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# Fenofibrate and Metabolic Syndrome

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## Abstract

The fibric acid derivative, fenofibrate (FF) has been used in the US since 1998 to manage patients with dyslipidemia. Typical changes in serum lipids as a result of FF treatment include clinically important mean reductions of serum triglycerides (TG) by a mean change of −93.7 mg/dL (−39.3%), increases of high density lipoprotein cholesterol (HDLC) by +5.5 mg/dL (+12.4%), and reductions in low density lipoprotein cholesterol (LDLC) by −17.9 mg/dL (−12.3%). The greatest reductions in serum TG are usually observed in subjects with elevated baseline TG including those with the metabolic syndrome (MetS). Although statins remain the mainstay of therapy for most dyslipidemic patients, their combined use with FF would be expected to address residual risk resulting from less than optimal TG and HDLC levels in such patients. Clinical trials examining the cardiovascular benefits of FF alone or combined with statins have produced mixed results. These observations underscore our lack of understanding of which patients may benefit from FF therapy and which do not. Although FF's basic mechanism of action is known to involve PPAR-α agonist activity resulting in altered transcription of several genes, the actual genetic bases for variability in lipid response is poorly understood. Studies, such as our GOLDN study and others were designed to better understand the genetic determinants of variability in the response to FF treatment and lipid levels. As a result several important genetic determinants of lipid levels have been identified. For example, in the GOLDN study SNPs from different genes were significantly associated with baseline lipid levels before treatment (*APOA5*-rs662799, rs3135506; *APOC3*-rs5128, rs2854117, rs4520); *APOA4*-rs5104; *PPARA*-rs9626730, rs135543, rs11703495; *LPL*-rs1801177), after treatment *PPARA*-rs11708495; *LPL*-rs1801177, and appeared to modulate overall response to FF treatment (*NOS3*-rs1799983). In this article, we will review the literature

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**CONFLICTS OF INTERESTS**

None to declare.

**SUPPLEMENTARY MATERIAL**

Supplementary material is available on the publishers Web site along with the published article.

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leading up to the contemporary use of FF as an agent to manage patients with dyslipidemia and focus on emerging understanding of the genetic variability in response to FF treatment. On the basis of the available evidence, we conclude that FF is of benefit in the treatment of dyslipidemia, especially among those with MetS. However, more work is needed to specifically identify which individuals derive a benefit from FF administration in terms of clinical outcomes and which do not – particularly in the context of type 2 diabetes.

**Keywords**

Fenofibrate; clinical trials; lipids; metabolic syndrome; single nucleotide polymorphism; random coefficients model; multivariate analysis

## 1. BACKGROUND SETTING OF FENOFIBRATE'S USE

Fenofibrate (FF) has been known to positively affect dyslipidemic profiles of most patients by dramatically reducing plasma triglycerides (TG), raising high density lipoprotein cholesterol (HDLC) levels while generally reducing low density lipoprotein cholesterol (LDLC). With the LDLC identified as a primary target in the management of dyslipidemia and the volume of evidence based literature supporting the benefit and safety of HMG CoA reductase inhibitors (statins), the role of fibric acid derivatives and specifically FF has been relatively modest. The contemporary role of fibric acid derivatives and specifically FF, continues to be further refined as clinicians weigh the mixed outcomes from several large clinical trials [1, 2]. In the absence of changes to these guidelines, contemporary practice appears to follow the recommendations by the American Heart Association (AHA) and the National Heart Lung and Blood Institute (NHLBI) for metabolic syndrome (MetS) [3], which identify fibrates and niacin as two options to manage patients whose non-HDLC and/or low HDLC fail to reach targeted levels. The paucity of alternative therapeutic drug entities, which address both TG and HDLC (two MetS components) and non-HDLC targets, supports FF continued use for carefully selected patients.

The clinical diagnosis of MetS and therapeutic management of patients with this condition has been the subject of a special scientific statement by the AHA and NHLBI meeting [3], representing the most commonly followed guide within the US. The current definition of the criteria for the clinical diagnosis of MetS includes the presence of 3 or more of either elevated waist circumference, elevated triglycerides, reduced HDLC, elevated blood pressure, or elevated fasting glucose (see North *et al.* review paper in this issue for the definition of MetS and Kraja *et al.* review [4, 5]). In general, the clinical management of patients with the metabolic syndrome focuses on addressing these criteria through both lifestyle modifications and managing metabolic risk factors. Lifestyle changes which address physical inactivity, the atherogenic diet or abdominal obesity each have their positive effects on the metabolic risk factors including the lipid fractions (TG, HDL or non-HDL targets) as well as elevated blood pressure and serum glucose. Consequently, given that two of the 5 criteria are specifically targeted by fibric acid derivatives such as FF, it is natural that drug therapy with FF makes up one of the key therapeutic entities recommended for patients with this syndrome. Given that the prevalence of individuals classified as having

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MetS within the US is as high as 24–29% [6–8] and increasing and furthermore since obesity and T2DM and/or insulin resistance continues to rise, it is therefore logical that FF's role be further defined as a logical consideration to address the dyslipidemia associated with each of these phenotypes.

