 (<1%)
Breast	38 (<1%)	37 (<1%)
Urinary	31 (<1%)	24 (<1%)
Clinically important events in <2% of patients*		
Deep-vein thrombosis	48 (1.0%)	67 (1.4%)
Pulmonary embolism	32 (0.7%)	53 (1.1%)
Pancreatitis	23 (0.5%)	40 (0.8%)
Myositis	1 (<1%)	2 (<1%)
Rhabdomyolysis	1 (<1%)	3 (<1%)
Renal disease needing dialysis	21 (<1%)	16 (<1%)
Laboratory variable measurements		
Raised alanine aminotransferase		
3–5 X upper limit of normal	26 (<1%)	11 (<1%)
>5X upper limit of normal	12 (<1%)	11 (<1%)
Raised creatine phosphokinase		
5–10X upper limit of normal	7 (<1%)	11 (<1%)
>10X upper limit of normal	3 (<1%)	4 (<1%)
Raised creatine		
>200 μmol/L	48 (1%)	73 (2%)
*Other than primary and secondary cardiovascular outcomes.		
†Includes invasive cancers, in situ cancers, nonmelanoma skin cancers, and benign tumors.		
‡Includes cataract and other eye and ear conditions.		
<i>Adapted from Lancet. 2005;366:1849–1861.</i>		

delay the progression of nephropathy. A recent study, however, failed to show any clinical benefit of combined ACE inhibitor and ARB therapy, and indeed increased adverse events were associated with the combination regimen.¹⁹

Randomized clinical trials have demonstrated a reduction of CHD events, stroke, and nephropathy by lowering blood pressure to <140 mm Hg systolic and <80 mm Hg diastolic in diabetic patients.²⁰ A target blood pressure goal of <130/80 mm Hg is reasonable if it can be safely achieved for most patients with diabetes. The recent ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicon MR Controlled Evaluation) study showed some further added benefit from reducing blood pressure <140/80 mm Hg.²¹ Lower targets are still advised in patients with nephropathy.

Lowering triglycerides and increasing HDL with a fibrate is associated with a reduction of cardiovascular events in patients with clinical CVD, low HDL, and near-normal LDL.

Lowering triglycerides and increasing HDL cholesterol with a fibrate is associated with a reduction in cardiovascular events in patients with clinical CVD, low HDL, and near-normal levels of LDL. Combination therapy using statins and other lipid-lowering agents may be necessary to achieve lipid targets but is still being evaluated in outcomes studies such as ACCORD.

The first priority of pharmacological therapy is to lower LDL cholesterol to a target goal of <2.60 mmol/L (100 mg/dL) or therapy to achieve a reduction in LDL of 30% to 40%, although different opinions are held about optimal targets.²² For LDL lowering, statins are the drugs of choice. Other drugs that lower LDL include nicotinic acid, ezetimibe—which acts by decreasing cholesterol absorption in the intestine—bile acid sequestrants, and fenofibrate.

Post hoc analysis of several clinical trials with fibrates suggests that they reduce risk for CHD events in patients with high triglyceride levels and low HDL levels, especially when the patients have diabetes or characteristics of metabolic syndrome.²³ Although the evidence supporting fibrate therapy is not as strong as that for statins, fibrates may have an

adjunct role in treating patients with high triglycerides/low HDL, especially in combination with statins. Concern about myopathy with this combination have diminished with the recent finding that fenofibrate does not interfere with catabolism of statins and does not substantially increase the risk for clinical myopathy in patients treated with moderate doses of statins.

SAFETY PROFILE OF FENOFIBRATE

Metabolism and Adverse Events, Creatinine, and Combination With Statins

Metabolism. Generally, fibrates are hepatically metabolized and renally excreted and require careful monitoring due to a reported increased risk of rhabdomyolysis. Fenofibrate is otherwise generally well tolerated, alone or in combination with other lipid-lowering drugs.

Adverse events. In FIELD, which included nearly 5,000 patients receiving the active drug, the safety profile of fenofibrate matched placebo over an average of 5-years follow-up (Table 3). Serious adverse events were reported in only 0.8% of patients assigned to fenofibrate therapy and 0.5% in the placebo group. Fenofibrate treatment was associated with a small increase in pulmonary embolism (1.1% compared with 0.7%, [$P=.022$]) and a marginal increase in deep venous thrombosis ($P=.074$). There was a small increase in pancreatitis (0.8% vs 0.5%, $P=.031$), a previously reported side effect.

