STATIN-FIBRATE REPORT: Focus on Safety
VHA Pharmacy Benefits Management-Strategic Healthcare Group and The Medical Advisory Panel

Executive Summary: (Key Questions)

Efficacy

a. Is there evidence to demonstrate an advantage with regard to reducing coronary health outcomes in patients receiving a combination of statins plus fibrates compared to statins alone (e.g. especially in patients with TG in the 300 range-metabolic syndrome) to justify the risk of the combination?

At this time, there is a lack of evidence to support a reduction in coronary health outcomes with the statin-fibrate combination. The LDS study would have helped answer this question but was stopped due to withdrawal of cerivastatin from the market. The ACCORD study will have in excess of 5000 patients with type 2 diabetes on the combination of fenofibrate plus simvastatin vs. simvastatin alone. The primary outcome measures in this trial will include nonfatal myocardial infarction and nonfatal stroke, cardiovascular death and overall mortality. However, data from ACCORD will not be available until 2008 or 2009.

b. Which fibrates (e.g. fenofibrate or gemfibrozil) have evidence to support their benefit in reducing coronary heart disease health outcomes when used as monotherapy?

To summarize, when evaluated in primary prevention (WHO study), clofibrate was associated with a reduction in the risk for nonfatal MI. However, an excess in total mortality was also observed in the clofibrate group compared to placebo. This increase was attributed to deaths from diseases of the liver, intestines and gallbladder. In secondary prevention (CDP study), clofibrate was not significantly different from placebo with regard to reducing coronary heart disease (CHD) events. In both primary and secondary prevention, treatment with gemfibrozil in patients with low HDL-C and mildly elevated triglyceride levels ($\leq$300 mg/dL) was shown to reduce the risk for CHD events in HHS and VA-HIT studies. In the BIP study, bezafibrate produced beneficial changes in lipoprotein values, however, was not found to reduce coronary events. In a post hoc analysis, the subgroup of patients whose triglycerides exceeded 200 mg/dL experienced a significant reduction in nonfatal MI. In the LEADER trial, bezafibrate was associated with a reduction in nonfatal MI versus placebo in those patients aged less than 65 years. In the DAIS trial, treatment with fenofibrate was associated with a statistically significant reduction in angiographic progession compared to placebo. This study did not show a difference in clinical cardiac events but the study was not powered to do so. Although the data are not yet available, the FIELD study has been designed to examine if treatment with fenofibrate in patients with type 2 diabetes will result in a reduction in coronary events. The results of this trial are expected in 2005.

c. Are there differences between the fibrates on the lipid profile (e.g. HDL-C, Triglycerides, LDL-C, etc.) or other surrogate markers (ApoB, homocysteine, etc.) of coronary heart disease?

a) In crossover studies, published in full, HDL-C elevation, LDL-C and TG lowering were not statistically different between fibrates in most cases.
b) Although the clinical significance of any of these differences is not known, only those non-lipid parameters that differed between fibrates were included in detail. Homocysteine: In a systematic review of the effect of fibrates on homocysteine, fenofibrate was associated with a 30-40% increase in homocysteine and gemfibrozil did not raise homocysteine levels. However, in another prospective study with gemfibrozil, homocysteine increased by a median of 18%.

Fibrinogen: Fenofibrate reduces fibrinogen while gemfibrozil has an inconsistent effect.
Serum Creatinine: Elevation for fenofibrate and no change for gemfibrozil. The majority of patients had a reversal of the rise in creatinine with drug withdrawal.

Safety

a. Is there a difference in the risk of serious adverse events (e.g. rhabdomyolysis) between fibrates (e.g. gemfibrozil or fenofibrate) when used as monotherapy?

To summarize, data from large controlled trials, head to head fibrate trials, manufacturers prescribing information or other data do not support a difference in the rate of serious adverse events between gemfibrozil and fenofibrate when used as monotherapy for dyslipidemia.

b. Is there a difference in the risk of serious adverse events (e.g. rhabdomyolysis) between fibrates (e.g. gemfibrozil, fenofibrate) when combined with statins?

- What are the manufacturers (fibrates and statins) recommendations for combining statins and fibrates?

In general, the statin manufacturers discourage the combining of statins with fibrates unless the lipid-lowering benefit achieved outweighs the increased risk. Dose limits are recommended for simvastatin and rosuvastatin when combined with gemfibrozil. A dose limit is recommended for lovastatin when combined with "fibrates". Although not specified in the product labeling, atorvastatin should also be used at the lowest possible dose when combined with a fibrate. For 4 of the 6 available statins (fluvastatin, pravastatin, rosuvastatin and simvastatin), gemfibrozil is specified with no mention of fenofibrate.

- Review the controlled trials combining any fibrate with any statin and focus on the safety of the combinations in these trials.

a) In 2 systematic reviews, evaluating statin-fibrate combinations, there were no reported cases of rhabdomyolysis or renal failure. Many of the trials excluded patients predisposed to serious adverse events with the combination, had small sample sizes and were conducted in a controlled clinical trial setting.
b) Voluntary reporting of adverse events cannot be used to compare incidence rates between fibrates since many factors contribute to over or under reporting of events and the number of exposed individuals is not known.
c) From these data, we are unable to determine if combination with statin-fenofibrate is safer than statin-gemfibrozil. The best evidence to answer this question would be from a prospective head to head trial combining statin-gemfibrozil to statin-fenofibrate in a large number of individuals.

- Within the VA, using VA administrative databases, to determine if there are differences in the incidence rates of rhabdomyolysis or acute tubular necrosis (ATN) between different statin-fibrate combinations.

Using VA administrative data, there were 93,677 patients that received combination therapy with statins and gemfibrozil between September 2001 and October 2003 and only 1,830 patients that received fenofibrate with a statin during the evaluation period. As a result, it is possible that our data do not represent sufficient exposure of fenofibrate combined with statins to make any firm conclusions regarding differences in safety between fibrates. However during the two years evaluated, the overall rate of rhabdomyolysis or ATN was 0.16% in these patients (gemfibrozil-statin). There were no cases of rhabdomyolysis or ATN in 1,830 patients on

fenofibrate with any statin. Using the VA data, the rates of rhabdomyolysis or ATN were small and appeared to be dose-related.

c. If a difference in safety between fibrates combined with statins does exist, what is the mechanism(s) for the increased risk for muscle toxicity?

To summarize, the pharmacokinetic fate of 5 of the 6 available statins has been examined in combination with gemfibrozil in healthy patients. In 4 of the 5 studies, gemfibrozil significantly increased the AUC and Cmax of the respective statin (lovastatin, simvastatin pravastatin and rosuvastatin). In the fifth pharmacokinetic study, combination with gemfibrozil did not alter AUC or Cmax of fluvastatin. Although half-life was not reported in all studies, the half-life of pravastatin was not prolonged when combined with gemfibrozil. As for fenofibrates' effect on the pharmacokinetics of statins, data are only available when combined with pravastatin and rosuvastatin for a small increase in AUC and Cmax. There are several theories explaining the increased risk of muscle toxicity when statins and fibrates are combined. These include additive effects of statins and fibrates on skeletal muscle resulting in the increased risk, displaced protein binding (all statins are highly protein bound), and finally, inhibition of a recently recognized mode of statin metabolism via glucuronidation. Gemfibrozil and fenofibrate both undergo glucuronide-mediated metabolism. In two in-vitro studies using human and dog hepatocytes, the glucuronide mediated-metabolism of atorvastatin acid, simvastatin acid, cerivastatin acid and rosuvastatin acid were all inhibited by gemfibrozil. The effect of fenofibrate on statin metabolism was only examined for simvastatin. Fenofibrate reportedly did not significantly alter the metabolism of the simvastatin via oxidative or glucuronidation mediated metabolism.

d. Is there a difference in the risk of serious adverse events with individual statins (e.g. atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin or simvastatin) when combined with gemfibrozil or fenofibrate?

- Within the VA, using VA administrative databases, to determine if there are differences in the incidence rates of rhabdomyolysis or acute tubular necrosis (ATN) between different statin-fibrate combinations.

Data from the VA query of new cases of rhabdomyolysis or ATN, occurring with the statin-fibrate combination over a two year period, demonstrated that as the dose of a particular statin increased (e.g. atorvastatin, lovastatin and simvastatin), so did the risk of an adverse event. However, the overall risk appears to be relatively low with the highest rates of rhabdomyolysis being reported in those patients receiving more than 40 mg daily of either atorvastatin or simvastatin. Because of the nature of adverse effect reporting and the available evidence, the answer to the question of whether one statin is safer than the other with regard to combination therapy with a fibrate is unknown. However, a theoretical advantage of combining fluvastatin with gemfibrozil is that gemfibrozil does not significantly alter serum concentrations of fluvastatin. Also, combination of fenofibrate with pravastatin or rosuvastatin did not appreciably alter statin pharmacokinetics. Furthermore, limiting statin doses may also lessen the risk of serious muscle toxicity with the combinations. Due to the insufficient exposure of fenofibrate with any statin in the VA, it is difficult to make firm conclusions on differences in safety between fibrates.

MAP Recommendations and Conclusions

a) From the available published evidence and VA administrative data, no firm conclusions can be drawn between differences in serious adverse events between gemfibrozil and fenofibrate when combined with statins.
b) Since there is a lack of health outcome evidence to support using the statin-fibrate combination but there is a known increased risk of serious muscle toxicity, the combination cannot be routinely recommended. However, although there are no data to support a "treatment" triglyceride level in which patients would obtain the most benefit, several authors have recommended the statin-fibrate combination be considered in a patient with mixed dyslipidemia (LDL-C >100 mg/dl, HDL-C<40 mg/dl and/or TG in excess of 500 mg/dl) at high risk for CHD events. While patients with triglyceride levels >500 mg/dL were not enrolled in outcome studies of fibrates (e.g. VA-HIT), the risk of pancreatitis may be increased in these patients. In addition, while NCEP ATP III recognizes the combination in patients with elevated LDL-C and atherogenic dyslipidemia, they do state that objective data are not available to support their recommendation. NCEP ATP III and other experts also recommend the combination be considered only if the patient has normal liver, renal and thyroid function. Furthermore, the combination should be avoided in patients receiving known potent CYP 3A4 inhibiting medications (e.g. macrolides, azole antifungals, protease inhibitors, cyclosporine, etc.) or other medications known to alter statin metabolism.
c) Prior to adding a fibrate to statin therapy, consideration should be given to other available less toxic options such as n-3 polyunsaturated fatty acids (n3 PUFAs, a.k.a. fish oils) or niacin combined with statins. Triglyceride reduction is in the range of 20-30% with fish oils and 20-50% with niacin. In addition, niacin can increase HDL-C by 15-35%. However, like the statin-fibrate combination, there is a lack of health outcome evidence demonstrating a greater benefit of these combinations versus a statin alone. If the statin-fibrate combination is selected, the lowest effective statin dose should be used when combined with gemfibrozil or fenofibrate.
d) Providers choosing to prescribe statin-fibrate therapy, regardless of specific statin or fibrate used, should discuss the risks and benefits of such therapy with their patient. This discussion should be clearly documented in the patient's medical record. Patients should be educated to report any unexplained muscle pain, tenderness or weakness to their providers immediately.
e) When a statin-fibrate combination is used, NCEP ATP III recommends a baseline creatine kinase (CK) level prior to initiation of combination therapy. Measurement of CK is repeated if the patient reports muscle symptoms resembling myopathy. NCEP ATP III recommends discontinuing combination therapy (both statin and fibrate) if CK is greater than 10 times the upper limit of normal associated with muscle symptoms (tenderness, pain or weakness). Then, wait for symptoms to resolve completely and CK to normalize prior to restarting either drug and begin with a lower dose of the drug (s).

