2nd International Symposium on Triglycerides and HDL

Lipid abnormalities and their treatment

This is the second of two articles summarizing the 2nd International Symposium on Triglycerides and HDL, organized by the Giovanni Lorenzini Medical Foundation and held in New York, New York, 14–17 July 2005.

Lipoprotein subclasses

Robert S. Rosenson (Chicago IL) discussed lipoprotein subclasses, inflammation, and cardiovascular disease (CVD) risk in the metabolic syndrome. Insulin resistance impairs VLDL particle clearance, leading to greater interchange of core triglyceride from VLDL with LDL and HDL, with LDL and HDL triglyceride enrichment leading both to become substrates for hepatic lipase, resulting in smaller, denser particles. Insulin resistance also is associated with decreased levels of apolipoprotein (apo)A1, and elevated free fatty acid (FFA) levels downregulate the ABCA1 transporter, which is involved in reverse cholesterol transport. Insulin resistance then is associated with smaller LDL and HDL and with larger-sized VLDL. As the number of metabolic syndrome components increases, LDL particle number increases with increased small, dense LDL and decreased large LDL particle numbers. Persons with LDL <100, therefore, may or may not have low particle number, so that only one-quarter of persons with the metabolic syndrome in the Framingham Offspring Study who had LDL <100 had optimal LDL particle distribution (1). In the Women’s Health Study, LDL particle number was associated with risk, particularly if small and large particle numbers were included; the only additional lipid variable adding to risk in this analysis is HDL cholesterol. In the AFCAPS/TexCAPS (Air Force/Texas Coronary Atherosclerosis Prevention Study), low HDL was an important risk marker, with risk particularly related to apoB level. Rosenson noted that this again supports the “need to pay attention to atherogenic lipoproteins.”

Lipoprotein subclasses are related to inflammation, with smaller, usually negatively charged, particles more likely to pass through the extracellular matrix, enter the vascular wall, and interact with monocyte receptors, initiating an inflammatory cascade. Lipoprotein-associated phospholipase A2 is associated with increased LDL oxidation and with inflammatory response and may be important as an additional nontraditional marker independent of C-reactive protein (CRP). HDL particles have antioxidant effects, including prevention of LDL oxidation and reduction in vascular inflammation. A number of adipokines are involved in vascular inflammation, with protective effect of adiponectin, as well as proinflammatory effects of factors such as interleukin (IL)-6 and tumor necrosis factor (TNF)-α. Persons with metabolic syndrome “are in a chronic inflammatory state,” with inflammatory proteins such as serum amyloid A increasing as a function of BMI, with decreasing calorie intake lowering plasma serum amyloid A (2).

Anatol Kontush (Paris, France) further discussed the heterogeneity of HDL particles, ranging from lipid-poor apoA1-containing particles and pre-β HDL particles to larger HDL2 particles. Cholesteryl ester transfer protein (CETP), phospholipase transfer protein, and hepatic and endothelial lipases are involved in HDL metabolism. Various HDL subfractions have varying degrees of antioxidative activity, with evidence that changes in HDL in the metabolic syndrome reduce this protective effect. Kontush showed studies of the antioxidative activity of HDL in decreasing LDL oxidation, with the smaller and denser HDL3 particles more effectively decreasing LDL oxidation. Systemic oxidative stress was increased in persons with metabolic syndrome to an extent similar to that in persons with type 2 diabetes, as shown by increased plasma 8-isoprostane levels. The major difference between fractions of persons with and without metabolic syndrome is in the HDL3 fraction, particularly in the most dense subfraction, with strong correlation between the LDL oxidation rate in the presence of the most dense HDL3 fraction and the plasma 8-isoprostane level. Small dense HDLs are depleted of cholesterol esters and enriched in triglycerides in metabolic syndrome, suggesting a prooxidative effect of triglyceride, with dysfunction of small dense HDL3 particles in metabolic syndrome reflecting increased CETP activity with accelerated VLDL triglyceride incorporation in HDL and transfer of HDL cholesterol to VLDL. Kontush suggested that this represents a mechanism underlying the relationship between triglycerides and atherosclerosis, so that CETP inhibitors and perhaps niacin may have particular benefit in metabolic syndrome and type 2 diabetes.