Hepatic, muscle, and renal function. Fenofibrate was not associated with elevated levels of alanine aminotransferase or creatinine kinase, but creatinine levels >200 $\mu\text{mol/L}$ (2.2 mg/dL) were reported in 1.5% of fenofibrate patients compared with 1.0% of the placebo group. This appeared to be due to a systematic small increase of 10 to 12 $\mu\text{mol/L}$ (0.10–0.14 mg/dL) in plasma creatinine levels in the fenofibrate group, which was reversible after stopping the drug. The exact mechanism for the elevation of both serum urea and serum creatinine observed with fenofibrate is not known. It is important to note, however, that in the majority of patients, this effect reverses when the drug is withdrawn, and in most cases, patients return to baseline after discontinuation.²⁴

A crossover study found that fenofibrate was associated with short-term increases in serum/plasma creatinine concentrations but did not alter GFR by more than 20% in patients with normal kidney

TABLE 4. NKF DOSING MODIFICATIONS FOR FIBRATES IN CKD

Agent	GFR 60–90 mL/min/1.73 m ² (Stage 2 CKD)	GFR 15–59 mL/min/1.73 m ² (Stage 3 and 4 CKD)	GFR <15 mL/min/1.73 m ² (Stage 5 CKD)	Notes
Fenofibrate	Reduce to 50%	Reduce to 25%	Avoid	May increase serum creatinine
Gemfibrozil	No change	No change	No change	NLA recommends a dose of 600 mg/day in Stage 3 and 4 CKD and avoiding use in Stage 5 CKD

function.²⁵ In the study, conducted in 24 middle-aged patients with normal kidney function (estimated creatinine clearance of ≥ 80 mL/min), 160 mg/day of fenofibrate or placebo was administered for 6-week periods separated by a washout interval. Glomerular and tubular damage was evaluated with albumin and retinol-binding protein levels and N-acetyl-beta-d-glucosaminidase activity. Inulin clearance did not change after fenofibrate (0.8 mL/min; 95% CI, -10.5–12.2; $P=.09$). Para-aminohippurate clearance decreased (-33; 95% CI, -66 to -1; $P=.05$). Creatinine secretion and urinary creatinine excretion did not change.

Additionally, rat studies have shown that fenofibrate reduced glomerular size by 19% in Zucker diabetic fatty rats. This effect was seen without significant changes in glucose, insulin, or lipid levels, but the relevance to man is uncertain.²⁶

Further data regarding the effect of fenofibrate on long-term renal function in the FIELD study is expected to be published in the near future.

Combination with statins. Fenofibrate and gemfibrozil are the available fibrates in the United States. Although gemfibrozil is apparently less likely to cause a significant increase in serum creatinine levels, it is more likely to cause rhabdomyolysis when combined with a statin, due to a specific pharmacokinetic interaction.²⁷ Gemfibrozil raises the plasma concentration of statins by impairing their glucuronidation, whereas fenofibrate's effect on the glucuronidation of statins is minimal.²⁸

Recently conducted metabolic and pharmacokinetic drug-drug interaction studies using gemfibrozil or fenofibrate in combination with five commonly used statins demonstrated a widely different drug interaction potential for these two fibrates.²⁹ In this

investigation, gemfibrozil caused a two- to sixfold increase in statin area under the curve, and fenofibrate did not adversely affect either the metabolism or pharmacokinetics of the statins studied. This implies less potential for interactions with fenofibrate/statin combination therapy compared with gemfibrozil/statin coadministration. Gemfibrozil increases the plasma levels of all of the statins with the exception of fluvastatin, and this forms the suspected mechanism for an observed increase in rhabdomyolysis.³⁰

Another retrospective study collected data from the US Food and Drug Administration Adverse Event Reporting System database from January 1998 through March 2002 to evaluate myopathy rates reported for each drug when combined with a statin.³¹ There were 140 cases of rhabdomyolysis reported per million prescriptions dispensed of cerivastatin in combination with fenofibrate versus 4,600 cases reported per million prescriptions dispensed for cerivastatin in combination with gemfibrozil. Fenofibrate resulted in a 33 times lower rhabdomyolysis reporting rate than did gemfibrozil.

NATIONAL KIDNEY FOUNDATION AND THE NATIONAL LIPID ASSOCIATION GUIDELINES

Based in part on the evidence outlined here, the National Kidney Foundation (NKF) and the National Lipid Association (NLA) issued recommendations for caution in using fibrates in patients with CKD.³² It does, however, appear that the NKF guidelines from 2003 are probably now outdated, in light of more recent data and experience, and these recommendations can no longer be considered evidence based.