Background

Coronary heart disease (CHD) continues to be the leading cause of mortality and a significant cause of morbidity among Americans. In 2001, CHD claimed 669,000 lives, translating into about 1 out of every 5 deaths in the United States.[1] Elevated cholesterol, or hypercholesterolemia, is an important risk factor for CHD. The 3-hydroxy-3-methylglutaryl-coenzyme (HMG-CoA) reductase inhibitors, also known as statins, are an important component of care in the management of hypercholesterolemia because of their effectiveness in reducing low-density lipoprotein (LDL-C), their safety and tolerability, and because of their demonstrated ability to reduce cardiovascular morbidity and mortality in clinical trials.[2-8, 80] Data also exist for niacin and gemfibrozil demonstrating a reduction in coronary events.[9-11] However, there are no published clinical trials examining the effect of combination therapy with fibrates and statins on reducing CHD outcomes and only small studies observing a benefit with statins and niacin.[12]

The Lipids in Diabetes Study (LDS) was designed to compare cerivastatin and fenofibrate for primary prevention in 5000 diabetic subjects followed for 5 years. Additionally, 1,250 of those subjects would have been on both ceriviastatin and fenofibrate. However, this trial was stopped due to the withdrawal of cerivastatin in August 2001 and as a result no outcomes were reported.[13]

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) is a large trial with plans to enroll 10,000 type 2 diabetics to determine the effects of aggressive versus standard glycemic control and blood

pressure or blood lipid control on cardiovascular risk in diabetics in the presence of good glycemic control. The lipids portion of the trial will include 5,800 patients and will compare the cardiovascular risk of a statin plus a fibrate (fenofibrate plus simvastatin) versus a statin alone (simvastatin). Participants will be followed for 5.5-8.5 years with the study concluding in June 2009.[14]

Despite the lack of health outcome data with combination therapy, the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III recognizes use of these combinations in high-risk patients with mixed dyslipidemias including those with "metabolic syndrome". Metabolic syndrome is described as a group of specific risk factors occurring in an individual. NCEP ATP III has proposed a specific definition for the metabolic syndrome and identification of these individuals is dependent upon a person having three or more of the following factors: abdominal obesity, atherogenic dyslipidemia (e.g. elevated triglycerides and low HDL-C), elevated blood pressure, and insulin resistance or glucose intolerance.[15]

Many experts believe that the lipid-lowering benefit of combining a statin with a fibrate or niacin outweighs the risk in patients with mixed dyslipidemia at high risk for coronary events. However, risk for muscle toxicity with combination therapy is greater than that for either statins or fibrates alone[52] and should therefore be used with caution. Certain factors can also increase an individual's risk for muscle toxicity with the combination including drug-drug interactions, advanced age, impaired renal function, female gender, alcoholism and hypothyroidism. The benefit to risk ratio in the case of combination therapy with statins and fibrates is difficult to determine since the benefit of the combination has not been fully elucidated.

This document will focus on published evidence to determine if there are differences with regard to efficacy and safety between the available fibrates, gemfibrozil and fenofibrate, when combined with statins.

Fibrates: Efficacy

Coronary Heart Disease Risk Reduction

Although there is evidence to support a reduction in CHD events with gemfibrozil, it is not clear whether all fibrates possess a similar cardioprotective effect.

Clofibrate

Primary Prevention

In the World Health Organization (WHO) Cooperative Trial, 15,745 males without coronary artery disease were enrolled and followed for a mean of 5.3 years.[81] Serum cholesterol was measured in 30,000 volunteers and 10,000 of those patients, in the upper third distribution of serum cholesterol concentrations, were randomized to receive clofibrate 1.6 grams daily (group I) or placebo (Group II). A third group was used as a second control (Group III) and included 5,000 men in the lowest distribution of serum cholesterol. The primary endpoint was the incidence of major ischemic heart disease (IHD) events (including fatal and nonfatal MI) and overall mortality. The incidence of major IHD events occurred significantly less often in the clofibrate group vs. placebo (RRR 20%, 5.9 events/1000/year vs. 7.4 events/1000/year, $p<0.05$). However, the difference was confined to a reduction in nonfatal MI. Death due to cardiac causes was not different between groups. Overall mortality was higher in the clofibrate group vs. placebo (162 events in Group I vs. 127 events in Group II, $p<0.05$). The increased incidence of death in the clofibrate group was attributed to diseases of the liver, intestines and gallbladder and not due to an increased rate of death from IHD. Group III (low serum cholesterol control) was associated with a significantly lower risk of IHD events vs. either Group I or II. The authors concluded that because of the possibility for serious adverse events with clofibrate, aside from a potential reduction in IHD, that only those patients with the highest risk for IHD and the highest cholesterol levels be considered candidates.

Secondary Prevention

In the Coronary Drug Project (CDP), 8,341 men having one or more myocardial infarctions were randomized to 1 of 6 treatment groups.[82] Three of those treatment groups were stopped early due to increased events (e.g. nonfatal MI, death, thromboembolism and cancer) compared to placebo. These

included both estrogen groups and the dextrothyroxine group. The remaining 3 groups included clofibrate 1.8 grams daily, niacin 3 grams daily and placebo. The primary endpoint was total mortality. Secondary endpoints included cardiac and noncardiac mortality and nonfatal events (e.g. MI, angina, CHF, stroke, pulmonary embolism and arrhythmias). The trial had a planned follow up of 5 years but actual follow up ranged from 5-8.5 years. For overall mortality, there was no significant difference between clofibrate and placebo (20% vs. 20.9 %, respectively, no statistics provided). There was also no difference between clofibrate and placebo in definite nonfatal MI or cardiac death combined with nonfatal MI (p-values not provided). Although there was no difference in total mortality in the niacin vs. placebo groups, there was a significantly lower risk for nonfatal MI in favor of niacin vs. placebo.

Gemfibrozil

Primary Prevention

In the Helsinki Heart Study (HHS)[10], 4,081 asymptomatic men with primary dyslipidemia were randomized to receive gemfibrozil 600 mg twice daily or placebo for 5 years. The primary outcome was a reduction in the risk for cardiac outcomes (fatal and nonfatal myocardial infarction and cardiac death). At 5 years, the cumulative rate of cardiac outcomes was 27.3 per 1,000 patients in the gemfibrozil group versus 41.4 per 1,000 patients in the placebo group (RRR 34%, 95% CI 8.2-52.6, $p<0.02$). The authors concluded that the reduction in cardiac events seen with gemfibrozil was in proportion to reductions seen in prior trials with other pharmacologic agents (e.g. Resins and Niacin).

Secondary Prevention

A sub study of the Helsinki Heart Study was conducted in males excluded from the primary prevention cohort due to a history of myocardial infarction, angina or prior ECG changes. There were 628 subjects enrolled in the secondary prevention component of the study who received either gemfibrozil or placebo for 5 years. The primary outcome in this study was cardiac events (combined fatal and non-fatal MI and sudden cardiac death). There was no difference in the primary endpoint between gemfibrozil and placebo ($p=0.14$, 95% CI 0.88-2.48). The authors concluded that because of missing key prognostic factors (e.g. extent of coronary artery obstruction, degree of left ventricular dysfunction, true prevalence of CHD, etc.) the results are considered to be less conclusive.[16]

In the Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial (VA-HIT),[11] 2,531 men with CHD, low HDL-C ($\leq$40 mg/dL) and moderately elevated LDL-C ($\leq$140 mg/dL), were randomized to receive gemfibrozil 600 mg twice daily or placebo for 5 years. Participants were included if their triglyceride level was $\leq$300 mg/dL or 3.38 mmol/L. The primary outcome in this trial was nonfatal myocardial infarction or death of cardiac origin. A primary event occurred in 21.7% of those receiving placebo versus 17.3% receiving gemfibrozil for a relative risk reduction of 22% (95% CI 7-35, $p=0.006$). The relative risk reduction for combined cardiac events (nonfatal MI, death from coronary causes or stroke) with gemfibrozil was 24% compared to placebo (95% CI 11-36, $p<0.001$). There was no difference between groups in the rates of coronary revascularization, hospitalization for unstable angina, overall death or cancer. The authors concluded that raising HDL-C and lowering triglycerides with gemfibrozil, without lowering LDL-C, reduced major CHD events.

Bezafibrate (not available in the U.S.)

Secondary Prevention

The bezafibrate infarction prevention (BIP) study was designed to investigate whether treatment with bezafibrate would reduce the risk of nonfatal myocardial infarction or cardiac death in patients with coronary heart disease. Inclusion lipoprotein values were as follows: cholesterol 180-250 mg/dL, HDL-C $\leq$45 mg/dL, triglycerides $\leq$300 mg/dL and LDL-C $\leq$180 mg/dL In BIP, 3,122 patients were randomized to bezafibrate 400 mg or placebo daily and followed for a mean of 6.2 years. A primary event occurred in 13.6% on bezafibrate versus 15% on placebo ($p=0.26$) and was not statistically significant. However, a post hoc analysis revealed a significant reduction in the risk of a primary endpoint occurring in patients with higher baseline triglyceride levels ($\geq$200 mg/dL) ($p=0.02$). This difference was restricted to nonfatal MI occurring less often in the treatment group. Total and noncardiac death were similar between groups.[17]

Table 1. Comparison of VA-HIT and BIP

	VA-HIT	BIP
Intervention	Gemfibrozil 600 mg twice daily	Bezafibrate 400 mg daily
Mean Study Duration	5.1 years	6.2 years
Population	Men (n=2,531)	Men (2,857) and Women (n=265)
Baseline LDL-C	111 mg/dL	148 mg/dL
Baseline HDL-C	32 mg/dL	34.6 mg/dL
Baseline Triglycerides	161 mg/dL	145 mg/dL
% Change LDL-C	0%	-6.5%
% Change HDL-C	6%	18%
% Change Triglycerides	-31%	-21%
RRR in nonfatal MI and Cardiac Death	22%	9.4%
95% CI for Events	7-35%	NR

NR=not reported

A second trial involving bezafibrate was the lower extremity arterial disease event reduction (LEADER) study. In LEADER, men with lower extremity arterial disease were randomized to bezafibrate 400 mg daily or placebo for a median follow up period of 4.6 years. The primary outcome measure in the LEADER trial was a composite of all fatal and nonfatal CHD events and all strokes. Secondary endpoints included analysis of individual CHD events (fatal and nonfatal) and stroke. For the primary endpoint, there was no difference between treatment groups in the incidence of combined fatal and nonfatal CHD events and stroke (n=150 vs. 160 events, bezafibrate vs. placebo, respectively, p=0.72, 95% CI 0.76-1.21). As for the secondary endpoint of individual CHD events and stroke, the only difference was in nonfatal CHD events occurring less often in the bezafibrate group (n=26 vs. 46 events, bezafibrate vs. placebo, respectively, p=0.05, 95% CI 0.36-0.99). Upon further review of the event data, the reduction in nonfatal CHD events was noted primarily in patients less than 65 years of age. The authors do not provide specific data but comment that the subgroup of patients, who experienced a reduction in nonfatal MI with bezafibrate in BIP (those with elevated triglycerides), did not experience a similar benefit in LEADER.[96]