HDL

Allen Taylor (Washington, DC) discussed evidence to support aggressive management of HDL cholesterol, focusing on the combination of niacin with statins. He reviewed the 4S (Scandinavian Simvastatin Survival Study) finding that a 38% LDL reduction with simvastatin was associated with a 30% decrease in CVD events, suggesting that “we have to go beyond this,” to “ultra-low LDL,” although even with...
such approaches, the 5% annual event rate in the most aggressively treated group is still unacceptably high. Given the epidemiological evidence that low HDL is associated with CVD, it is noteworthy that low HDL is becoming more prevalent in the population, with a 3.1-mg/dl decrease in mean HDL cholesterol between 1981 and 1993, presumably related to obesity and sedentary lifestyle. Taylor termed exercise “very overrated as a treatment for low HDL,” with particular benefit appearing to require very intensive exercise (3). Exercise does, however, have a good effect on HDL cholesterol in persons with high triglyceride (4).

The most effective pharmacologic treatment for low HDL is niacin. The Coronary Drug Project, carried out from 1966 to 1975, showed that niacin reduced myocardial infarction at 6-year (5) and mortality at 15-year (6) follow-up. In combination with simvastatin, niacin lowered LDL from 132 to 75 mg/dl, increased HDL from 31 to 40 mg/dl, lowered triglyceride from 202 to 126 mg/dl, and prevented angiographic progression with a 90% reduction in end points (7). In the Armed Forces Regression Study, niacin in combination with gemfibrozil and cholestyramine lowered LDL and triglyceride and substantially increased HDL, with angiographic regression and a 14% reduction in events. The ARBITER (Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol) 2 trial studied simvastatin-treated persons with coronary disease given placebo versus extended-release niacin (1 g daily) (8). Forty-nine percent of participants had metabolic syndrome and 25% diabetes. LDL decreased from 87 to 85 mg/dl, HDL increased from 40 to 47 mg/dl, and carotid intima-media thickness increased 0.044 vs. 0.014 mm/year, a 68% decrease in progression that suggested benefit. There is a suggestion that HDL levels continue to increase even after 1 year. Although lack of effect on carotid intima-media thickness was reported in the metabolic syndrome subset, Taylor noted that this was found in persons who continued to show metabolic syndrome abnormality while on treatment and may have had particularly severe abnormality. Persons with diabetes did show benefit, and the strongest predictor of benefit was the on-trial increase in HDL cholesterol. Taylor reviewed approaches to helping patients tolerate the flushing sensation occurring with niacin treatment, recommending that it be called “prickly heat” in speaking with patients and that this common side effect tends to decrease with time and should be considered “normal, harmless, and expected.” Flushing can be reduced with concurrent administration of aspirin, but not in an entericoated slowly absorbed form, by administering the agent at bedtime with food and by avoiding high-fat meals and alcohol, and episodes of flushing can be treated with low-dose ibuprofen, with caution for renal or active peptic ulcer disease. He pointed out that there are minimal changes in long-term glycemic control in persons with diabetes and noted that the dietary supplement niacin may not be as safe or as reproducible in effect as prescription niacin products.

Alan R. Tall (New York, NY) discussed potential mechanisms of HDL on reversal of foam cell formation from macrophages, with apoA1, which is also a liver X receptor and peroxisome proliferator–activated receptor (PPAR-γ) target, upregulating the macrophage ABCA1 transporter. ABCA1 may be the major target of apoA1_Milano. Niacin decreases HDL catabolism, with accumulation of large HDL2 particles and evidence of clinical benefit. Studies of CETP deficiency states (9) led to development of therapies to inhibit CETP, with torcetrapib now shown to lead to HDL elevation to levels not attained with other treatment approaches. CETP inhibitors also block catabolism, again leading to an elevation in HDL2 rather than HDL3, with the resultant “fat HDL” accumulation leading to some concern that a less functional particle is produced, although CETP heterozygotes, whose HDL level is increased ~10%, have normal or decreased CVD risk. It remains a concern that CETP inhibition does not increase pre-β HDL. Tall discussed the “uncomfortable paradox” that ABCA1 only acts on cholesterol-poor particles, with limited effect on HDL2. Liver X receptor does, however, stimulate macrophage cholesterol efflux to HDL2 independent of ABCA1, an effect not mediated by scavenger receptor (SR)-B1 or apoE but by another ATP-binding cassette transporter, ABCG1, which particularly increases reverse cholesterol transport to larger HDL particles. ABCG1 is found on the cell surface, in the Golgi, and in recycling endosomes, suggesting a role in cellular metabolism. It does not directly bind HDL but may act to increase cholesterol availability at the cell surface. In addition to ABCA1, then, ABCG1 may contribute to the effect of HDL on atherosclerosis.