MetS can significantly increase one's chances for developing threatening diseases such as diabetes mellitus (T2DM) and coronary heart disease (CHD). Individuals with the MetS have 2–4 times greater risk than those who do not have MetS for CHD death [6–8]. Even dyslipidemia in the absence of MetS may qualify a patient for consideration of FF. However, specific recommendations by the National Cholesterol Education Program ATP III (NCEP) panel report [9] identified both FF and niacin as therapeutic options for patients not meeting their non-HDL goal. Non-HDL goals are defined as 30mg/dL greater than an individual's LDLC goal which may be either 100, 130 or 160 mg/dL based on a count of risk factors (i.e. age, family history, HDLC, smoking status, and systolic blood pressure (SBP) level, 10-year Framingham, Risk, score (http://hp2010.nhlbihin.net/atpiii/calculator.asp) and presence of CHD or CHD risk equivalents (diabetes, stroke, aortic arch atheromatosis, peripheral vascular disease etc.) [9]. Treatment for elevated TG (> 200 mg/dL; normal < 150 mg/dL) based on the NCEP ATP III criteria were considered secondary targets, compared to reaching goals of LDLC, and normalizing HDLC was considered important after reaching goals for LDLC and non-HDLC. Hence, since FF is useful to lower TG and raise HDLC, then it remains an option to consider for those patients not achieving their non-HDL or HDLC goals.

This review is focused on FF role in MetS. Fenofibrate, earlier known also as *p-(4-chlorobenzoyl)-phenoxy isobutyrate isopropyl ester*, is useful for the treatment of adult patients with very high elevations of serum TG levels and/or high cholesterol levels. About half a century ago, the original fibrate, clofibrate, was developed as a fatty acid analog with clinical studies confirming a marked effect on fatty acids and TG's metabolism [10, 11]. Later, fibrates were identified to modify the expression of several genes involved in lipoprotein and fatty acid metabolism [12–16]. Such a role was attributed to the fact that FF activated the peroxisome proliferator-activated receptor alpha (PPAR-α) [17].

The determinant role of *PPAR-α* in mediating many of the effects of fibrates was illustrated by gene knock-out mice with non-functional PPAR-α [18]. Edgar *et al.* [19] showed that fibrates modify the expression of genes implicated in lipoprotein and fatty acid metabolism *via* the PPAR-α in liver cells. In addition when FF were used were found to be present in both liver and kidney [20, 21].

Along with dietary advice, several classes of agents have been utilized to help manage patients with dyslipidemia. Of the available classes of agents, HMG CoA reductase inhibitors (statins) have emerged as the most effective, safe and clearly have an overall favorable impact the lipid levels contributing to atherosclerotic cardiovascular disease and cardiovascular outcomes. Given the independent association of elevated cardiovascular risk for those individuals with elevated triglycerides and/or low HDLC- even with modest LDLC levels, the addition of niacin, fish oils or fibrate products remain an option. As a class, fibric acid derivatives, the most common of which include clofibrate, gemfibrozil, bezafibrate, and

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fenofibrate, have enjoyed a long history of study including their independent or combined use in patients who have markedly high TG or low HDLC. In the US, clofibrate was approved in 1967 with gemfibrozil being introduced in the early 1980s. Although its use in Europe began in the early 1980's, fenofibrate was approved for use in the US in February 1998 [21]. With the introduction of statins beginning with lovastatin in 1985 the use of fibrates proceeded at a modest pace. With the publications of the Helsinki Heart Study using gemfibrozil in 1987, and the Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial (VA-HIT) in 1999, both demonstrating reductions in coronary heart disease events [22, 23], a renewed interest in fibrates ensued. As a chemical entity, FF is well absorbed, but requires conversion *via* esterases to its active metabolite, fenofibric acid before it will produce its intended pharmacological effect. In an effort to normalize the impact of variability in drug absorption as a result of ingestion in a fed or fasting state, Stamm and Pawan (1998) representing Fournier Laboratories filed Patent No. US6074670, continued to modify the crystalline form of the product. The dosage formulation changes ultimately resulted in an improved bioavailability and therefore necessitated a change in the magnitude of FF per dose from 100 and 300 mg tablets, to 67 mg and 200 mg daily tablets [24]. Guivarc'h *et al.* [25] and Sauron *et al.* [26] reported experimental evidence of improved bioavailability of fenofibric acid of drugs in the form of tablet as nanofibrate, in the form of microcoated FF, and in the form of micronized FF and that they eventually had a lack of food effect on their absorption.

Indeed, fenofibric acid delayed release capsules (135 and 45mg) are currently marketed (Trilipix®) by Abbott labs in addition to several contemporary formulations of FF available in the US which include; Tricor® (48 mg or 145 mg of FF tablets), Antara (43 mg or 130 mg of micronized FF), Lipofen® (50 or 150 mg of FF), and Triglide® (50 mg or 160 mg of FF) to mention a few (see Table 1).