Fenofibrate

Secondary Prevention

Investigators, in the Diabetes Atherosclerosis Intervention Study (DAIS), randomized 418 type 2 diabetics to fenofibrate 200 mg or placebo daily for a minimum of 3 years. All eligible patients had to have at least one visible coronary lesion so that both progression and regression could be determined. The primary endpoint of DAIS was angiographic progession. Lipid entry criteria were as follows: LDL-C 135-174 mg/dL and triglycerides of <450 mg/dL or LDL-C $\leq$174 mg/dL and triglycerides of 150-460 mg/dL plus total cholesterol to HDL-C ratio of 4 or greater. Although clinical outcomes were measured, DAIS was not powered to observe a reduction in clinical outcomes. Patients on fenofibrate experienced less atherosclerotic progression (e.g. smaller increase in percent diameter stenosis and smaller decrease in minimum lumen diameter p=0.02, p=0.029, respectively) in the fenofibrate versus the placebo group. Clinical events occurred in 38 patients receiving fenofibrate versus 50 on placebo. The difference in events was not statistically significant. [18]

The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) Study was designed to determine whether treatment with fenofibrate reduces cardiovascular mortality in type 2 diabetics. To date, 9,795 patients with type 2 diabetes have been enrolled and will be followed for 5-7 years. Results from FIELD are expected in 2005.[19]

In summary, when evaluated in primary prevention (WHO study), clofibrate was associated with a reduction in the risk for nonfatal MI. However, an excess in total mortality was also observed in the clofibrate group compared to placebo. This increase was attributed to deaths from diseases of the liver, intestines and gallbladder. In secondary prevention (CDP study), clofibrate was not significantly different from placebo with regard to reducing CHD events. In both primary and secondary prevention, treatment with gemfibrozil in patients with low HDL-C and mildly elevated triglyceride levels ($\leq$300 mg/dL) has been shown to reduce the risk for CHD events in HHS and VA-HIT studies. In the BIP study, bezafibrate produced positive changes in lipoprotein values, however, was not found to reduce coronary events. In a post hoc analysis, the subgroup of patients whose triglycerides exceeded 200 mg/dL experienced a significant reduction in nonfatal MI. Although the BIP and VA-HIT studies were similarly designed trials,

with similar populations, it is unknown why their findings differed. One author speculates on the differences in the results of these two trials with two of his theories being due to chance or differences in the agents.[20] In the LEADER trial, bezafibrate was associated with a reduction in nonfatal MI versus placebo in those patients aged less than 65 years. In DAIS, treatment with fenofibrate was associated with a statistically significant reduction in angiographic progession compared to placebo. This study did not show a difference in clinical cardiac events but the study was not powered to do so. Although the data are not yet available, the FIELD study has been designed to examine if treatment with fenofibrate in patients with type 2 diabetes will result in a reduction in coronary events.

Effect of Fibrates on Lipoprotein Values

In general, fibrates can produce a 20-50% reduction in triglyceride levels, a 10-20% increase in HDL-C and anywhere from no change to up to a 20% reduction in LDL-C. Fenofibrate appears to reduce LDL-C to a greater extent than gemfibrozil.[38]

Table 2. Effect of Fibrates on LDL-C, HDL-C and Triglycerides

	Bezafibrate (not available in the US)			**Fenofibrate (Tricor)®**			**Gemfibrozil** (Park Davis, various manufacturers)		
	Mean % Change			**Mean % Change**			**Mean % Change**		
Reference	**LDL-C**	**HDL-C**	**TG**	**LDL-C**	**HDL-C**	**TG**	**LDL-C**	**HDL-C**	**TG**
VA-HIT[11]							0	6	-31
HHS[10]							-10	10	-43
BIP[16]	-6.5	18	-21						
DAIS[17]				-5*	6.5*	-26*			
Product Information Tricor [21]				-20.6	11	-28.9			
Product Information Lopid [22]							NR	NR	NR

NR=not available in the US, NR=not reported, TG=triglycerides
*Estimate from DAIS in figure 3.

To date, there have been a limited number of published studies comparing the effect of gemfibrozil versus fenofibrate on the lipid profile. The majority of these comparative studies are based upon conversion of gemfibrozil to fenofibrate in small numbers of patients. As a result, baseline lipoprotein data are not available. In general, converted patients had been receiving gemfibrozil 600 mg twice daily for a minimum of 3 months prior to conversion. The dose of fenofibrate was approximately 200 mg daily. In many cases, statins were used in combination with the fibrates but the dose of the statin was maintained throughout the study period. (Table 3)

Table 3. Comparison of Gemfibrozil and Fenofibrate on LDL-C, HDL-C and Triglycerides

	After Treatment Value Gemfibrozil	**After Treatment Value Fenofibrate**	**Approximate Difference**	**Comments**
Packard, etal.[23] N=80, crossover LDL-C (mg/dL) HDL-C (mg/dL) TG (mg/dL)	 140 46 190	 132 47 171	 -9 (p<0.001) 2 (p<0.001) -18 (p<0.001)	Patients with CAD and TG >200 mg/dL despite gemfibrozil for at least 3 months. A repeat lipid profile was done 12 weeks after switch.
Corbelli, etal.[24] N=92, retrospective, crossover LDL-C (mg/dL) HDL-C (mg/dL) TG (mg/dL)	 113 37 405	 114 38 337	 0.8 (NS) 0.8 (NS) -68 (p<0.05)	Most patients were considered to have inadequate lipid control (TG) and the switch was made from G to F. Statin doses were only stable up to 6 weeks after switch. Mean statin dose was slightly higher after switch. Authors concluded that relative effectiveness between agents not be compared from these results.
Backes, etal.[26] N=21, crossover LDL-C (mg/dL) HDL-C (mg/dL)	 84.4 29.6	 88.8 36.1	 4.4 (NS) 6.5 (p=0.03)	Published only as abstract in 2001.

TG (mg/dL)	1211.7	534.4	-677.3 (p=0.003)	
Westphal, etal.[34] N=22 Type III dyslipidemia , randomized, crossover LDL-C not measured HDL-C TG	 -- 39.4 363	 -- 39.8 372	 -- p=.263 p=0.211	Patients were randomized to treatment for 6 weeks of each fibrate separated by a washout period of 6 weeks.
Klosiewicz-Latoszek, etal.[41] N=29, crossover (5 fibrates) Type IIb n=12 LDL-C (mg/dL0 HLD-C (mg/dL) TG (mg/dL) Type III n=6 LDL-C (mg/dL0 HLD-C (mg/dL) TG (mg/dL) Type IV n=11 LDL-C (mg/dL0 HLD-C (mg/dL) TG (mg/dL)	 <u>Type IIb</u> 183 67.8 140 <u>Type III</u> 145 53.8 176 <u>Type IV</u> 156 48.5 260	 <u>Type IIb</u> 173 62.1 192 <u>Type III</u> 142 55.5 194 <u>Type IV</u> 142 51.6 300	 -10 (NS) -5.7 (NS) +52 (p<0.01) -3 (NS) +1.7 (NS) +28 (NS) -14 (NS) +3.1 (N/A) +40 (p<0.02)	Each patient received monotherapy with each of 6 fibrates in random order for 6 weeks separated by 8-week intervals. Only results for fenofibrate and gemfibrozil reported here.
	Gemfibrozil (Mean % Change fro m Baseline)	**Fenofibrate (Mean % Change fro m Baseline)**	**Significance (p Value)**	**Comments**
Dzavik, etal.[27] N=234, randomized, DB LDL-C (mg/dL) HDL-C (mg/dL) TG (mg/dL)	 3.7% 11.8% -41.5%	 -5.9% 16% -39.3	 P=0.003 NS NS	Published only as abstract in 1999. Study was 24 weeks.
Insua, etal.[25] N=21, crossover LDL-C (mg/dL) HDL-C (mg/dL) TG (mg/dL)	 -16% 9% -46.5%	 -27% 9% 54%	 P<0.02 NS NS	Patients each received gemfibrozil 900 mg and fenofibrate 200 mg for a duration of 6 weeks each with a 4-week washout period separating treatments.

DB=double-blind, F=fenofibrate, G=gemfibrozil, N=number, N/A=p-value not available, TG=triglycerides

Effect of Fibrates on Non-Lipid Parameters

Although there is not a consensus regarding the importance of certain serum metabolic parameters in risk of CHD in clinical practice, a brief discussion of the effect of fibrates on these parameters will follow. Only the non-lipid measures that have been observed to consistently differ between fibrates will be addressed in detail.

Homocysteine

At elevated plasma concentrations, homocysteine is considered to be toxic to endothelial cells, promotes platelet aggregation and adhesion, influences clotting factors towards thrombosis and stimulates multiplication of smooth muscle cells.[28] Several series of articles have been published with the majority of them identifying elevated homocysteine as a risk factor for cardiovascular disease or total mortality.[29-31]

In a recently published article, investigators set out to determine the association of elevated homocysteine and cardiovascular disease in 830 patients with type 2 diabetes.[32] Eligible diabetics were enrolled and followed for 7 years. The primary outcome measures in this trial were CHD mortality and incidence of nonfatal MI. Those subjects with baseline plasma homocysteine levels of 15 μmol/L or greater were at a higher risk for CHD deaths than those with homocysteine levels less than 15 μmol/L (26.1% vs. 15.3%; RR 2.94; 95% CI 1.72-5.01; p<0.001, multivariate COX regression analysis). The risk for CHD mortality or nonfatal MI was also significantly greater in those with homocysteine levels of 15 μmol/L or greater

(36.2% vs. 22.6%; RR 2.21; 95% CI 1.38-3.54; p=0.001, multivariate analysis) compared to those with lower homocysteine levels. The authors concluded from their data that plasma homocysteine level was a strong and independent risk factor for CHD events.

Alternatively, authors of a recent prospective study set out to determine if high-dose versus low-dose B vitamin supplements, to lower plasma homocysteine levels, resulted in a reduction in second or recurrent stroke, CHD events or death.[33] In this study, 3,680 patients experiencing a nondisabling ischemic stroke were randomized to receive 25 mg of pyridoxine (B_6), 0.4 mg of cobalamin (B_{12}) and 2.5 mg of folic acid (high-dose group) or 200 μg of pyridoxine, 6 μg of cobalamin and 20 μg of folic acid (low-dose group) for a period of 2 years. The mean homocysteine level at baseline was 13.4 μmol/L. At 2 years, plasma homocysteine levels were 2 μmol/L lower in the high-dose vitamin group versus the low dose group. However, there was no difference in risk for second stroke, CHD events or death. The authors did note an association between baseline homocysteine levels and events. A 3 μmol/L reduction in homocysteine from baseline resulted in a statistically lower incidence of CHD events and death. The lower risk of recurrent stroke in this subgroup did not meet statistical significance with a p=0.05.