TABLE 5. JOINT NATIONAL COMMITTEE VII BLOOD PRESSURE STAGING

Category	Systolic Blood Pressure mm Hg	Diastolic Blood Pressure mm Hg
Normal	<120	<80
Prehypertension	120–139	80–89
Hypertension, stage 1	140–159	90–99
Hypertension, stage 2	≥160	≥100

• Treat to <140/90 mm Hg or <130/80 mm Hg in patients with diabetes or chronic kidney disease.*

• The majority of patients will require at least two medications to reach goal.

* *The 2008 American Diabetes Association Standard of Medical Care in Diabetes states that patients with diabetes should be treated to a goal of systolic blood pressure of <130 mm Hg and a diastolic blood pressure of <80 mm Hg.*

The NKF recommends that in patients with GFR 60 to 90 mL/min/1.73 m², fenofibrate dosing should be reduced by 50%, among those with GFR 15 to 59 mL/min/1.73 m² reduce dosing by 75%, and fenofibrate use should be avoided in those on hemodialysis or with GFR <15 mL/min/1.73 m². NKF guidelines designate gemfibrozil as the fibrate of choice in patients with CKD, and no dose adjustments are required for reduction in GFR (Table 4)

NLA guidelines³³ for fenofibrate use are similar to NKF guidelines. The recommended dose of gemfibrozil in CKD patients with GFR <60 mL/min/1.73 m² is 600 mg/day (50% reduction). It is recommended to avoid all fibrates for GFR <15 mL/min/1.73 m². In addition, the NLA recommends measuring serum creatinine levels before starting fibrate therapy, as indeed is essential in any patient starting cardiovascular protective therapy. Apart from safety issues, the presence of even mild renal impairment indicates a higher cardiovascular event rate and mortality in both the general population and in those with diabetes and/or hypertension.

Patients with CKD, particularly with diabetes or metabolic syndrome, frequently have a mixed dyslipidemia, and fibrates make an attractive choice as an adjunct to statin therapy for these high-risk patients. Although NKF guidelines state a preference for gemfibrozil, regarding the currently available evidence, fenofibrate is the preferred option to combine with a statin. Both statins and fenofibrate, however, are independently associated with an increased risk of myopathy, and therefore, there is increased

risk of myopathy and rhabdomyolysis when these drugs are combined. Recent data suggest this is not a frequent occurrence; for example, in FIELD, there were two cases of myositis and three of rhabdomyolysis in fenofibrate-assigned patients versus one of myositis and one of rhabdomyolysis in placebo (Table 3). For optimal safety in fibrate-statin combination treatment, the NLA also recommends not using the maximum dose of a statin in combination therapy.

QUALITY OF LIFE

A study of people with diabetes showed that microvascular complications have more of an adverse impact than macrovascular complications on patients' self-reported health-related quality of life (QOL).³⁴ QOL is an important measure of how disease affects patients' lives. This UK study conducted a mail survey of 1,578 type 2 diabetics at four centers and compared them to the general population and people with diabetes in the 1996 Health Survey of England. The results showed a significant deficit in those with diabetes when compared with age-matched peers who did not have diabetes.

Dialysis patients certainly have decreased QOL relative to their healthy counterparts, however, little is known about QOL in patients with CKD before renal replacement therapy.³⁵ An investigation used the Medical Outcomes Study Short Form-36 (SF-36) (a standard QOL instrument) to evaluate 634 patients (mean GFR, 23.6 ±9.6 mL/min/1.73 m²)

enrolled in an observational study of CKD. SF-36 scores were compared with those found in a prevalent cohort of hemodialysis patients and in healthy controls. The patients with CKD had higher SF-36 scores than a large cohort of hemodialysis patients ($P < .0001$) but lower scores than those reported for the US adult population ($P < .0001$).

SUMMARY AND RECOMMENDATIONS FOR TREATMENT

It is important to consider the potential cardioprotective effects of fenofibrate in the context of the rising rates of ESRD and its growing burden on the health care system—any added benefit in protecting the kidney or the retina would be a bonus. The rate of incidence of ESRD in the United States is 336 per 1 million people:³⁶ when broken down by race, the rate is 256 per million in whites compared with 982 per million in blacks.³⁷ The estimated costs of this treatment could reach \$29 billion. Again, these statistics are mirrored in Europe, and indeed, worldwide—especially in non-European populations.