## 2. FENOFIBRATE MONOTHERAPY

Therapeutic lifestyle changes remain the first consideration before contemplating any drug therapy in the case of managing patients with dyslipidemia. (See details in the review of Djoussé *et al.* in this issue [27]). As a general rule pharmacotherapy follows lifestyle interventions, if lipid levels are beyond normal values and persist to be abnormal despite life style therapies (see §1). In reviewing nine guidelines for the treatment of patients with low HDLC, Devroey *et al.* [28] found the majority of them consider low HDLC as a marker of an increased risk for CHD, but only NCEP AT-PIII includes HDLC level in the calculation of coronary risk. Grundy *et al.* (2005) [3], specifically identifies reduced HDLC as a tertiary target but acknowledges there is not no specific goal to target increases in HDLC. Nonetheless, FF could be considered as an option for raising HDLC. FF has been demonstrated to have a somewhat variable effect raising HDLC in large clinical trials ranging from 1.5–7.4% [29]. For example, a study of 3,090 patients with a previous myocardial infarction or stable angina were treated with bezafibrate (a fibrate drug) 400 mg/day or a placebo and followed for 6.2 years. Bezafibrate raised HDLC 18% and reduced TG 21%. The frequency of the primary end point was 13.6% on bezafibrate versus 15.0% on placebo (p=0.26) [30]. In comparison, FF's effects in lowering plasma TG levels have been quite variable and clearly depend on baseline levels before therapy. For instance, individuals

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receiving FF, with highest baseline TG and lowest HDLC seem to demonstrate the greatest benefit in terms of improving their lipid profiles compared to those with only modest elevations in baseline TG and near normal baseline HDLC values [1]. A review of 53 studies enrolling 16,802 subjects showed that FF lowered plasma TG on average by −36%, LDLC by −8%, and increased HDLC by +10% [31]. However, considerable inter-study variability in lipid response exists. In part this is due to the nature of subjects recruited for these studies (having different baseline lipid values) but also as a consequence of other factors which may include the length of study period, baseline lipid values and possibly the use of different formulations and conditions of administration (fasting versus fed). Consequently we conducted our own review of 15 clinical trials utilizing the TriCor® brand of FF which was the formulation used in the GOLDN study which will be discussed later in this article (see §7). In this review, we found the average change, associated with FF treatment was −93.7 mg/dl (−39.3%) for TG, −17.9 mg/dl (−12.3%) for LDLC and +5.5 mg/dl (+12.4%) for HDLC [32–44] (see Fig. 1). Although we recognize that clinicians usually use serum lipid values as their most trusted biomarker of cardiovascular risk and thus measure of drug effect, it is also widely recognized that markers of inflammation are key to the underlying pathophysiology of atherosclerosis. Fenofibrate's effect of lowered levels of inflammation markers suggests it's potential to address other biological processes involved in atherogenesis [45]. As a result, the beneficial effects of FF can be easily extended to subjects classified with MetS. Although not systematically evaluated, FF's use in patients with T2DM seemed to produce mixed results. Specifically, the five year FIELD Study, which evaluated 9,795 subjects with type 2 diabetes who were 50–75 years of age, demonstrated a reduction of 24% of non-fatal myocardial infraction (MI) for those receiving FF-compared to placebo (p=0.01). However this, as well as a lower rate of progression to albuminuria (p=0.002), reduction in need for laser therapy for retinopathy (p=0.0003) and reduction in need for coronary revascularization (p=0.003) conflicted with a non-significant increase in coronary heart disease mortality (p=0.22) [46]. It is possible that such results on mortality were confounded by a larger number of patients allocated to placebo who received statins compared to those allocated to fenofibrate therapy. After four months of treatment LDLC decreased by 12%, TG by 29% and persisted at similar levels after 4 years of treatment. In contrast, HDLC increased by 5% and by the end of the clinical trial its increment leveled to 1% [46, 47]. It is not clear if the increase in mortality in the FIELD study was a result of unequal use of statins between the placebo and FF treated groups or simply the improvement on raised HDLC was too small to benefit from FF as monotherapy. As a result of the FIELD study, clinicians looked to the recently completed ACCORD trial to directly address the impact of adding FF or placebo to baseline statin use in T2DM patients (to be discussed later in §8) and would continue to wait until more still anticipating the role of FF in the treatment of CHD [40, 48–53].

## 3. FENOFIBRATE AS COMBINATION THERAPY WITH STATINS

Statins (Table 1) work primarily by inhibiting HMG-CoA reductase, which is a rate-limiting step in endogenous synthesis of cholesterol. They are also known to induce the expression of LDL receptors in the liver, which in turn increase the catabolism of plasma LDLC and lower the plasma concentrations of cholesterol. A meta-analysis of 14 statin trials (n=90,056

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randomized subjects) showed a 40% decrease in risk of coronary events over 5 years would be predicted by 29% decrease in LDL cholesterol levels [54]. These trials collectively demonstrated that there was no perceptible increase in risk for cancer or other substantial risk of life threatening complications associated with statin drug therapy. Statins are however, not without important toxicities. It is generally recommended that patients who are prescribed statins have a baseline and follow up measure of serum transaminases such as AST or ALT as a marker of potential liver damage. Furthermore myositis which can manifest as generalized muscle pain and/or weakness may be an indicator of muscle damage such that, if accompanied by an elevation in creatinine kinase, may represent myopathy. Factors associated with the risk of experiencing these side effects include dose of statin used, age of the patient, renal function or use of concomitant medications which inhibit the metabolism or hepatic uptake of the statins [55]. For a more comprehensive history of the data supporting the use of statin drug to manage patients with dyslipidemia, see Steinberg [56] and Davidson and Robinson [57] reviews.