Authors of a recent review examined the effect of fibrates on plasma homocysteine in published studies.[28] From their review, they noted that fenofibrate was the most well studied fibrate with a total of 173 patients included in the trials. In those studies examining the effect of fenofibrate on plasma homocysteine levels, fenofibrate was consistently associated with an increase of 30-40% from baseline in plasma homocysteine. Similar studies with other fibrates, including bezafibrate (3 studies, n=38 patients), noted a change in homocysteine ranging from a reduction from baseline to a 9-17% increase from baseline. In one study (n=26 patients), ciprofibrate was associated with a 57% increase in homocysteine levels from baseline.

In a crossover trial, 22 patients with hypertriglyceridemia were given gemfibrozil 900 mg daily or fenofibrate 200 mg daily for 6 weeks. Patients were then crossed over to the alternate fibrate for 6 weeks following a 6-week wash out period. The authors noted that lipids were altered similarly but only fenofibrate (10.7 to 14.4 μmol/L) and not gemfibrozil (12.9 to 12.4 μmol/L) increased homocysteine from baseline. The differences were statistically significant (p=0.007).[34] As a result of these observations, the investigators proposed that gemfibrozil be the fibrate of choice.

Authors of a more recent study set out to examine the effect of gemfibrozil on total serum homocysteine concentrations and the effect of homocysteine on angiographically determined progression of coronary atherosclerosis in 395 men with low HDL-C.[35] The trial was randomized, placebo-controlled and lasted for 16 months. Gemfibrozil was associated with a median increase in serum homocysteine concentrations of 18%. Levels of homocysteine did not influence baseline extent or progression of angiographically determined coronary atherosclerosis. The authors concluded that although gemfibrozil caused a median 18% increase in serum homocysteine concentrations, the clinical significance is not known.

In summary, there is no consensus that plasma homocysteine should be routinely monitored in patients at risk for CHD. Several studies have demonstrated an increased risk for CHD events in those patients with elevated plasma homocysteine levels. However, a recent study examining high-dose versus low-dose B vitamins in reducing the occurrence of second stroke or CHD events was only able to show a significant difference in reducing CHD events, and not recurrent stroke, after a reduction in plasma homocysteine of 3 μmol/L. It appears that all fibrates have the ability to increase plasma homocysteine levels to varying degrees with fenofibrate and ciprofibrate having the greatest effect. There is some data that providing folic acid or folic acid with cobalamin and pyridoxine can blunt the increase in homocysteine caused by fenofibrate.[36-37] However, the usual reduction in homocysteine, seen with B vitamins, was not observed in those patients on fenofibrate plus the vitamin supplements. At this time, the clinical significance of these elevations is not known.

Fibrinogen

Fibrinogen is known to be involved in the final stage of the coagulation process occurring in response to vascular and tissue injury.[83] Fibrinogen has other functions that may be responsible for its role as a contributor to cardiovascular disease including vasoconstriction at sites of tissue injury, activation of platelet aggregation, etc.[84] Epidemiologic data do support a correlation between elevated levels of fibrinogen and cardiovascular events. Two separate meta-analyses demonstrated a statistically significant increase in the risk ratio for developing cardiovascular events in those individuals with the highest baseline levels of fibrinogen versus those with lower baseline levels, independent of other well accepted risk factors.[85-86] In ATP III, fibrinogen levels are reported to be highly variable on a daily basis and tend to be elevated in those patients with known risk factors (e.g. patients with diabetes, tobacco use, hypertension, obesity, and a sedentary lifestyle) [84] and in one study were observed to have a seasonal variation.[87] In the LEADER study, men with lower extremity arterial disease were randomized to bezafibrate 400 mg daily or placebo for a median follow up period of 4.6 years. The primary outcome measure in the LEADER trial was a composite of all fatal and nonfatal CHD events and all strokes. Secondary endpoints included analysis of individual CHD events (fatal and nonfatal) and stroke. In this trial, fibrinogen was reduced in the bezafibrate group by 13%. For the primary endpoint, there was no difference between treatment groups in the incidence of combined fatal and nonfatal CHD events and stroke (n=150 vs. 160 events, bezafibrate vs. placebo, respectively, p=0.72, 95% CI 0.76-1.21). Despite an improved lipid profile (TC, LDL-C, HDL-C and triglycerides) and a reduction in fibrinogen, no difference in the primary outcome was observed. Although there are no known agents that selectively reduce fibrinogen without altering other CHD surrogates, investigators have recommended additional prospective trials of the effect of lowering fibrinogen with lipid-altering agents to better determine if fibrinogen has a causal role in cardiovascular disease or is simply a marker of present vascular injury.[84] Animal data from fibrinogen knock-out mice crossed with a highly atherosclerotic mouse did not show a reduced degree of atherosclerosis. Alternatively, in a fibrinogen over-expressing strain of mouse, there was not an increased degree of atherosclerosis.[88] Authors of this animal study concluded, from their data, that fibrinogen was merely a marker of disease and would not be worth targeting as a preventative or therapeutic approach to CHD.

Fibrates and niacin are known to lower fibrinogen levels.[84] Statins do not have an effect on fibrinogen. Gemfibrozil, however, has been observed to have an inconsistent effect on fibrinogen levels. We were able to identify two publications in which gemfibrozil had no effect on fibrinogen[89-90], two in which gemfibrozil reduced fibrinogen[91-92] and three in which fibrinogen increased in patients receiving gemfibrozil.[93-95] However, the clinical significance of this is not known. To date, gemfibrozil has been demonstrated to reduce CHD events in two randomized controlled trials (e.g. HHS and VA-HIT). The FIELD study is currently underway in patients with type 2 diabetes to determine if fenofibrate is associated with a reduction in CHD events. Results are expected in 2005.

Serum Creatinine

With the possible exception of gemfibrozil, fibrates have the ability to significantly increase serum creatinine levels.[28,38] The exact mechanism for the elevation of both serum urea and serum creatinine, observed with fenofibrate, ciprofibrate and bezafibrate, is not known.

In a study by Westphal, etal[34], 22 patients were randomized to receive gemfibrozil 900 mg daily or fenofibrate 200 mg daily for 6 weeks. Patients were then crossed over to the other fibrate for 6 weeks following a 6-week wash out period. Although not the primary focus of the trial, serum creatinine was measured. Creatinine was noted to be significantly elevated from baseline with fenofibrate but not with gemfibrozil. The after treatment serum creatinine was significantly different between gemfibrozil and fenofibrate, favoring gemfibrozil (p=0.006).

A retrospective chart review was undertaken since several physicians at one institution observed deterioration in renal function in some patients on fibrate therapy. After review of charts, 10 men experiencing an increase in their serum creatinine with fibrate therapy were identified. Six of them had

received renal transplants and 5 of those were on cyclosporine. Baseline serum creatinine ranged from 1.4-3 mg/dl. Patients received a total of 17 courses of fibrate therapy (13-fenofibrate, 3-gemfibrozil and 1-bezafibrate) and in all cases, there was a rise in serum creatinine. The mean increase in serum creatinine was reported to be 35%. Rise in serum creatinine was not reported by individual fibrate. As a result, a difference between fibrates in their ability to increase serum creatinine was not determined. Authors suggest caution and regular monitoring of renal function when prescribing fibrates to those patients with pre-existing renal impairment.[59]

In a letter to the editor, a group of investigators describe serum creatinine elevation in 5 patients with normal renal function receiving fibrates. Ciprofibrate was used in 4 cases and fenofibrate in one. Mean elevation in serum creatinine was 14.5%. Authors caution regular monitoring of renal function not only in those with pre-existing renal impairment, but also in those with normal renal function.[60]

In order to characterize the renal adverse effect profile of fibrates, a retrospective chart review of 27 patients experiencing renal dysfunction during fibrate therapy was undertaken.[40] Of the 27 patients experiencing renal dysfunction during fibrate therapy, 25 were on fenofibrate, 1 on bezafibrate and 1 on ciprofibrate. Fifteen patients had undergone renal transplantation, 4 had undergone heart or combined heart-lung transplantation, and 8 were non-transplant subjects. The authors observed a mean increase in serum creatinine of 40% in these patients. Renal function returned to baseline in 18 out of 24 patients discontinuing their fibrate. The remaining 6 patients, all with solid organ transplants, had irreversible creatinine elevations.

The authors identified 10 additional patients (renal transplant) on fibrate therapy that did not develop a rise in serum creatinine to serve as control subjects. These controls were used to determine the incidence of fibrate-induced elevations in creatinine in this specific population (renal transplant) and also to identify factors that may contribute to this adverse effect. Of the 25 (10+15) renal transplant patients receiving fibrate therapy, 60% developed this adverse effect. There were no differences with regard to age, sex, baseline creatinine, type and dose of fibrate, patients on cyclosporine (CSA), mean CSA levels before or during fibrate treatment or time from transplantation to initiation of fibrate between those developing or those not developing a rise in serum creatinine.

A second goal of these authors was to review the literature reporting data on renal function in patients using fibrates. A total of 24 studies were included for a total of 2,676 patients. Of the 24 studies, only 1 reported information on glomerular filtration rate and creatinine clearance which was not significantly altered with fenofibrate. A statistically significant rise in serum creatinine was noted in all 14 studies with fenofibrate or bezafibrate, in 3 out of 4 studies with ciprofibrate and none out of 8 studies with gemfibrozil. The range in mean elevation between studies for fenofibrate was 8-18%, 8-40% for bezafibrate and 6-16% for ciprofibrate. The elevation in serum creatinine was observed in patients with normal renal function, those with renal impairment and in transplant recipients. When reported, the increase in serum creatinine was reversible upon discontinuation of the fibrate. The authors of this retrospective study and literature review noted that fenofibrate, bezafibrate or ciprofibrate may induce renal dysfunction and that gemfibrozil appeared to lack this adverse event.

In most cases the increase in serum creatinine, observed with fibrates, return to baseline after discontinuation of the fibrate. However, there have been cases of irreversible elevation in serum creatinine. Authors of these studies evaluating fibrates and their effect on renal function advise using great caution in those patients with pre-exising renal impairment, especially in those following renal transplantation.

Fibrates: Safety

Is there a difference in the development of serious adverse events (e.g. myopathy or rhabdomyolysis) between gemfibrozil and fenofibrate when used as monotherapy for dyslipidemia?

To answer this question, safety data from HHS, VA-HIT and DAIS were reviewed. Although these safety data are not head to head comparisons of the two fibrates, they do provide some information on how each agent compared to placebo. Also, data on safety from head to head (gemfibrozil compared to fenofibrate)

trials were evaluated for differences. Adverse event sections of the manufacturers prescribing information were reviewed for potential differences and finally a population-based study utilizing a prescription database was reviewed.

In HHS and VA-HIT, the only adverse events that were statistically different between gemfibrozil and placebo were not serious and were gastrointestinal in nature. There were no reported differences in liver or muscle toxicity compared to placebo. In DAIS, only serious adverse events were reported and there were no differences between fenofibrate and placebo.