The large HDL that accumulates in CETP deficiency is functional, with evidence of increased net cholesterol efflux from macrophages to HDL3, but not to HDL2, from CETP-deficient persons, an effect due to ABCG1, with Tall suggesting that there may be multiple approaches of potential benefit in promoting cholesterol efflux involving the different cholesterol transporters.

Bryan Brewer (Bethesda, MD) discussed increasing HDL as an emerging approach to the treatment of CVD, pointing out that “even with aggressive lowering of LDL, we’re having a challenge.” HDL mediates reverse cholesterol transport, protects LDL against oxidation, modulates endothelial function by affecting endothelial nitric oxide synthase (eNOS), and has anti-inflammatory effects. HDL-directed therapy may play roles acutely in management of acute coronary syndrome (ACS) to “clean out the pipes,” and chronically for CVD risk reduction. Brewer noted that ABCA1 increases reverse cholesterol transport to pre-β HDL, which comprises ~5% of circulating HDL. Acutely, infusion of A1 and of A1-mimetic peptides increases pre-β HDL, leading to cholesterol efflux by increasing expression of ABCA1 by critical cells, such as arterial wall macrophages, rather than through the SR-B1 pathway. Regression of plaque has been demonstrated with administration of apoA1_Milano. Infusion of delipidated HDL is another approach, again promoting cholesterol efflux from the ABCA1 pathway and leading to production of pre-β HDL. This treatment approach requires plasmapheresis, addition of an organic solvent that selectively removes HDL cholesterol, and then reinfusion of the delipidated plasma; the overall procedure takes ~4 h. Total HDL decreases ~75% with a 20-fold increase in pre-β HDL, facilitating efflux from the ABCA1 pathway. LDL rises slightly with this approach, and an intravascular ultrasound (IVUS) study is being planned.

A second approach involves the infusion of A1-mimetic peptides. There are eight amphipathic (one side hydrophobic, the other side hydrophilic) sequences in apoA1, helices 1 and 8 having the highest lipid affinity, with synthetic amphipathic helical peptides having the potential to mimic the structure of apoA1. ESP 24218, a synthetic peptide having the helix 1 and 8 structures, causes cytotoxic cholesterol efflux in vitro by acting as a detergent rather than by increasing expression of the ABCA1 transporter.
Brewer considered the question of whether the intervening helices 2–7 play a role in producing specific ABCA1-mediated efflux. Modification of the synthetic peptide p-4F, composed of 18 p-amino acids forming an amphipathic molecule, which can be taken orally, with evidence of anti-inflammatory effect and reduction of atheroma in animal models. Brewer suggested that for patients with ACS, in several years the initial approach will be to give statins to reduce LDL to 70 mg/dl and to give acute HDL therapy to prevent plaque rupture in areas other than the single lesion, which may be stented, with subsequent chronic HDL therapy, perhaps with synthetic oral A1-mimetic peptides or torcetrapib, having the potential to reduce events by 70–80% rather than the current 30–50%.

Cesare R. Sitori (Milan, Italy) was involved in the initial identification of the apoA1Milano mutation among persons with dyslipidemia with low HDL cholesterol but low levels of coronary disease, with ABCA1 cholesterol removal approximately twice as great as normal. Sitori has played a key role in the development of biosynthetic apoA1Milano as a treatment for atherosclerosis. He recalled that cholesterol crystallizes in tissues, presumably leading to its toxic effects. Lowering LDL reduces arterial inflow, but cholesterol turnover occurs over a period of years, and there is limited evidence that LDL lowering mobilizes tissue cholesterol. However, use of an apoA1 mimetic dramatically increases cholesterol excretion, which indicates cholesterol mobilization and suggests that HDL treatment has the capacity to reduce arterial wall cholesterol burden. There appears to be a maximal protective HDL cholesterol level around 75 mg/dl, and Sitori reviewed evidence that low HDL “is as bad as having high LDL.” Approaches to increase HDL include the “fraudulent fatty acids,” such as fibrates and 3H agents, which increase hepatic apoA1 and A2 synthesis, stimulate lipoprotein lipase (LPL), and reduce apoC-III, enzyme inducers, and nicotinic acid. Sitori termed CETP a “fascinating target,” but he noted that probucol and its monosuccinic acid ester, AGI-1067, are CETP agonists and may be beneficial despite reducing HDL. Parenteral administration of synthetic HDL leads to plaque stabilization in ACS. apoA1Milano forms homodimers with an extremely long half-life as well as heterodimerizing with apoA2. Infusion of recombinant apoA1Milano prevents the atherosclerotic response to carotid artery collar ligation, and infusion during myocardial infarction caused by left anterior descending coronary artery ligation has been shown to reduce the extent of myocardial damage in animal models. Acute apoA1Milano infusion can actually demonstrate regression of atherosclerotic lesions with IVUS (10). Sitori noted that in human atherosclerosis, the amount of reversible lesion (nonfibrotic) is limited (11), so that the degree of regression seen in animal models would not be anticipated to occur with clinical treatment.