Although the data supporting the use of statins to improve dyslipidemia profiles were accumulating, so too was experience in combination drug therapy with other lipid lowering agents including fibrates [58–62]. Similar precautions exist for combination therapy with statins and FF in that co-administration should proceed cautiously to the elderly based on expected impaired renal function [63]. Failure to identify indicators of potential myositis may lead to more serious side effects including a greater risk in developing rhabdomyolysis, which can be life threatening or lead to kidney failure. Generally speaking, FF is less likely to interfere with CYP based metabolism of most statins compared to gemfibrozil as fenofibrate is less potent of an inhibitor of those critical pathways of metabolism of statin [64]. Moreover, a survey of the reports from the United States Food and Drug Administration from January 1998–March 2002 showed that the combined use of gemfibrozil and a statin resulted in 590 cases of rhabdomyolysis compared with 16 cases with FF and statin therapy per million prescriptions [65]. Another study named SAFARI showed that a combination therapy of simvastatin 20 mg and FF 160 mg in patients (n=411) with combined hyperlipidemia resulted in additional improvement in all lipoprotein parameters measured compared with simvastatin 20 mg monotherapy (n=207) and was well tolerated [66]. Based on these results and that of several other studies, combination therapy of statins and fibrates, appear promising [67].

## 4. FENOFIBRATE’S EFFECT ON THE METABOLIC SYNDROME AND CARDIOVASCULAR OUTCOMES

Given that FF favorably affects serum TG and HDLC, its use in patients with MetS is logical [9]. Indeed, FF would be expected to address both of these two out of five components of the MetS either as monotherapy or more likely in combination therapy with a statin [68, 69]. Similarly, patients with T2DM often have elevated TG and low HDLC making this high CAD risk population ideal targets for fenofibrate therapy. Several studies have been done which explore FF’s role in such patients and provide an indication of its potential benefits. For example, the Diabetes Atherosclerosis Intervention Study (DIAS) reported a significant reduction in CAD progression in subjects with T2D. In a subpopulation of the overall study,

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25 patients assigned to once daily 200 mg FF, compared to 21 patients assigned to placebo demonstrated changes in lipid particle size (larger plasma LDL size) and ratio of total cholesterol to HDLC was lower in the FF group [70]. Also Lemieux *et al.* [71] studying the effects of FF (n=36) or pravastatin (n=43), found a favorable effect of FF therapy on LDLC peak particle size compared with placebo therapy. Unfortunately there have been a limited number of outcome trials using FF as the study drug. Nonetheless, we should be able to glean some sense of the value of FF from analyzing the findings of outcome trials using other fibrates. For example, the VA-HIT Trial, with a total of 2,531 men with a history of CHD who had low HDLC levels (mean, 32 mg/dl) and low LDLC levels (mean, 111 mg/dl), assigned subjects to receive either 1,200 mg/day of gemfibrozil or placebo. After a 5 year follow-up, treatment with gemfibrozil resulted in a significant 22% reduction in the combined incidence of nonfatal myocardial infarction (MI) and CHD death. A considerable number of these individuals fit the profile of having MetS. Specifically, 50% of individuals had high TG (>150 mg/dl), 75% had low HDLC (< 35 mg/dl), 57% had hypertension, 25% had diabetes and 13% had impaired fasting glucose [72].

Over 80% of The FIELD Study subjects would be later classified with MetS. Analysis of their data showed that MetS components identified higher CVD risk in individuals with type 2 diabetes, so the absolute benefits of FF was likely to be greater when metabolic syndrome features were present [46]. Rosenson *et al.* [73] reported that 3 months of FF therapy (once daily 160mg/dl) improved lipoproteinemia, oxidative stress, and inflammatory response in subjects with hypertriglyceridemia and MetS.

Rationally, given that FF favorably generally has positive effects on an individual's lipid profile including LDLC, TG and HDLC, one might expect that the establishment between FF drug therapy and risk for CHD would have been established long ago [74–78]. Moreover, individuals that have T2DM have as much as a two to four fold higher risk of myocardial infarction, stroke, and death from cardiovascular disease compared to those without T2DM. Consequently the opportunity to favorably impact outcomes should have been all that easier to establish. A sub study was conducted on patients with diabetes participating in the VA-HIT Trial (n=627) compared to those without diabetes (n=142). Following 5 years of treatment with gemfibrozil the investigators observed an average reduction of TG levels by 31% and a corresponding increase in HDLC of 6%. More importantly, these changes were associated with a, statistically significant 22% reduction in relative risk of CHD and a 24% reduction in combined outcome of death from CHD, nonfatal myocardial infarction, or stroke [72, 74]. Additional information on the effects of antihyperlipidemics on CHD is provided also in the review article of this issue by de Las Fuentes *et al.* [79].