There were 7 trials comparing the effect of gemfibrozil and fenofibrate on the lipid profile in approximately 500 patients. Two of the trials were published in abstract only form. There was no difference in safety between gemfibrozil and fenofibrate in any of these trials.[23-27, 41]

Both gemfibrozil and fenofibrate, when used alone, have been infrequently associated with the development of myopathy and rhabdomyolysis, especially in those patients with renal impairment.[21-22]

In a large population-based study, 3 separate cohorts of patients were identified in order to estimate the risk of myopathy associated with lipid-lowering medications.[42] The 3 cohorts included those with a diagnosis of dyslipidemia receiving lipid-altering agents (n=17,219); those with a diagnosis of dyslipidemia not receiving lipid-lowering agents (n=28,974); and those without a diagnosis of hyperlipidemia receiving no lipid-lowering medication (n=50,000). For this investigation, data were derived from general practices in the United Kingdom from January 1991 to September 1997 encompassing about 3 million individuals. After a rigorous screening process, 13 cases of myopathy were identified and confirmed by a neurologist to be idiopathic in nature.

Table 4. Incidence Rate of Myopathy and Relative Risk in All 3 Cohorts

	Cases of Myopathy (n)	Incidence of Myopathy/ 10,000 Patient Years	95% Confidence Intervals (CI)	Relative Risk (95% CI)
Dyslipidemia; Treated	9	2.3	1.2-4.4	
Current Fibrate Use	2*	6.6	3-14.3	42.4 (11.6-170.5)
Current Statin Use	6*	1.2	0.3-4.7	7.6 (1.4-41.3)
Past User	2**	1.8	0.5-6.7	11.8 (2.2-64.5
Dyslipidemia; Untreated	0	0	0-0.4	0 (0-2.9)
No Dyslipidemia Diagnosis; Untreated	4	0.2	0.1-0.4	1

*One patient was identified as both a current user of a statin and a fibrate. They had been receiving a fibrate and then were switched to a statin. **Both past users had been on simvastatin. Table adapted from table 4 of article.[42]

In this study, authors reported than fenofibrate was associated with the greatest risk of myopathy whereas simvastatin the lowest. Simvastatin and bezafibrate were the most commonly prescribed agents in this analysis. Fenofibrate was used by 474 patients for a total of 5,454 prescriptions and gemfibrozil was used by 522 patients for a total of 6,581 prescriptions. There was one case of confirmed myopathy for fenofibrate and none for gemfibrozil. There were no cases of myopathy seen with resins or niacin in this analysis. The authors concluded that there is an increased risk for myopathy in patients receiving lipid-lowering agents, with fibrates being associated with the greatest risk. However, the absolute risk of myopathy with lipid-lowering agents (statin and fibrates) is small.

In summary, data from large controlled trials, head to head fibrate trials, manufacturers prescribing information or other data do not support a difference in the rate of serious adverse events between gemfibrozil and fenofibrate when used as monotherapy for dyslipidemia.

Is there a difference in the development of serious adverse events (e.g. myopathy or rhabdomyolysis) between gemfibrozil and fenofibrate when combined with statins for dyslipidemia?

To answer this question, recommendations from prescribing information regarding combination therapy (statins and fibrates) were reviewed. In addition, safety data from controlled trials combining statins and

fibrates were reviewed. Finally, VA data were analyzed to determine if there are differences in rates of myopathy, rhabdomyolysis or acute tubular necrosis between fibrates when combined with statins.

Table 5. Manufacturer Recommendations In Combination with A Fibrate[43-48]

Statin	Gemfibrozil	Fenofibrate
Atorvastatin	The combination of statins and fibrates should generally be avoided. (No mention of any particular fibrate.)	See gemfibrozil.
Fluvastatin	Concomitant therapy with statins and gemfibrozil is generally not recommended.	No mention of fenofibrate
Pravastatin	Concomitant therapy with statins and gemfibrozil is generally not recommended.	No mention of fenofibrate
Lovastatin	Combination with fibrates should be avoided unless the benefit outweighs the risk. If combined, the dose of lovastatin should be limited to 20 mg daily. (No mention of a particular fibrate)	See gemfibrozil
Rosuvastatin	Combination with gemfibrozil should generally be avoided. If combined, the dose of rosuvastatin should be limited to 10 mg daily.	No mention of fenofibrate
Simvastatin	Combination with gemfibrozil should be avoided. If combined, the dose of simvastatin should not exceed 10 mg daily.	Caution should be used when prescribing other fibrates with simvastatin and the benefit should outweigh the risk of such combinations.

The manufacturer's recommendations for gemfibrozil state that in patients who have had an unsatisfactory lipid response to either drug alone, the benefit of combined therapy with gemfibrozil and statins does not outweigh the risks of severe myopathy, rhabdomyolysis and acute renal failure.[21]

The manufacturer's recommendations for fenofibrate state that combined use of fenofibrate and statins should be avoided unless the benefit of further alterations in lipid levels is likely to outweigh the increased risk of this drug combination.[22]

The increased risk of muscle toxicity when combining a statin with a fibrate is well known. In the past few years, there have been 2 reviews attempting to quantify the incidence of myopathy and rhabdomyolysis from published, controlled clinical trials. In one of the reviews, authors provide guidance for using combination therapy for dyslipidemia.

In the first systematic review, authors identified 36 published clinical trials for a total of 1,674 patients receiving combination therapy.[49] The patients received statins and fibrates for a duration ranging from 2-184 weeks. Sixty-nine percent of patients in the trials were men. Twenty-one of the trials were unblinded, 6 were retrospective and 10 were prospective. In twenty of the 36 studies, gemfibrozil was used for a total of 63% of patients studied. The most common dose of gemfibrozil was 1200 mg daily. Of the 16 remaining studies, 10 used bezafibrate, 2 used fenofibrate (n=86), one used ciprofibrate, one used bezafibrate or ciprofibrate, one used bezafibrate or fenofibrate (n=102) and one used either ciprofibrate or gemfibrozil. In these studies, the statin dose ranged from lovastatin 20-80 mg (n=10), pravastatin 10-40 mg (n=11), fluvastatin 20-80 mg (n=8), simvastatin 5-40 mg (n=12), and atorvastatin 10 mg (n=1) and one final study with a mean dose atorvastatin 14.3 mg daily. The total number of representative statin studies does not equal 36 since some of the studies included more than one statin.

None of the patients on combination therapy in the 36 controlled clinical trials developed rhabdomyolysis or acute renal failure. Two patients experienced myopathy (see definition in appendix 1) (0.12%) and 33 (1.9%) developed other muscle-related symptoms including myalgias, myositis, muscle weakness or musculoskeletal pain. Finally, elevation of CK of usually 3-5 times the upper limit of normal was recorded in 2.1% of patients. A total of 19 (1.14%) patients withdrew from treatment due to muscle symptoms or elevated creatine kinase (CK). The authors stated that the incidence of muscle damage from combined therapy with statins and fibrates from controlled clinical trials was lower (0.12%) than that reported by other authors (incidence of 1-5%).[52-53]

As previously noted, there were no reported cases of rhabdomyolysis reported in the 36 studies. However, this should not be considered adequate evidence to imply safety of the combination. One obvious limitation to the analysis was the exclusion of patients with predisposing factors for muscle toxicity. The majority of studies excluded patients with renal and liver impairment, those with thyroid disorders, and about 1/3 of the

trials excluded diabetics. The most important risk factors for the development of rhabdomyolysis with statins, fibrates or the combination include renal impairment, advanced age (>80, especially females), drug-drug interactions, hypothyroidism and frailty.[51,54] A second limitation to the analysis was that most of the trials were conducted in a controlled setting so the observed safety should not be extrapolated to a usual care population. A final limitation may be that there were a relatively small number of patients (n=1876) receiving combination therapy in these 36 studies. As a result of excluding patients that may be predisposed to serious muscle toxicity from the statin-fibrate combination and of studies being conducted in a controlled environment in a relatively small number of patients, the actual risk in an uncontrolled setting may be higher.

In addition to systematically identifying controlled trials of combined statin-fibrates, authors also located 29 published case reports of rhabdomyolysis or myopathy associated with these combinations (MEDLINE 1966-July 2000). In all 29 reports, gemfibrozil was the fibrate used. The number of cases of rhabdomyolysis versus myopathy was not provided. It is difficult to determine the actual incidence of serious adverse events in an uncontrolled environment since not all cases are reported and it is possible that only the most serious are ever published. The authors provide an example of being able to identify only 3 published cases of rhabdomyolysis with cerivastatin combined with gemfibrozil from 1989 to August 2000. At that time, the FDAs MedWatch System had received 51 reports of myalgia with the combination and cerivastatin's manufacturer had filed for a label change with the FDA.

In another review of the literature (MEDLINE January 1985-October 2000), authors located all published cases of statin-associated rhabdomyolysis. During the period searched, there were 74 reported cases. Of those 74 cases, 19 were in patients receiving concomitant gemfibrozil and 2 in those receiving concomitant fenofibrate. Of the 19 cases reported with gemfibrozil and a statin, 5 patients were also receiving a drug known to alter statin metabolism (cyclosporine (3), clarithromycin (1)) or considered to contribute to muscle toxicity when combined with statins (niacin (1)).[55]

In a second systematic review, authors included 16 statin-fibrate combination studies for a total of 1,815 patients represented.[56] In this series of trials, serious muscle-related adverse events were rare. The same limitations, for determining the actual incidence of serious muscle-related events in a general clinic population, would apply. The authors provide a table of suggested recommendations when considering combination therapy with statins and fibrates. Gemfibrozil is listed as being contraindicated due to a possible drug-drug interaction with statins. Fenofibrate is listed as an option. The authors go on to reiterate that there are no trials proving beneficial outcomes in patients receiving statin-fibrate combinations. However, the statin-fibrate combination can be considered only after an inadequate response to other lipid-lowering agents (e.g. niacin, fish oils) combined with statins. Furthermore, should be reserved for high-risk patients with mixed dyslipidemia (LDL-C >100 mg/dL,HDL-C <40 mg/dL, and/or triglycerides >500 mg/dL). The authors also state that candidates should have normal renal, liver and thyroid function, and not be receiving drugs that may increase the serum concentration of statins (macrolides, azole antifungals, protease inhibitors, cyclosporine or other medications that may alter statin metabolism).

The efficacy and safety of combined fluvastatin with a fibrate (gemfibrozil (n=367), bezafibrate (n=493) or fenofibrate (n=158) was determined from a pooled analysis of 10 studies conducted by the manufacturer of fluvastatin.[57-58] There were 1,018 patients represented in the 10 studies. The mean dose of fluvastatin was 56 mg and the mean duration of exposure to combination therapy was 38 weeks. Safety measurements included frequency of adverse events and clinically relevant elevations in liver function tests (LFTs-ALT and AST) and CK. Of the 1,018 patients, only 688 had adverse event information available. Myalgia was reported in 3% of patients. There were no serious adverse events considered to be related to the combination. Two patients on combination therapy had CK elevations $\geq$10 X ULN (1-fluvastatin 80 mg + gemfibrozil 1200 mg daily and 1-fluvastatin 20 mg + fenofibrate 200 mg daily). The authors concluded from this analysis that the adverse event profile for fluvastatin combined with a fibrate was similar to fluvastatin alone.