Primary prevention of diabetic microvascular complications, (nephropathy, retinopathy, and neuropathy) in both type 1 and type 2 diabetes is best achieved by good glycemic control from the time of diagnosis³⁸⁻⁴⁰ and for macrovascular disease weight loss in the obese, exercise, and cessation/avoidance of smoking with active treatment of raised blood pressure, so frequently present in type 2 diabetes, are vital.

Early detection of renal disease is essential to allow health care providers to initiate earlier treatment in these patients.

Early detection of renal disease is essential to allow health care providers to initiate earlier treatment in these patients. Early aggressive blood pressure treatment with appropriate agents and targets (Table 5) can slow the progression of kidney disease and, in many patients, potentially prevent the eventual outcome of kidney failure. Microalbuminuria

(one definition is persistent albuminuria of 30–299 mg/24 hr) is the earliest marker of diabetic nephropathy and, even at that stage, is associated with increased blood pressure.⁴¹ There is evidence that renal function may be abnormal in many patients without albuminuria.⁴² Microalbuminuria has long been known to be a marker of potential diabetic nephropathy and increased cardiovascular risk in type 1 diabetes; those with microalbuminuria who progress to macroalbuminuria (≥ 300 mg/24 hr) are likely to continue to progress to ESRD.

With increasing age and diabetes duration and the presence of any microvascular complication in either type 1 or type 2 diabetes, comes an increased risk of CVD. The role of statins here is unequivocal, as shown by the HPS (Heart Protection Study)⁴³ and numerous other trials.

It appears as though fenofibrate, in combination with statins, may potentially have the capacity to reduce further the risk of some cardiovascular events and has now shown early signs of having a beneficial effect on the progression of microvascular disease. The adjunctive use of fibrates has been shown to be effective, and future guidelines may assist physicians in deciding when and how to best use them.⁴⁴

CONCLUSION

The potential benefits of fibrates in patients with diabetes appear to extend with these new specific effects seen with fenofibrate. It is a well-tolerated medication that can be successfully used in combination with statins, potentially to help patients with diabetes from progressing into macro- or microvascular events, particularly those that involve albuminuria or macular edema. Additional research is ongoing to further elucidate the role fenofibrate may have in the treatment of diabetes patients. Renal damage is essentially irreversible, and prevention is the single most effective way to address the devastating effects of ESRD, as well as vision loss and amputations. It appears that previous safety concerns regarding the use of fenofibrate in mild-to-moderate renal impairment and in combination with statins, may have been overstated. Further data are expected soon. ■