## 5. FENOFIBRATE'S MECHANISM OF ACTION

Given that FF's mechanism of action is through agonist activity of the *PPAR-α* gene, it is natural to expect it to have a positive impact on the key components making up MetS (TG and HDLC) and thereby reducing their contributions to macro or microvascular disease. As a PPAR-α agonist, FF in turn modulates expression of target genes implicated in lipoprotein and fatty acid metabolism (Supplemental Fig. 1). PPAR-α binds the retinoid X receptor, forming a complex or heterodimer that interacts with a DNA response element. This

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interaction modulates the expression of lipoprotein lipase and suppresses the production of lipoprotein lipase inhibitor apolipoprotein C-III. It has also the effect of reducing the availability of free fatty acids for TG synthesis *via* an increase in β- oxidation of fatty acids and the inhibition of de novo synthesis of fatty acids [80–82]. In addition, production of apolipoprotein B and VLDL is also reduced. Correspondingly, an increase in the synthesis of apolipoprotein A-I and apolipoprotein A-II, the main apolipoproteins in HDLC, together with reduced cholesteryl ester transfer protein–mediated transfer of lipid from HDLC to VLDL contribute to the observed increase in plasma levels of HDLC (Supplemental Fig. 1) [29].

The HDLC concentrations are also increased by fibrates secondary to the reduction in plasma TG concentrations from the increased activity of lipoprotein lipase [80]. Fibrates also appear to stimulate reverse cholesterol transport by modulating macrophage cholesterol efflux, and bile acid synthesis, ultimately enhancing HDL concentrations [83].

## 6. CLINICAL TRIALS ON FENOFIBRATE

Fig. (1) and Supplemental Table 1 summarize several clinical trial findings on FF effects on TG, HDLC and LDLC. Based on www.clinicaltrials.gov (accessed on March 20, 2010), which represents a service of National Institutes of Health (NIH) in the US for registered clinical trials, we found 99 clinical trials have/are studying FF, and of those 38 focus at FF in combination with statins. Among the major clinical trials in chronological order, are the World Health Organization (WHO) trial (n=7,194 men) which studied clofibrate's effects on non-fatal MI. The authors reported an increase of 11% more deaths in the clofibrate treated group in a period of 13.2 years which was higher during the treatment period and its origins remain unexplained [84]. The Helsinki Heart Study (n=4,081 men) investigated gemfibrozil's effects on non-fatal MI/CHD deaths. Tenkanen *et al.*, [85] reported an 18 year follow up on mortality with finding on a decrease of relative risks (RR) 32% of CHD mortality, and for individuals in the original gemfibrozil group with both body mass index and TG level in the highest tertiles had a 71% lower RR of CHD mortality. The VA-HIT studied gemfibrozil's (n=2,531 men with CHD) effect on non-fatal MI/CHD death. This study reported a 22% reduction on the endpoints [23]. The FIELD study aimed to assess the effect of FF on CVD in patients with diabetes (n=9,795 men and women). Although an improvement in lipids profile, in the original report the end points did not improve versus placebo. Recently, Burgess *et al.* [86] reported that among The FIELD Study subjects having silent MI, fenofibrate reduced subsequent clinical CVD events by 78%. Also based on The FIELD Study a significant 30% reduction in the need for laser therapy, less albuminuria progression and less non traumatic distal amputations were found, which suggest a benefit in preventing of diabetes [87]. Recently the ACCORD trial has started to analyze and summarize its results (see §8).

## 7. A CASE STUDY: FENOFIBRATE TREATMENT IN THE GOLDN STUDY AND GENETIC ASSOCIATIONS WITH METABOLIC SYNDROME FACTORS

The Genetics of Lipid Lowering Drugs and Diet Network (GOLDN) study is a clinical familial study with two treatment arms, one related to FF treatment and one to a fat-load

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meal (see Supplemental Methods and Supplemental Fig. (2) for details of the design). Our study focused on examining the effects of FF on the lipid profiles in relation to MetS. In addition, we tested association of candidate single nucleotide polymorphisms (SNPs) of 29 candidate genes with lipids and their change as result of FF treatment. The maximal sampled population consisted of 1,107 white subjects with no missing phenotypes on 10 traits studied (Table 2). Most of the subjects participated in all clinical visits as part of the GOLDN study which, in part recruited from participants of the NHLBI Family Heart Study [88, 89].

Previous publications have described a number of polymorphisms in the GOLDN study in relation to lipid levels and their change in response to FF treatment [90–94]. Smith *et al.* [93], for example, with the GOLDN study data reported 4 SNPs (*APOA4_M35, APOC3_3U386, ABCA1_I27943*, and *LIPC_T224T*) responsible for a large portion of the SNP-covariate interaction that predicted the TG change. Different from previous studies, we performed multivariate factor analysis and random coefficients growth curves on the repeated measures. In addition, we assessed the association among a larger set of candidate genes for lipids with two types of responses a) a metabolic syndrome lipid factor from factor analysis for each time point and b) the slopes that represent change before (visits 1 and 2) versus after FF treatment (visits 3 and 4) (see Supplemental Methods). Moreover, the best findings were tested for their association with single traits LDLC, HDLC, and TG.