In summary, the statin and fibrate manufacturers discourage the prescribing of statin-fibrate combinations unless the alteration in lipid levels achieved is considered to outweigh the risk of the combination. Two of the six statin manufacturers refer to "fibrates" as a group when cautioning against concomitant use. The

other four specify gemfibrozil as the agent to be avoided. Two of the four specify a dose limit when combining their statin (simvastatin and rosuvastatin) with gemfibrozil but no dose limit is recommended for these agents when combined with "other fibrates". A dose limit is specified for lovastatin when combined with fibrates. Although not specified in the product labeling, atorvastatin should also be used at the lowest possible dose when combined with a fibrate.

In both of the systematic reviews of trials in patients on statin-fibrate combinations, there were no reports of rhabdomyolysis. Gemfibrozil was represented in a large portion of those studies. However, because patients that may be predisposed to serious muscle toxicity from these combinations were excluded from the trials and because of the controlled environment of a study, the differences in safety between fibrates cannot be determined from this evidence.

In one report, gemfibrozil was implicated in 29 published case reports combined with statins as contributing to the development of rhabdomyolysis or myopathy. In another paper, 19 of 74 cases of statin associated rhabdomyolysis were reported when combined with gemfibrozil and 2 with fenofibrate. These reports cannot be used to determine and/or compare incidence rates between fibrates because of the nature of voluntary reporting and publishing of adverse events. Furthermore, the number of exposed individuals is not known. Gemfibrozil was FDA approved in November 1986 and fenofibrate was FDA approved in February 1998. The higher number of reports of serious adverse events with gemfibrozil may be partially explained by a greater clinical exposure.

As a result, because of the nature of adverse effect reporting and the available evidence presented in this section, the answer to the question of whether one fibrate is safer than the other with regard to combination therapy with a statin is unknown.

Within the VA, using VA administrative databases, are there differences in the incidence rates of rhabdomyolysis or acute tubular necrosis (ATN) between different statin-fibrate combinations?

VA administrative databases were queried for prescription medications, diagnoses and procedure data to evaluate the new event rate of rhabdomyolysis or acute tubular necrosis (ATN) in patients receiving statin-fibrate combinations. All patients with overlapping prescriptions for any statin plus any fibrate for $\geq$14 days during the period from October 1, 2001 through September 30, 2003 were included in the analysis. The new event rate was defined as events occurring after the first overlap date. A total of 113 new cases of rhabdomyolysis and 36 new cases of ATN were identified. The data are continuing to be analyzed.

From the VA data, there were 93,677 patients that received combination therapy with statins and gemfibrozil and only 1,830 patients that received fenofibrate with a statin during the evaluation period. As a result, it is possible that our data do not represent sufficient exposure of fenofibrate combined with statins to make any firm conclusions regarding differences in safety between fibrates. However during the 2 years evaluated, there were 149 identified cases of rhabdomyolysis or ATN in 93,677 patients on gemfibrozil with any statin for an overall rate of 0.16%. There were no cases of rhabdomyolysis or ATN in 1,830 patients on fenofibrate with any statin. From the VA data, the rates of rhabdomyolysis or ATN were small and appeared to be dose-related.

What is the effect of gemfibrozil and fenofibrate on the serum concentration of statins?

Table 6. Pharmacokinetic Properties of Gemfibrozil and Fenofibrate [22, 39,66-68]

Pharmacokinetic Parameter	Gemfibrozil	Fenofibrate (micronized)
Major Metabolic Pathway	Glucuronidation	Glucuronidation
Effect on Oxidative Metabolism via CYP 450 Isoenzymes	Data inconsistent	Weak inhibitor of CYP 2C19, 2A6, mild to moderate inhibitor of CYP 2C9
Route of Elimination	Renal	Renal
Half-Life (h)	1.3	19-27
Protein Binding	98%	99%
Effect of Food on Absorption	UNK	Extent of absorption is increased by 35% under fed vs. fasted conditions.
Bioavailability	100%	Nearly 100% (micronized)
Dose Reduction in Renal Impairment	CrCl 10-50 mL/min, reduce dose by 50%,	CrCl <50 mL/min, reduce dose

	<10 mL/min, reduce dose by 75%	

CrCl=creatinine clearance, UNK=unknown

Myopathy and rhabdomyolysis have been reported in patients receiving monotherapy with statins and fibrates. Although the mechanism of the interaction is not completely known, the combination of any statin with a fibrate can further increase the risk of muscle toxicity.[52]

Certain drug-statin combinations can increase blood levels of the affected statin resulting in an elevated risk of muscle toxicity. One of the most significant of these drug-drug interactions occurs most commonly when potent cytochrome P450 (CYP) 3A4 inhibitors (e.g. macrolide antibiotics, azole antifungals, cyclosporine, protease inhibitors) are combined with CYP 3A4 metabolized statins (e.g. lovastatin, simvastatin or atorvastatin). These drug combinations can increase blood levels of the affected statin, thereby increasing the risk. However, combination of these potent inhibitors with non-3A4 metabolized statins (e.g. fluvastatin, pravastatin or rosuvastatin) does not increase blood levels of these statins theoretically affording an additional margin of safety.

Although the mechanism of increased myotoxicity with the statin-fibrate combination has not been fully elucidated, there are several potential theories.[61] Experts have previously believed that the increased muscle toxicity with the combination was due to an additive adverse effect on skeletal muscles since gemfibrozil and fenofibrate are not inhibitors of CYP 3A4 metabolism.[62] Others believe that since both fibrates and statins are highly protein bound, displacement of statins by fibrates may lead to increased muscle toxicity.[63] Finally, a previously unrecognized metabolic pathway for elimination of the hydroxy acid forms of simvastatin, atorvastatin rosuvastatin and cerivastatin is via glucuronidation. This pathway has been demonstrated, in vitro, to be inhibited by gemfibrozil leading to increased serum concentrations of certain statins.

The pharmacokinetic interaction between simvastatin and gemfibrozil was explored in a series of in vivo pharmacokinetic experiments using dogs and in vitro experiments using human and dog hepatocytes. In these experiments, alteration in the metabolic clearance of statins via oxidation (CYP 3A) or glucuronidation was assessed. The effect of gemfibrozil on statin metabolism was measured by comparing percentages of statin metabolites formed in the presence and in the absence of gemfibrozil. The concentration of gemfibrozil producing a 50% reduction in statin metabolism (IC_{50}) was used to determine degree of inhibition using nonlinear regression analysis. The investigators observed a significant increase in systemic exposure (reduction in formation of SVA metabolites) to the hydroxy acid form of simvastatin (SVA) and atorvastatin (AVA). The increased exposure was attributed to inhibition of glucuronidation by competing with gemfibrozil for glucuronidation. Gemfibrozil minimally altered clearance of simvastatin or atorvastatin via oxidative metabolic pathways (CYP 3A4). However, gemfibrozil reduced clearance of the hydroxy acid of cerivastatin (CVA) in both pathways (inhibition of 2C8 and 3A4 oxidation and glucuronidation). Investigators suspect that statins may exhibit differing degrees of susceptibility to the inhibitory effects of gemfibrozil on elimination by glucuronidation or oxidative pathways as evidenced by the varied response of CVA compared to SVA and AVA.[64]

A second study by the same primary investigator examined the effect of gemfibrozil and fenofibrate on the metabolic clearance of statins in human hepatocytes. In this study, gemfibrozil did not appreciably affect the CYP 3A4 mediated-oxidative metabolism of SVA but significantly inhibited metabolism of SVA via the glucuronidation pathway. Fenofibrate was reported to have a minimal effect on either metabolic pathway of SVA. Oxidative metabolism was reduced significantly for CVA and rosuvastatin (RVA) but not for AVA in the presence of gemfibrozil. However, the glucuronidative metabolic pathway was significantly reduced for CVA, RVA and AVA. The effect of fenofibrate on the metabolism of CVA, AVA and RVA was not examined. The authors concluded that the reduced metabolism of the hydroxy acid forms of certain statins, in the presence of gemfibrozil, can be explained by inhibition of both glucuronidation and non-CYP 3A4 mediated oxidative metabolism (CYP 2C8). Furthermore, there appears to be a difference between fibrates in their ability to alter the metabolic elimination of statins and in the susceptibility of statins to these interactions.[65]

Table 7. Effect of Fibrate on Serum Concentration of Statins[21-22,43-48]

Product Information (PI) /Pharmacokinetic Study (PKS)	Gemfibrozil	Fenofibrate
Atorvastatin **PI**	No information on combined PK	No information on combined PK
PKS	No PKS identified	No PKS identified
Fluvastatin **PI**	No change in fluva or gem PK	No information on combined PK
PKS **Spence JD, etal.**[69]	No change in AUC, Tmax or Cmax of either fluva or gem.	No PKS identified
Lovastatin **PI**	No available data on combined PK	No available data on combined PK
PKS **Kyrkland C, etal.**[70]	Lova acid AUC ↑ 280%, Cmax ↑280%	No PKS identified
Pravastatin **PI**	Significant ↓ in urinary excretion and protein binding of prava resulting in ↑ AUC, Cmax and Tmax of prava metabolites.	No available data on combined PK
PKS **Gemfibrozil: Kyrklund C, etal.**[71] **Fenofibrate: Pan WJ, etal.**[72]	Prava AUC↑ 202% during gemfibrozil but there was no change in prava half-life. There was a reduction in renal clearance of prava but cumulative renal excretion did not change. May involve intereference of gemfibrozil with transport protein.	AUC and Cmax of lower potency metabolite of pravastatin was increased by 26% and 29%, respectively in the presence of fenofibrate.
Rosuvastatin **PI**	AUC ↑ 1.9 fold and Cmax↑ 2.2 fold	No available data on combined PK
PKS: **Martin, etal**[73]	No PKS identified	AUC ↑ 7%, Cmax ↑ 21%
Simvastatin **PI**	No available data on combined PK	No available data on combined PK
PKS **Backman JT, etal**.[74]	AUC of simva ↑by 35% and simva acid by 185%. Half-life of simva ↑ by 74% and of simva acid by 51%. Cmax of simva acid ↑ by 112%.	No PKS identified

AUC=area under the plasma concentration-time curve, Cmax=maximum plasma concentration, PI=product information, PK=pharmacokinetics, PKS=pharmacokinetic study

In summary, the pharmacokinetic fate of 5 of the 6 available statins has been examined in combination with gemfibrozil in healthy patients. In 4 of the 5 studies, gemfibrozil significantly increased the AUC and Cmax of the respective statin (lovastatin, simvastatin pravastatin and rosuvastatin). In the fifth pharmacokinetic study, combination with gemfibrozil did not alter AUC or Cmax of fluvastatin. Although half-life was not reported in all studies, the half-life of pravastatin was not prolonged when combined with gemfibrozil. As for fenofibrates' effect on the pharmacokinetics of statins, data are only available when combined with pravastatin and rosuvastatin for a small increase in AUC and Cmax.

As previously mentioned, there are several theories explaining the increased risk of muscle toxicity when statins and fibrates are combined. These include additive effects of statins and fibrates on skeletal muscle resulting in the increased risk, displaced protein binding (all statins are highly protein bound), and finally, inhibition of a recently recognized mode of statin metabolism via glucuronidation. Gemfibrozil and fenofibrate both undergo glucuronide-mediated metabolism. In 2 in vitro studies using human and dog hepatocytes, the glucuronide mediated-metabolism of atorvastatin acid, simvastatin acid, cerivastatin acid and rosuvastatin acid were all inhibited by gemfibrozil. The effect of fenofibrate on statin metabolism was only examined for simvastatin. Fenofibrate reportedly did not significantly alter the metabolism of the simvastatin via oxidative or glucuronidation mediated metabolism.