Philip J. Barter (Sydney, Australia) presented evidence of vascular anti-inflammatory effects of HDL. HDL promotes cholesterol efflux but also has antioxidant, antithrombotic, and anti-inflammatory properties, as well as effects on endothelial function and apoptosis. Using a chow-fed NZW (New Zealand white) rabbit model without evidence of atherosclerosis, placement of a nonocclusive sutureless collar around the carotid artery produces an acute inflammatory effect, with demonstration at 24 h of marked adventitial and, to lesser extent, intimal infiltration of neutrophils, with subsequent attenuation of neutrophil infiltration in the adventitia and increase in intimal levels. Levels of vascular cell adhesion molecule-1 and intracellular adhesion molecule-1 increase in this model, which has been used in the assessment of potential treatments. Pretreatment at 24 h or at the time of placement of the collar with apoA1 reduces most of all the neutrophil infiltrate and reduces adhesion molecule expression, suggesting that “apoA1 has evolved for many other roles than promoting the efflux of cholesterol.” A lipid-free apoA1 preparation is even more effective in this approach, perhaps due to generation of discoid HDL particles.

**Triglycerides**

Francine K. Welty (Boston, MA) discussed the relationship between triglyceride-rich lipoproteins and HDL, noting the inverse relationship between HDL and CVD risk, which is more pronounced in women than in men, and the inverse relationship between triglyceride and HDL cholesterol levels. A potential explanation is the transfer of triglyceride from apoB to apoA1-containing particles via CETP, leading to small, triglyceride-rich, cholesterol ester–depleted HDL particles. Chylomicrons and VLDL are the main triglyceride carriers in human plasma, chylomicrons containing apoB-48, produced in the intestine, while VLDLs contain apoB-100, produced in the liver. Whether intestinal and/or hepatic triglyceride production is directly related to apoA1 is not known. In a study of 23 healthy persons with mean LDL 157, HDL 45, and triglyceride 117 mg/dl, with measurement of apoB-48, apoB-100, and apoA1 kinetics, the LDL apoB-100 pool size was positively correlated with the apoA1 production rate, suggesting that higher pool size increases need for reverse cholesterol transport. The apoA1 fractional catabolic rate was inversely correlated with the apoB-48 fractional catabolic rate, which implies that when chylomicron clearance is delayed, triglyceride-rich apoB particles accumulate, resulting in triglyceride enrichment of HDL, which becomes a better substrate for hepatic lipase, leading to remodeling of HDL to smaller cholesterol-depleted particles that are more readily cleared. Welty concluded that high LDL apoB-100 increases apoA1 production to prevent cholesterol overloading of cells and that the inverse relationship between triglyceride and HDL cholesterol level may be influenced more by chylomicron than by VLDL levels.