1. International Diabetes Federation. Available at <http://www.idf.org/home/index.cfm?unode=3B96906B-C026-2FD3-87B73F80BC22682A>. Accessed August 1, 2008.
2. American Diabetes Association: Standards of medical care in diabetes-2006 (Position Statement) *Diabetes Care*. 2006;29 (Suppl.1):S4–42.
3. National Kidney Foundation. Available at www.kidney.org. Accessed August 1, 2008.
4. Kidney Disease Research Updates. National Kidney and Urologic Diseases Information Clearinghouse NIH Publication No. 06–4531. July 2006.
5. World Health Organization. Available at <http://www.who.int/diabetes/facts/en/index.html>. Accessed August 1, 2008.
6. Centers for Disease Control and Prevention. Available at <http://www.cdc.gov/diabetes/statistics/esrd/fig1.htm>. Accessed August 1, 2008.
7. National Institutes of Health Fact Sheet on Chronic Kidney Disease and Kidney Failure. Available at <http://www.nih.gov/about/researchresultsforthepublic/kidney.pdf>. Accessed August 1, 2008.
8. CDC. (2000) 1997 National Health Interview Survey (NHIS) public use data release: NHIS survey description. Hyattsville, MD: US Department of Health and Human Services. CDC Available at ftp://ftp.cdc.gov/pub/health_statistics/nchs/dataset_documentation/nhis/1997/srvydesc.pdf. Accessed August 1, 2008.
9. Burrows NR, Wang J, Geiss LS, et al. Div of Diabetes Translation, National Center for Chronic Disease Prevention and Health Promotion. Morbidity and Mortality Weekly Report (Centers for Disease Control and Prevention, Atlanta, GA). 2005;54:1097–1100.
10. Friedman EA, Friedman AL. Is there really good news about pandemic diabetic nephropathy? *Nephrol Dial Transplant*. 2007;22:681–683.
11. Forcheron F, Cachefo A. Mechanisms of the triglyceride- and cholesterol-lowering effect of fenofibrate in hyperlipidemic type 2 diabetic patients. *Diabetes*. 2002;51:3486–3491.
12. FIELD Study Investigators. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes. *Lancet*. 2005;366:1849–1861.
13. Kazumi T, Hirano T. Effects of fenofibrate on albuminuria in patients with hypertriglyceridemia and/or hyperuricemia: a multicenter, randomized, double-blind, placebo-controlled, crossover study. *Current Therapeutic Research*. 2003;64:434–446.
14. Diabetes Atherosclerosis Intervention Study Investigators. Effect of fenofibrate on progression of coronary-artery disease in type 2 diabetes: the Diabetes Atherosclerosis Intervention Study, a randomised study. *Lancet*. 2001;357:905–910.
15. Keech AC, Mitchell P, Summanen PA, et al for the FIELD investigators. Effect of fenofibrate on the need for laser treatment for diabetic retinopathy (FIELD study): a randomised controlled trial. *Lancet*. 2007;370:1687–1697.
16. The Action to Control Cardiovascular Risk in Diabetes Study Group. Effects of glucose lowering in type 2 diabetes. *N Engl J Med*. 2008;358:2545–2559.
17. National Kidney Foundation. Available at www.kidney.org. Accessed August 1, 2008.
18. So WY, Kong APS, Ma RCW, et al. Glomerular filtration rate, cardiorenal end points, and all-cause mortality in type 2 diabetic patients. *Diabetes Care*. 2006;29:2046–2052.
19. Mann JFE, Schmieder RE, McQueen M, et al. Renal outcomes with telmisartan, ramipril, or both, in people at high vascular risk (the ONTARGET study): a multicentre, randomised, double-blind, controlled trial. *Lancet*. 2008;372:547–553.
20. UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. *Br Med J*. 1998;317:703–713.
21. Patel A, ADVANCE Collaborative Group, MacMahon S, et al. Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): a randomised controlled trial. *Lancet*. 2007;370:829–840.
22. Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA*. 2001;285:2486–2497.
23. Prueksaritanont T, Tang C, Qiu Y, Mu L, Subramanian R, Lin JH. Effects of fibrates on metabolism of statins in human hepatocytes. *Drug Metab Dispos*. 2002;30:1280–1287.
24. United States Department of Veterans Affairs. Available at <http://www.pbm.va.gov/safety%20reports/87ry38statin-fibrate-final.pdf>. Accessed August 1, 2008.
25. Ansquer JC, Dalton RN. Effect of fenofibrate on kidney function: a 6-week randomized crossover trial in healthy people. *Am J Kidney Dis*. 2008;51:904–13.
26. Zhao X, Li L. PPAR-Alpha Agonist Fenofibrate Induces Renal CYP Enzymes and Reduces Blood Pressure and Glomerular Hypertrophy in Zucker Diabetic Fatty Rats. *Am J Nephrol*. 2008;28:598–606.
27. Davidson MH, Armani A, McKenney JM, Jacobson TA. Safety considerations with fibrate therapy. *Am J Cardiol*. 2007;99:3C–18C.
28. Prueksaritanont T, Tang C, Qiu Y, et al. Effects of fibrates on metabolism of statins in human hepatocytes. *Drug Metab Dispos*. 2002;30:1280–1287.
29. Davidson MH. Statin/fibrate combination in patients with metabolic syndrome or diabetes: evaluating the risks of pharmacokinetic drug interactions. *Expert Opin Drug Saf*. 2006;5:145–156.
30. Jacobson TA, Zimmerman FH. Fibrates in combination with statins in the management of dyslipidemia. *J Clin Hypertens*. 2006;8:35–41.
31. Jones PH, Davidson MH. Reporting rate of rhabdomyolysis with fenofibrate + statin versus gemfibrozil + any statin. *Am J Cardiol*. 2005;95:120–122.
32. K/DOQI clinical practice guidelines for managing dyslipidemia in chronic kidney disease. *Am J Kidney Dis*. 2003;41(Suppl)3:S1–S27.
33. National Lipid Association. Available at lipid.org. Accessed August 1, 2008.
34. Holmes J, McGill S. Health-related quality of life in type 2 diabetes (TARDIS-2). *Value Health*. 2000;3(suppl 1):47–51.
35. Perlman RL, Finkelstein FO, Liu L, et al. Quality of life in chronic kidney disease (CKD): A cross-sectional analysis in the Renal Research Institute-CKD study. *Am J Kidney Disease*. 2005;45:658–666.
36. Hamer RA, El Nahas A. The burden of chronic kidney disease is rising rapidly worldwide. *Br Med J*. 2006;332:563–564.
37. United States Renal Data System (USRDS). 2004 annual report. *Am J Kidney Dis*. 2005;45(suppl 1).
38. The DCCT Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *New Engl J Med*. 1993;329: 977–986.
39. UK Prospective Diabetes Study Group: Intensive blood-glucose control with sulphonylurea or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet*. 1998;352:837–853.
40. Shichiri M, Kishikawa H, Ohkubo Y, Wake N. Long-term results of the Kumamoto Study on optimal diabetes control in type 2 diabetic patients. *Diabetes Care*. 2000;23: (Suppl. 2):B21–B29.
41. Ansquer JC, Foucher C. Fenofibrate reduces progression to microalbuminuria over 3 years in a placebo-controlled study in type 2 diabetes: results from the Diabetes Atherosclerosis Intervention Study (DAIS). *Am J Kidney Dis*. 2005;45:485–93.
42. MacIsaac RJ, Tsalamandris C, Panagiotopoulos S et al. Nonalbuminuric renal insufficiency in type 2 diabetes. *Diabetes Care* 27:195–200, 2004
43. Heart Protection Study Collaborative Group (2002). MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: A randomised placebo-controlled trial. *Lancet* 2002; 360:7–22.
44. Harper CR, Jacobson TA. Managing Dyslipidemia in Chronic Kidney disease. *J Am Coll Cardiol*. 51:2375–84, 2008.