Is there a difference in the risk of serious adverse events (e.g. myopathy or rhabdomyolysis) with individual statins (e.g. atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, or simvastatin) when combined with gemfibrozil or fenofibrate?

To answer this question, safety data from controlled clinical trials evaluating the statin-fibrate combination were reviewed. In addition, FDA reported cases of statin-associated rhabdomyolysis were reviewed to determine if there was evidence for differences in the risk for severe muscle toxicity with certain statin-fibrate combinations. Although published nearly 2 years ago, authors of a clinical advisory from the American College of Cardiology, the American Heart Association and the National Heart Lung Blood Institute on the use and safety of statins, state that it is reasonable to believe that the increase in creatine kinase, seen in trials involving lovastatin with gemfibrozil, would be similar with other statin-fibrate combinations.[79]

In a systematic review by Shek, etal.[49], 36 trials combining a statin with a fibrate in the management of hypercholesterolemia were identified. No reports of rhabdomyolysis were observed in the 1,674 patients receiving the combination. A total of 19 (1.14%) patients withdrew secondary to myalgia or CK elevation. Two patients (0.12%) developed myopathy (defined as myalgia with CK >10 X the upper limit of normal [ULN]) and 33 (1.9%) patients experienced other muscle symptoms including myalgia, musculoskeletal pain or weakness, or myositis. There were 35 reports (2.1%) of subclinical elevation of CK (<10X ULN) in 16 of the included studies. Some of the studies did not report whether the CK elevation was symptomatic or if treatment was discontinued as a result. In one of the included studies, a patient tolerated the combination of pravastatin and gemfibrozil for 4 years and then developed myopathy with clinically important elevation in CK after being switched to simvastatin. In these studies, the statin dose ranged from lovastatin 20-80 mg (n=10), pravastatin 10-40 mg (n=11), fluvastatin 20-80 mg (n=8), simvastatin 5-40 mg (n=12), and atorvastatin 10 mg (n=1) and one final study with a mean dose atorvastatin 14.3 mg daily. The total number of representative statin studies does not equal 36 since some of the studies included more than one statin.

The authors of the systematic review admit that there are several limitations to their findings. First, as stated in a previous section, clinical trials exclude most patients that have risk factors for developing adverse outcomes. Therefore, data from controlled clinical trials may underestimate rates of adverse effects in a general clinic population. Also, some of the included studies did not report numbers and reasons for study withdrawal and were not of the best quality.

The authors of the same systematic review also searched MEDLINE (1966-July 2000) and identified 29 published cases of statin-fibrate rhabdomyolysis or myopathy. Of those 29 cases reports, there were no case reports of severe myopathy or rhabdomyolysis in patients receiving pravastatin or fluvastatin combined with a fibrate. However, cases of pravastatin or fluvastatin combined with a fibrate resulting in rhabdomyolysis have been reported.[75] The suggested mechanism responsible for this difference is that lipophilic drugs are metabolized by the liver to more hydrophilic compounds while hydrophilic agents (e.g. pravastatin) are more likely to be renally excreted unchanged and have a lower risk for drug interactions.[76] With regard to fluvastatin, it has been suggested that in patients with more severe, mixed hyperlipidemia, maximum doses of fluvastatin may not achieve desired LDL-c goals and may be switched to a more potent LDL-c lowering statin prior to using combination therapy. The authors conclude that the theoretical advantage of pravastatin has not been adequately addressed in comparative statin trials and requires further investigation.

In 2002, authors queried the Food and Drug Administrations (FDA) adverse event reporting system database to determine the number of reported cases of statin-associated rhabdomyolysis over a 29 month period (November 1997-March 2000).[75] The paper provides the number of unique reports of rhabdomyolysis, percentage of unique reports occurring with individual statins and potentially interacting medications (Table 8). Authors urge caution when making comparisons between statins due to the inherent limitations of a voluntary adverse event reporting system. Furthermore, it is important to note that the database contains only numbers of reports and not incidence rates or actual occurrences. Incidence rates can only be determined if the number of exposed individuals and the number of actual cases are known. Obviously, the number of cases can be dependent on under or over reporting of an event.

Table 8. FDA Adverse Event Reporting System Statin-Associated Cases of Rhabdomyolysis[75]

Measure	Atorvastatin	Cerivastatin	Fluvastatin	Lovastatin	Pravastatin	Simvastatin
Number of Unique Cases	73	192	10	40	71	215
Percentage of Total Cases	12%	31.95	1.66%	6.65%	11.8%	35.77%
Number with Fibrate	10	22	4	5	6	33
Number of Deaths*	7	7	1	4	8	11
Percent Died of Unique Cases	9.6%	3.6%	10%	10%	11.3%	5.1%

*Not specified whether deaths occurred with fibrates, other interacting drugs, or as monotherapy with statin.

In a letter to the editor, pharmacists working with the FDA collected all cases of statin-associated fatal rhabdomyolysis that had been reported to the FDA before June 26, 2001.[77] Cases were included if there was a clinical diagnosis of rhabdomyolysis, a temporal association between rhabdomyolysis and the use of a statin, and death was either directly or indirectly from rhabdomyolysis. As part of the analysis, authors included data from the "National Prescription Audit Plus" accounting for the number of prescriptions dispensed since marketing of the respective statins (Table 9). Reporting rates, not incidence rates, were determined by dividing the number of fatal cases of rhabdomyolysis by the number of prescriptions dispensed since marketing. Authors suggest caution against making rigorous comparisons between drugs since reporting rates are not actual rates and may be influenced by multiple factors.

Table 9. Fatal Cases of Statin-Associated Rhabdomyolysis Reported To The FDA Since Marketing[77]

Measure	Atorvastatin	Cerivastatin	Fluvastatin	Lovastatin	Pravastatin	Simvastatin
FDA Approval Date	12-17-96	6-26-97	12-31-93	8-31-87	10-31-91	12-23-91
Cases of Fatal Rhabdo	6	31	0	19	3	14
Number of RX Dispensed Since Marketing	140,360,000	9,815,000	37,392,000	99,197,000	81,364,000	116,145,000
Reporting Rate (per 1 million prescriptions)	0.04	3.16	0	0.19	0.04	0.12

*Table adapted from Staffa, etal.

In a petition from the Health Research Group of Public Citizen, a National, non-profit, patient advocacy group, requested reports of statin-associated rhabdomyolysis and death due the rhabdomyolysis from the FDA (October 1997-December 2000). The intent of the petition was to convince the FDA to require a black box warning in the prescribing information for all statins warning of the risk of rhabdomyolysis. During the period requested, there were 772 cases of statin-associated reports of rhabdomyolysis and 72 deaths due to rhabdomyolysis in statin users. The petition separated those cases of rhabdomyolysis or death due to rhabdomyolysis reported to occur with a statin-fibrate combination or without a concomitant fibrate (Table 10).[78] One of the authors goals, in separating the number of cases of serious muscle toxicity occurring in those patients with and without concomitant fibrates, was to demonstrate that in the majority of cases, statins were not combined with fibrates. These data are reporting rates and not incidence rates and should not be used to compare rates of severe muscle toxicity between statins.

Table 10. Cases of Statin-Associated Rhabdomyolysis and Death Due to Rhabdomyolysis by Statin[78]

Measure	Atorvastatin	Cerivastatin	Fluvastatin	Lovastatin	Pravastatin	Simvastatin
Number of Rhabdo Cases	86	387	10	32	70	187
Number **with** Fibrate (%)	13 (15%)	200 (52%)	2 (20%)	2 (6%)	8 (11%)	23 (12%)
Number **without** Fibrate (%)	73 (85%)	187 (48%)	8 (80%)	30 (94%)	62 (89%)	164 (88%)
Number of Rhabdo Deaths	13	20	1	5	9	24
Number of Rhabdo Deaths while Combined **with** Fibrate (%)	2 (15%)	10 (50%)	0 (0%)	0 (0%)	1 (11%)	5 (21%)
Number of Rhabdo Deaths **without** Combined Fibrate (%)	11 (85%)	10 (50%)	1 (100%)	5 (100%)	8 (89%)	19 (79%)

Table adapted from Pubic Citizen Petition

Data from the VA query of new cases of rhabdomyolysis or ATN, occurring with the statin-fibrate combination over a 2-year period, demonstrated that as the dose of a particular statin increased (e.g. atorvastatin, lovastatin and simvastatin), so did the risk of an adverse event. However, the overall risk

appears to be relatively low with the highest rates of rhabdomyolysis being reported in those patients receiving more than 40 mg daily of either atorvastatin or simvastatin.

Because of the nature of adverse effect reporting and the available evidence, the answer to the question of whether one statin is safer than the other with regard to combination therapy with a fibrate is unknown. However, a theoretical advantage of combining fluvastatin with gemfibrozil is that gemfibrozil does not significantly alter serum concentrations of fluvastatin. Furthermore, limiting statin doses may also lessen the risk of serious muscle toxicity with the combinations.

DATA SUMMARY TABLES:

Table 11. Summary of Evidence

Key Question	Type of Evidence Evaluated	Conclusion/Summary
Is there health outcome evidence to support using the statin-fibrate combination?	No health outcome evidence is not yet available	The LDS study would have helped to answer this question but it was stopped due to withdrawal of cerivastatin from the market. The ACCORD study will have in excess of 5000 patients on the combination but data will not be available until 2008 or 2009.
Which fibrates have evidence to support their benefit in reducing CHD outcomes when used as monotherapy?	Gemfibrozil-VA-HIT, HHS Fenofibrate-FIELD-results not available	Gemfibrozil reduced the rate of CHD events in patients in primary prevention (HHS) and secondary prevention (VA-HIT). DAIS was a coronary artery progression study with fenofibrate and was not powered to measure a reduction in CHD outcomes. FIELD is a CHD outcomes study with fenofibrate, however results are unavailable until 2005.
Are there differences between fibrates on the lipid profile or other surrogate markers of CHD?	Lipid profile: crossover studies comparing response to gemfibrozil vs. fenofibrate Homocysteine: Systematic review on effect of fibrates on homocysteine levels, crossover trial comparing effect on homocysteine with fenofibrate vs. gemfibrozil. Fibrinogen: Studies assessing effect of fibrates on fibrinogen and other markers. Serum Creatinine: Crossover study comparing gemfibrozil to fenofibrate, published retrospective chart review.	1) Lipid profile: From the crossover studies, published in full, HDL-C elevation, LDL-C and TG lowering were not statistically different between fibrates in most cases. 2) Homocysteine: In a systematic review of the effect of fibrates on homocysteine, fenofibrate was associated with a 30-40% increase in homocysteine and gemfibrozil did not raise homocysteine levels. However, in another prospective study with gemfibrozil, homocysteine increased by a median of 18%. The clinical significance of these findings is not known. 3) Fibrinogen: Fenofibrate reduces fibrinogen and gemfibrozil has an inconsistent effect. 4) Serum Creatinine: Elevation for fenofibrate and no change for gemfibrozil. The majority of patients had a reversal of the rise in creatinine with drug W/D.
Is there a difference in the risk of serious adverse events (e.g. rhabdomyolysis) between fibrates when used as monotherapy?	VA-HIT, HHS, DAIS, head to head trials comparing fenofibrate vs. gemfibrozil, adverse events sections of product information, and population-based study.	From the available evidence, no difference is apparent.
Is there a difference in the risk of serious adverse effects (e.g. rhabdomyolysis) between fibrates when combined with statins?	Manufacturers product information, systematic reviews, case reports, FDA AERs, VA data.	1) In general, statin manufacturers discourage the combining of statins with fibrates unless the lipid-lowering benefit achieved outweighs the increased risk. Dose limits are recommended for simva and rosuva combined with gemfibrozil. Dose limits are recommended for lova with "fibrates." For 4 of the 6 available statins (fluva, prava, rosuva, simva), gemfibrozil is specified with no mention of fenofibrate. 2) In the systematic reviews evaluating statin-fibrate combinations, there were no reported