FF 160 mg once daily for 3–4 weeks decreased plasma triglycerides (TG) from an average 145 mg/dL to 91 mg/dL (−37.2%). TG change, −108.3 mg/dL (−43.2%), was highest in GOLDN subjects classified with MetS based on the National Cholesterol Education Program [9] definition than non-MetS subjects −34.5 mg/dL (−31.4%). Because our association tests are for selected genes, thus we consider the Bonferroni p-value threshold of 0.0004 to secure a family wise of 5% false positives as conservative. Out of 115 SNPs of 29 candidate genes, eighteen selected candidate genes (*ABCA1, APOA1, APOA2, APOA4, APOA5, APOB, APOC3, APOE, FABP2, LPL, LIPC, LIPE, MMTP, NOS3, PPARA, PPARG, PPARGC1A*, and *TCFL2*) were classified as members of the MetS gene network [87]. Most of the remaining candidate genes selected were related in some way to lipid metabolism (*ABCG5, ABCG8, ADIPOQ, FABP1, LIPG, LRP1, SCARB1, SCD4, WDTC1*) and drug metabolism (*CYP7A1, PDZK1*). A number of SNPs on 11q23 from a cluster of genes *APOA5* (rs662799, rs3135506), *APOC3* (rs5128, rs2854117, rs4520), *APOA4* (rs5104), and from genes *PPARA* (22q13.31, rs9626730, rs135543, rs11703495) and *LPL* (8p22, rs1801177) showed significant associations to lipids factors before FF treatment.

Among others, these findings overlap with a linkage region (11q23–11q24) for MetS lipids factor reported in the HyperGEN study [95]. The SNP rs3135506 of APOA5 gene located on 116167617 bps is a coding exon for APOA5 and a promoter for ZNF259 gene. The minor allele of rs3135506 (minor allele frequency (MAF) of about 6% in whites) has been repeatedly associated with increased plasma TG concentrations [96–99]. In our study the rare genotype rs3135506 (C/C) was associated with higher TG levels than the most frequent (G/G) genotype before and after FF treatment. The rs662799 association to lipids-insulin factor in our data although highly significant was problematic, because the rare homozygote genotype was represented by only 1 subject. Hence, a meta p-value of $2.7\times10^{-10}$ for the same polymorphism reported by Willer *et al.* [99] in a sample of 8,684 subjects, and a meta

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p-value of $2.4\times10^{-15}$ for a sample of 3,248 subjects in association with TG represent a supportive replication evidence.

Although *APOA1, APOC3, APOA4*, and *APOA5* cluster together in 11q23, different haplotypes of *APOA5* and *APOC3* have been considered to be independently associated with TG levels [100]. The SNP rs4520 is part of a synonymous change in a coding region of APOC3 gene. The genotype (T/T) of less frequent allele (MAF 26.9%) was associated with higher levels of TG before FF treatment. After FF treatment the association of rs4520 was less evident. The SNP rs5104 represents a missense amino-acid change in the *APOA4* gene, from the amino acid Asn to Ser when the less frequent genotype (G/G, MAF 13.4%) is present. The G/G genotype for this SNP in our study was associated with higher mean values of TG before the FF treatment.

After FF treatment, *PPARA* (rs11708495) and *LPL* (rs1801177) were ranked the top significant associations with factor scores of lipids MetS domain. This shows that *PPARA* and *LPL* gene polymorphism association with lipids remain significant even after FF treatment changes in the lipid levels. The association tests on random coefficients of growth curves identified *NOS3* (rs1799983) as the top ranking candidate associated with the lipids change (see Supplemental Tables 2–7).

Diep *et al.* [101] and Goya *et al.* [102] reported that FF increases endothelial Nitric Oxide (NO) availability. They suggested FF reflect beneficial effects on vascular function by increasing NO levels. In our study, use of RCM model identified *NOS3* (the endothelial nitric oxide synthase gene) as the most significant gene tested for the association with lipids factor scores with three significant SNPs (rs1799983, rs1800783, rs743507). Of these, rs1799983 was associated with the greatest change in the lipids MetS factor before and after FF treatment. Rs1799983 represents a missense G/T polymorphism with a MAF of 31.9%. Focusing in particular to the association of each trait (LDLC, HDLC, TG and INS) to the most significant SNP (rs1799983), we found the G/G genotype associated with higher values of TG and lower values of HDLC compared to T/T genotype.

The rs1799983 polymorphism in *NOS3*, is reported to be associated also with significant diastolic blood pressure response to hydrochlorothiazide [103], has been proposed that it may increase the risk of developing diabetic nephropathy [104] and it has been found to be associated to central pulse pressure in the Framingham Heart Study [105]. FF are suggested to have effects on vessel wall for cardiovascular protection by improving endothelial function, besides lipid-lowering effects [106]. Based on the R-squared values identified (Supplemental Tables 2–7), all our top findings had a modest contribution to lipid profiles change. It is not a surprise that identifying *PPARA* introns in association with changes in the MetS lipids domain coincides with what is already known about FF action. It is important to mention that genes associated with lipids and lipid changes were already identified as part of the MetS gene network [5]. Also *PPARA*, lipid genes on 11q23 and LPL are part of the *PPARA* signaling pathway (hsa03320) shown in Supplemental Fig. (1). *LPL* is also part of the glycerolipid metabolism pathway (hsa00561) and the Alzheimer's disease (hsa05010) (see KEGG at www.genome.jp). Consequently FF treatment, which causes at least a

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lowering of TG and LDLC levels and an increment of HDLC, can contribute to ameliorate the progression of MetS.