INSTRUCTIONS FOR CME CREDIT

1 AMA PRA Category 1 Credit™

Expires September 2009

CME credit is available electronically via www.dulaneyfoundation.org.

To answer these questions online and receive real-time results, please visit www.dulaneyfoundation.org and click "Online Courses." If you are experiencing problems with the online test, please e-mail us at support@dulaneyfoundation.org and explain the details of any problems you encounter with the Web site. Alternatively, you can fax your exam to us at +1 610 771 4443. Indicate how you would like to receive your certificate below. Please print clearly or else we will be unable to issue your certificate.

Name _____ MD participant__ non-MD participant__

Phone (required) _____

I would like my certificate sent via fax _____

I would like my certificate sent via e-mail _____

CME QUESTIONS

1. Fibrates:

- (a) Primarily decrease LDL cholesterol
- (b) Primarily increase HDL cholesterol
- (c) Primarily decrease triglycerides and increase HDL
- (d) Primarily decrease triglycerides and LDL

2. Fenofibrate treatment in FIELD was associated with:

- (a) Less albuminuria progression
- (b) A reduction in nonfatal MI
- (c) Less diabetic retinopathy progression
- (d) All of the above

3. Fenofibrate's effect in FIELD suggest a beneficial impact that can most likely be explained by:

- (a) Changes in A1C level
- (b) Changes in blood pressure
- (c) Changes in lipid profile
- (d) Another mechanism is in effect
- (e) A combination of (a), (b), and (c)

4. According to the 2008 ADA *Standard of Medical Care of Diabetes*, goal blood pressure for diabetes patients is:

- (a) <140/90 mm Hg
- (b) <130/80 mm Hg
- (c) <120/90 mm Hg
- (d) <120/80 mm Hg

5. Fenofibrate interferes with the catabolism of statins and substantially increases the risk for clinical myopathy in patients treated with moderate-dose statins.

- (a) True
- (b) False

6. Which combination has LESS potential for interactions, according to the evidence?

- (a) Gemfibrozil/statin coadministration
- (b) Fenofibrate/statin combination therapy

7. The recommendations for caution in using fibrates in patients with CKD:

- (a) Are accurate according to the most recent evidence available.
- (b) Should be strengthened based on the available data.
- (c) Are probably now outdated, in light of more recent data and experience.

8. Which of the following statements is FALSE according to the activity?

- (a) The National Kidney Foundation guidelines state a preference for the combination of gemfibrozil and statins in CKD patients with diabetes.
- (b) Currently available evidence reveals that fenofibrate is the preferred option to combine with a statin.
- (c) The National Kidney Foundation guidelines state a preference for the combination of fenofibrate and statins in CKD patients with diabetes.
- (d) All of the above

9. For optimal safety in fibrate-statin combination treatment, the National Lipid Association recommends not using the maximum dose.

- (a) True
- (b) False