		cases of rhabdo or renal failure. Many of the trials excluded patients predisposed to serious adverse events with the combination. 3) Voluntary reporting of adverse events cannot be used to compare incidence rates between fibrates since many factors contribute to over or under reporting of events and the number of exposed individuals is not known. 4) From this data, we are unable to determine if combination with statin-fenofibrate is safer than statin-gemfibrozil. The best evidence to answer this question would be from a prospective head to head trial combining statin-gemfibrozil to statin-fenofibrate in a large number of individuals.
What effect does combining gemfibrozil or fenofibrate have on the serum concentrations of statins?	Manufacturers product information, pharmacokinetic studies.	1) PI-Gemfibrozil: Of the 6 statins, 3 no data, 2 increase in AUC and Cmax with gemfibrozil (prava and rosuva) and 1 no change with fluva. 2) PI-fenofibrate: Of the 6 statins, none contain data on PK combined with fenofibrate. 3) PKS-gemfibrozil: Of the 6 statins, 5 had PKS with gemfibrozil. Of the 5, fluva AUC and Cmax did not change. Gemfibrozil increased prava AUC but no change in half-life., AUC and Cmax increased significantly for lova, simva and rosuva. 4) PKS-fenofibrate: Of the 6 statins, only 2 were involved in PKS with fenofibrate. Prava AUC and Cmax only increased 26 and 29%, respectively and rosuva 7% and 21%, respectively. 5) 4) In an in vitro study, gemfibrozil was observed to inhibit metabolism of the hydroxy acid forms of lova, simva, atorva, ceriva and rosuva. In this same study, fenofibrate did not appreciably alter metabolism of simva acid. 5) Gemfibrozil can increase serum concentrations of atorva, lova, prava, rosuva and simva. Fenofibrate does not seem to significantly alter metabolism of simva (in vitro study only), prava or rosuva. Fenofibrates effect on atorva, fluva, and lova are not known. Increasing serum concentrations of statins can increase the risk for serious adverse events.
Is there a difference in the risk of serious adverse events (e.g. rhabdomyolysis) with individual statins when combined with fibrates?	Systematic reviews, case reports, FDA AERs, VA data.	From these data, it is not known whether there is a particular statin that is safer in combination with a fibrate. However, since gemfibrozil does not alter the serum concentrations of fluvastatin, this combination may theoretically be safer. Furthmore, limiting doses of statins when combined with gemfibrozil may also reduce the risk. Also combination of fenofibrate with prava or rosuva did not alter statin PK. In an in vitro study, simva acid (SVA) was not signficiantly altered by fenofibrate possibly conferring a safer combination. Due to the insufficient exposure of fenofibrate with any statin in the VA, it is difficult to make firm conclusions on differences in safety between fibrates combined with statins from these data. Furthermore, it appears that the risk of rhabdomyolysis increases with increasing doses of atorvastatin,

		lovastatin and simvastatin from VA data.

FDA AERs= Food and Drug Administration Adverse Event Reporting System, no info=no information, PI=product information, PK=pharmacokinetics, PKS=pharmacokinetic study, W/D=withdrawal

Recommendations and Conclusions

From the available published and VA administrative data, no firm conclusions can be drawn between differences in serious adverse events between gemfibrozil and fenofibrate when combined with statins.

Since there is a lack of health outcome evidence to support using the statin-fibrate combination but there is a known increased risk of serious muscle toxicity, the combination cannot be routinely recommended. However, although there are no data to support a "treatment" triglyceride level in which patients would obtain the most benefit, several authors have recommended the statin-fibrate combination be considered in a patient with mixed dyslipidemia (LDL-C >100 mg/dl, HDL-C<40 mg/dl and/or TG in excess of 500 mg/dl) at high risk for CHD events. While patients with triglyceride levels >500 mg/dL were not enrolled in outcome studies of fibrates (e.g. VA-HIT), the risk of pancreatitis may be increased in these patients. In addition, while NCEP ATP III recognizes the combination in patients with elevated LDL-C and atherogenic dyslipidemia, they do state that objective data are not available to support their recommendation. NCEP ATP III and other experts also recommend the combination be considered only if the patient has normal liver, renal and thyroid function. Furthermore, the combination should be avoided in patients receiving known potent CYP 3A4 inhibiting medications (e.g. macrolides, azole antifungals, protease inhibitors, cyclosporine, etc.) or other medications known to alter statin metabolism. Prior to adding a fibrate to statin therapy, consideration should be given to other available less toxic options such as n-3 polyunsaturated fatty acids (n3 PUFAs, a.k.a. fish oils) or niacin combined with statins. Triglyceride reduction is in the range of 20-30% with fish oils and 20-50% with niacin. In addition, niacin can increase HDL-C by 15-35%.[97] However, like the statin-fibrate combination, there is a lack of health outcome evidence demonstrating a greater benefit of these combinations versus a statin alone. If the statin-fibrate combination is selected, the lowest effective statin dose should be used when combined with gemfibrozil or fenofibrate.

Providers choosing to prescribe statin-fibrate therapy, regardless of specific statin or fibrate used, should discuss the risks and benefits of such therapy with their patient. This discussion should be clearly documented in the patient's medical record. Patients should be educated to report any unexplained muscle pain, tenderness or weakness to their providers immediately. NCEP ATP III recommends a baseline creatine kinase (CK) level prior to initiation of combination therapy. Measurement of CK is repeated if the patient reports muscle symptoms resembling myopathy. NCEP ATP III recommends discontinuing combination therapy (both statin and fibrate) if CK is greater than 10 times the upper limit of normal associated with muscle symptoms (tenderness, pain or weakness). Then, wait for symptoms to resolve completely and CK to normalize prior to restarting either drug and begin with a lower dose of the drug (s).

Prepared by: Catherine Kelley, Pharm.D., BCPS
Reviewed by: Chester B. Good, M.D., Chairman of the Medical Advisory Panel
David Parra, Pharm.D., BCPS
Peter Glassman, M.B.B.S, M.Sc. Medical Advisory Panel Member

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Appendix 1. ACC/AHA/NHLBI Definitions of Muscle Toxicity Associated with Statins or Fibrates (Definitions vary between studies and are not always consistent in their terminology. In most studies, definitions of terms used for describing muscle symptoms are not provided.) [79]

Myalgia:	Muscle aches or weakness without CK elevation
Myositiis:	Muscle symptoms (pain, tenderness and/or weakness) with CK elevation.
Myopathy:	General term referring to any disease of the muscle (acquired or inherited).
Rhabdomyolysis:	Muscle symptoms with significant CK elevation (typically more than 10 times the upper limit of normal). Also with creatinine elevation, brown urine and myoglobin present in the urine.

Appendix 2. Cost of Selected Lipid-Lowering Agents

Lipid-Lowering Agent	Typical Dose	Cost/Dose ($)	Cost/Day ($)	Cost/30 Days ($)
Atorvastatin	10-80 mg qd	1.35 (10 mg), 2.06 (20 mg, 2.17 (40 mg & 80 mg)	1.35-2.17	40.50-65.10
Fluvastatin	40-80 mg qd	0.51	0.51	15.30
Lovastatin	20-80 mg qd	0.26	0.26-0.52	7.80-15.60
Pravastatin	20-80 mg qd	1.68	1.68	50.40
Rosuvastatin	5-40 mg qd	1.48-1.55	1.48-1.55	44.40-46.50
Simvastatin	10-80 mg qd	0.26 (10 mg), 0.44 (20 mg), 0.66 (40 mg), 0.89 (80 mg)	0.26-0.89	7.80-26.70
Gemfibrozil	600 mg bid	0.31	0.62	18.60
Fenofibrate	160 mg qd	1.32	1.32	39.60
Fish Oils (n-3 PUFA)	DHA+EPA=3-4 gm	0.04	(4-5 caps) 0.16	4.80
Niaspan	500-2 grams qd	0.25 (500 mg), 0.42 (1000mg)	0.25-0.88	7.50-26.40
Ezetimibe	10 mg qd	1.44	1.44	43.20
Atorva +Gemfibrozil			1.97-2.79	59.10-83.70
Atorva + Fish Oils			1.51-2.33	45.30-69.90
Atorva + Niaspan	Niaspan 1000 mg qd		1.77-2.59	53.10-77.70
Atorva + Fenofibrate			2.67-3.49	80.10-104.70
Atorva + Ezetimibe			2.79-3.61	83.70-108.30
Fluva + Gemfibrozil			1.13	33.90
Fluva + Fish Oils			0.67	20.10
Fluva + Niaspan	Niaspan 1000 mg qd		0.93	27.90
Fluva + Fenofibrate			1.83	54.90
Fluva + Ezetimibe			1.95	58.50
Lova + Gemfibrozil	Limit lova to 20 mg/d		0.88-1.14	26.40-34.20
Lova + Fish Oils			0.42-0.68	12.60-20.40
Lova + Niaspan	Niaspan 1000 mg qd		0.68-0.94	20.40-28.20
Lova + Fenofibrate			1.58-1.84	47.40-55.20
Lova + Ezetimibe			1.70-1.96	51-58.80
Prava + Gemfibrozil			2.30	69
Prava + Fish Oils			1.84	55.20
Prava + Niaspan	Niaspan 1000 mg qd		2.10	63
Prava + Fenofibrate			3	90
Prava + Ezetimibe			3.12	93.60
Rosuva + Gemfibrozil	Limit Rosuva to 10 mg/d		2.1	63
Rosuva + Fish Oils			1.64-1.71	49.20-51.30
Rosuva + Niaspan	Niaspan 1000 mg qd		1.90-1.97	57-59.10
Rosuva + Fenofibrate			2.80-2.87	84-86.10
Rosuva + Ezetimibe			2.92-2.99	87.60-89.70
Simva + Gemfibrozil	Limit simva to 10 mg/d		0.88-1.51	26.40-45.30
Simva + Fish Oils			0.42-1.05	12.60-31.50
Simva + Niaspan	Niaspan 1000 mg qd		0.68-1.31	20.40-39.30
Simva + Fenofibrate			1.58-2.21	47.40-66.30
Simva + Ezetimibe			1.70-2.33	51-69.90

*****Prices are as of March 1, 2004 and do not take into account tablet splitting