The GOLDN study showed also that FF treatment substantially alters plasma lipids and can ameliorate MetS profiles (Fig. 1). Our study was based on selected MetS and lipid domains candidate genes. Although the GOLDN study is a large clinical trials using FF, the treatment period of 3–4 weeks does not provide the opportunity to judge the effects of long term FF treatment in terms of clinical outcomes such as morbidity and mortality. We reported in this review several other studies that underlined the benefits of FF use. Recently Blanco-Rivero *et al.* [107] showed that long term FF treatment in rats induces endothelial dysfunction. Future GWAs and gene expression studies in human and model animals quite possibly may discover a larger network of genes and we will have a better understanding of the systems affected by FF treatment.

## 8. NEW CHALLENGES

As this article focusing on MetS was being prepared, several new outcome based trials were published on the cardiovascular benefits of various medications in patients with diabetes. Because our article is part of this special issue on MetS, we will merely draw parallels to a few of these studies as they relate to the remaining challenges to our understanding FF's clinical benefits. The Navigator study followed 9,306 patients with impaired glucose tolerance for 5 years to test the benefits of receiving once daily Valsartan versus placebo. Normally prescribed for patients with hypertension or heart failure, this angiotensin II receptor antagonist had no overall effect on cardiovascular mortality in spite of its benefits in reducing the risk of the incidence of diabetes [108]. So, even though we would expect a medication that corrects hypertension would improve the MetS outcomes, for the end points CHD events, there were no improvements compared to placebo.

Similar findings were observed in the recently completed ACCORD study. This study selected 5,518 patients with T2DM who were treated with open-label simvastatin to receive either masked FF or placebo. In general, the addition of FF to baseline simvastatin therapy failed to demonstrate an improvement in the prospectively selected primary or secondary cardiovascular endpoints which were prospectively monitored (fatal CV events, nonfatal MI, nonfatal stroke etc.). Only in pre-specified subgroup analyses was there a suggested heterogeneity in treatment effect according to sex, with a benefit for men (P=0.01 for interaction), and a possible interaction according to lipid subgroup, favoring those patients with both a high baseline TG level and a low baseline level of HLDC (P=0.057 for interaction) [2]. Despite these findings, and perhaps in light of them, our understanding of precisely which patients benefit from this drug and which do not, remain to be a challenge which may be enlightened by our improved understanding of FF genetic pathway(s) of action. Regardless, it is clear that FF remains an effective therapeutic option for managing the dyslipidemic phenotype relevant to those with MetS and likely select individuals with T2DM as well.

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## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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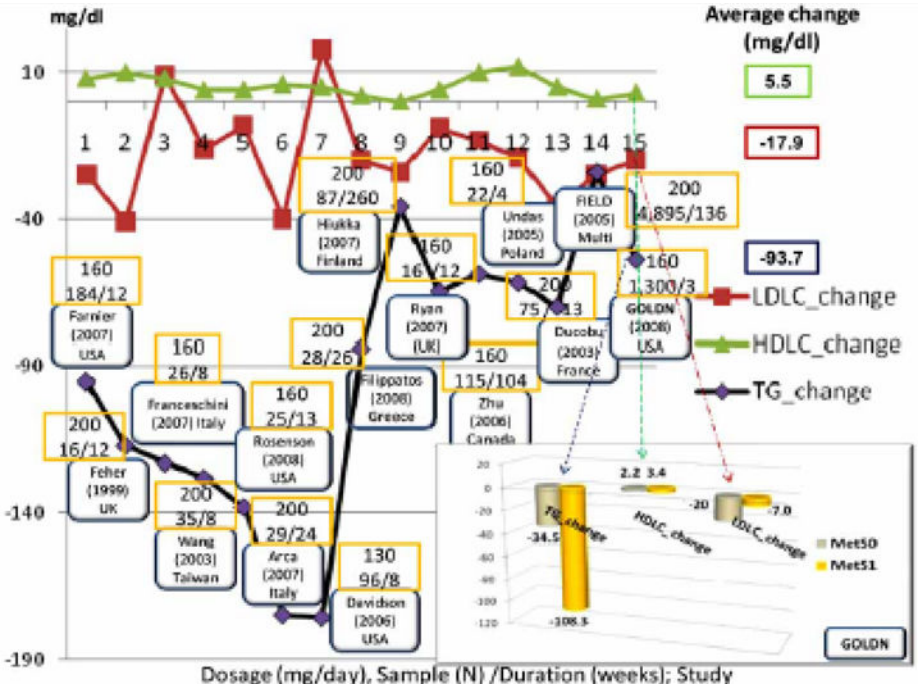