**Lipid treatment**

PPARs. Henry Ginsberg (New York, NY) further discussed the pathophysiology and approach to treatment of atherogenic dyslipidemia. The largest CVD follow-up dataset is that of the MRFIT (Multiple Risk Factor Intervention Trial) study, with >360,000 persons screened, ~5,000 of whom had diabetes. Mortality increased with increasing number of CVD risk factors to a greater extent in persons with than without diabetes (12). Ginsberg reviewed the reduction in CVD from 1950–1966 to 1977–1995 in the Framingham Heart Study, with considerably higher rates in both periods among persons with diabetes. Age-adjusted mortality improved for CVD but not for diabetes. An important cause of worse outcome among persons with diabetes is their dyslipidemia, characterized by increased triglyceride, VLDL cholesterol, LDL cholesterol, small dense LDL, and apoB and decreased apoA1 and HDL cholesterol, as well as...
abnormal reverse cholesterol transport. Postprandial lipemia may be a risk factor, although this has not been as well categorized. Ginsberg reviewed factors responsible for the production of various HDL particles, with mature HDL taking up cholesterol from macrophages via ABCG1 and leading to hepatic cholesterol uptake via SR-B, with subsequent enteric cholesterol excretion. CETP may act as a recirculation pathway to prolong the plasma half-life of all the lipid fractions, leading to alteration in HDL particle structure potentially contributing to atherogenic abnormality. Addressing approaches to therapy, a question is whether LDL cholesterol, HDL cholesterol, triglyceride, or LDL size should be the primary lipid targets. Ginsberg agreed that LDL cholesterol should be the primary goal of treatment, noting that at any LDL level event rates are higher among persons with diabetes. Bile acid–binding resins, plant sterols and stanols, cholesterol absorption blockers, and fiber can further reduce LDL cholesterol, but Ginsberg suggested that for this group, it becomes particularly important to address the additional potential adverse effects of HDL cholesterol, triglyceride, and LDL size. PPAR-α agonists may increase hepatic fatty acid oxidation, increase LPL, decrease apoCIII, and increase apoA1, leading to triglyceride reduction by 35–50%, HDL cholesterol increase by 10–20%, and variable change in LDL cholesterol, although there are potential concerns that fibrates raise creatinine with fenofibrate also raising homocysteine levels. The combination of PPAR-α and statins is particularly important (13), with fenofibrate appearing to be safer than gemfibrozil. Niacin reduces LDL 10–15%, triglyceride 25–35%, and lipoprotein(a) 10–15% and raises HDL 15–30%. Niacin may increase glucose levels, so although recent studies in persons with diabetes show that the agent is safe (14), a caveat is that persons with borderline glycermia may become overtly hyperglycemic with niacin.

PPAR-γ agonists suppress fatty acid release from adipocytes, increase LPL, decrease VLDL and chylomicron remnant triglyceride, increase hepatic apoB degradation, and decrease lipogenesis by reducing insulin levels, with Ginsberg observing that pioglitazone appears to be more potent in raising HDL cholesterol and lowering triglyceride than rosiglitazone. PPAR-δ agonists may also play a role in the treatment of atherogenic dyslipidemia. Jean-Charles Fruchtart (Lille, France) discussed mechanisms of PPAR-α/γ action, addressing their effect on vascular inflammation, which he termed the initiating processes of atherosclerosis. PPAR-γ is present in endothelial cells and macrophages, and PPAR-α in all cell types involved in atherosclerosis, with the transcription factor nuclear factor (NF)-κB, a key cellular regulator of inflammation, inhibited by fibrates in activating PPAR-α, both directly and by increasing production of inhibitor of κB. PPAR-α decreases cell recruitment, increases cholesterol efflux, decreases the inflammatory response, decreases vasoconstriction and cell migration, and decreases thrombosis and increases plaque stability, all potentially antiatherosclerotic effects. PPAR-α activation by fibrates inhibits IL-1β and reduces both IL-6 and CRP in persons with coronary artery disease, the latter via inhibition of hepatic IL-1–stimulated CRP secretion. PPAR-α activators reduce adhesion molecule production by interfering with the NF-κB signaling pathway. Fibrinogen, which is an independent risk factor for atherosclerosis, is negatively regulated by the fbrate PPAR-α agonist fenofibrate, although gemfibrozil does not have this effect. PPAR-α and -γ agonists decrease endothelin-1 production by interfering with the activator protein-1 transcription factor. Expression of tissue factor, the initiator of thrombosis in vivo, also is decreased by fibrates via NF-κB and activator protein-1. PPAR-α has effects in vascular smooth muscle cell (VSMC) proliferation and migration within the vascular wall, with PPAR-α inhibiting the progression of VSMC from G1 to S phase via induction of cyclin-dependent kinase inhibitors, nuclear transcription regulators critical for cell cycle control. In a mouse model of carotid vascular arterial injury, PPAR-α activation inhibits intimal hyperplasia. PPAR-γ action also modulates inflammatory processes and the atherosclerotic process. PPAR-γ agonists inhibit VSMC growth via different nuclear signals, improve vascular insulin sensitivity by increasing the phosphatidylinositol-3 kinase and decreasing the mitogen-activated protein kinase pathway activities. In type 2 diabetes, PPAR-γ agonists decrease CRP and matrix metalloproteinase-9 and increase adipocyte adiponectin, further reducing atherosclerosis. The adiponectin gene promoter contains a sequence activated by PPAR-γ agonists. PPAR-γ has effects on inflammation, on reverse cholesterol transport, and on VSMC, with antithrombotic and antiatherosclerotic effects in animal models. Combined PPAR-α/γ agonist administration has particular antithrombotic and antiatherosclerotic effects (15).