**Fig. 1.**

Several clinical trials studying the effects of TriCor® (Fenofibrate) on lipids profile, particularly on LDLC, HDLC and TG. MetS0-non-MetS subjects; MetS1- subjects classified with the NCEP ATPIII MetS. (These clinical trials were classified as part of TriCor® clinical trials based on the information collected from DrugLib.com). In the GOLDN study treatment with FF 160 mg daily for at least 3 weeks decreased plasma triglycerides (TG) from an average 145 mg/dL to 91 mg/dL (−37.2%). TG change was highest for the GOLDN subjects classified with MetS −108.3 mg/dL (−43.2%) than non-MetS subjects −34.5 mg/dL (−31.4%). As expected, the results of the GOLDN study agreed with other studies, where TG was the trait most altered by fenofibrate treatment. LDLC in general had a similar trend as TG, but with a smaller change, whereas the HDLC increased.

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**Table 1**

Statins, Fenofibrate and a Fibric Acid Marketed in the US

| No | Statin | Brand Name | Manufacturer | Fenofibrate | Brand Name | Manufacturer |
|---|---|---|---|---|---|---|
| 1 | **Rosuvastatin** | Crestor | AstraZeneca | **Tricor** | Fenofibrate | Abbott Labs |
| 2 | **Atorvastatin** | Lipitor | Pfizer | **Lipofen** | Fenofibrate | Kowa Pharmaceuticals |
| 3 | **Simvastatin** | Zocor | Merck and Co | **Lofibra** | Fenofibrate | Teva |
| 4 | **Pravastatin** | Pravachol | Bristol-Meyers Squibb | **Antara** | Fenofibrate | Oscient Pharmaceuticals |
| 5 | **Fluvastatin** | Lescol | Novartis | | | |
| 6 | **Lovastatin** | Mevacor | Merck and Co | **Trilipix** | Fibric acid | Abbott Labs |

*Marketed in the US (Drugs.com, accessed March 21, 2010)

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**Table 2**

Summary of GOLDN Participants' Characteristics

| Variables | Mean | Median | St. Dev. | Maximum | Minimum | N |
|---|---|---|---|---|---|---|
| Age | 48 | 47 | 16 | 87 | 18 | 1,292 |
| BMI v2 | 28.3 | 27.8 | 5.6 | 52.7 | 16.6 | 1,121 |
| BMI v4 | 28.7 | 28.2 | 5.6 | 52.5 | 16.4 | 792 |
| WAIST | 96.5 | 96 | 16.6 | 222 | 60 | 1,121 |
| WHR v2 | 0.9 | 0.98 | 0.1 | 1.92 | 0.48 | 1,121 |
| GLUC v0 * | 98.7 | 95 | 19.4 | 332 | 62 | 1,291 |
| GLUC v2d1 | 101.5 | 98 | 18.7 | 298 | 68 | 1,119 |
| GLUC v4d1 | 99.4 | 96 | 19.1 | 295 | 73 | 860 |
| INS v2d1 | 13.7 | 12 | 8.2 | 82 | 2 | 1,117 |
| INS v4d1 | 13.5 | 11 | 8.4 | 92 | 3 | 857 |
| SBP v2 | 115.2 | 112 | 16.6 | 209 | 70 | 1,121 |
| DBP v2 | 68.1 | 67 | 9.3 | 108 | 41 | 1,121 |
| LDL v0 | 117.8 | 116 | 30.8 | 237 | 46 | 1,290 |
| LDL v1 | 124 | 121 | 31.9 | 245 | 36 | 805 |
| LDL v2d1 | 121.4 | 120 | 31.4 | 236 | 44 | 1,120 |
| LDL v3 | 104.6 | 102 | 31.2 | 216 | 35 | 793 |
| LDL v4d1 | 104.3 | 101 | 31.7 | 209 | 34 | 860 |
| HDL v0 | 48.8 | 47 | 13.3 | 105 | 21 | 1,291 |
| HDL v1 | 46.4 | 44 | 13.2 | 110 | 22 | 804 |
| HDL v2d1 | 47.1 | 45 | 13.1 | 110 | 22 | 1,120 |
| HDL v3 | 49.3 | 47 | 13.4 | 118 | 21 | 793 |
| HDL v4d1 | 49.4 | 47 | 13.6 | 114 | 22 | 860 |
| TG v0 | 133.4 | 108 | 93.9 | 1,380 | 27 | 1,291 |
| TG v1 | 145.5 | 119.5 | 109 | 1,320 | 24 | 804 |
| TG v2d1 | 138.9 | 110 | 115.8 | 2,260 | 23 | 1,119 |
| TG v3 | 91.9 | 75 | 57.1 | 454 | 20 | 788 |

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| Variables | Mean | Median | St. Dev. | Maximum | Minimum | N |
|---|---|---|---|---|---|---|
| TG v4d1 | 89.9 | 75 | 54.6 | 455 | 16 | 860 |

*
v0- visit 0; v1-visit 1; v2- visit 2; v2d1- visit 2, first blood draw; v3- visit 3; v4d1- visit 4, first blood draw.