Ralph DeFronzo (San Antonio, TX) discussed the potential role of dual PPAR-α/γ activators in management of diabetes. He noted that while diabetic microvascular disease is primarily caused by hyperglycemia, macrovascular disease is multifactorial in its pathogenesis, with stronger epidemiologic relationships between glycermia and microvascular complications than between glycermia and myocardial infarction or stroke. The additional causative processes involve the components of the metabolic syndrome, all of which are related to insulin resistance. An ideal approach to treatment would correct hyperglycemia and prevent microvascular complications, improve known cardiovascular risk factors and prevent macrovascular complications, and reverse the basic pathophysiologic defects characterizing type 2 diabetes. Both pioglitazone and rosiglitazone similarly increase insulin-stimulated glycogen deposition, although there are few PPAR-γ receptors in muscle, with the explanation appearing to be the lipotoxic effect of increased tissue fat in liver and muscle, as well as β-cells, due to increased adipocyte FFA and cytokine secretion. Rosiglitazone decreases both basal and insulin-stimulated FFA levels with a parallel effect on FFA turnover, in association with improvement in insulin receptor substrate-1 and insulin-stimulated glucose uptake. DeFronzo noted that FFA can enter cells both via binding proteins and directly, with increased intracellular fatty acid CoA leading to dissociation of inhibitor of κB from the NF-κB complex as well as increasing serum kinases, diacylglycerol, and ceramides, inactivating a variety of postreceptor processes of insulin action. All these FFA effects increase inflammation and atherosclerosis, with the thiazolidinediones improving these abnormalities. DeFronzo reviewed effects of thiazolidinediones on “fat topography,” suggesting that these agents increase subcutaneous and decrease intra-abdominal fat levels, with weight gain appearing to correlate with the benefit of these agents, leading DeFronzo to go so far as to say that “weight gain should be considered a cosmetic issue” in the use of these agents (16). Considering adipocyte fat to “overflow” into muscle and liver, causing insulin resistance, there also is evidence of

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spillover into β-cells, causing insulin resistance. Thiazolidinediones decrease islet fat, leading to decreased fatty acid CoA, reducing ceramide and a consequent decrease in β-cell apoptosis. Muraglitazar is a novel PPAR-α/γ activator, with this dual effect potentially increasing insulin sensitivity and decreasing hepatic triglyceride secretion (as well as increasing VLDL clearance). Study of this agent shows glucose lowering with a decrease in triglyceride, increase in HDL cholesterol, and decrease in non-HDL cholesterol and to a lesser extent in LDL cholesterol. In a study of 1,059 persons treated with >1,500 mg metformin daily plus either 5 mg muraglitazar or 30 mg pioglitazone daily, triglyceride decreased 28 vs. 14%, HDL increased 19 vs. 14%, and apoB decreased 12 vs. 6%, although we do not know whether a higher pioglitazone dose would have led to a greater effect.

Statins. Paul M. Ridker (Boston, MA) discussed the role of CRP in dyslipidemia and the concept that inflammation and atherosclerosis are tightly linked. CRP may be, he said, “more than a marker,” playing a role in atherosclerotic processes. Combined measurement of both CRP and LDL gives additional information regarding risk (17), with evidence that CRP adds prognostic information beyond the Framingham risk score in all major cohorts evaluated. CRP and IL-6 are also predictive of risk of type 2 diabetes, suggesting a relationship between inflammation and the metabolic syndrome, and within the metabolic syndrome stratification based on CRP may give additional information as to both risk of atherosclerotic events and risk of type 2 diabetes, although the number of metabolic syndrome components is also proportional to the CRP level, showing the complex interaction of these factors (18). CVD risk increases with increasing CRP in persons with diabetes, in those with metabolic syndrome, and in those with neither (19), leading Ridker to suggest that a CRP-modified Framingham risk score may be appropriate (20). There may also be a role for a CRP-modified definition of the metabolic syndrome, with Ridker suggesting three or more of the following factors: waist, triglyceride-to-HDL ratio, glucose, blood pressure, and CRP. Obesity is, however, an important determinant of elevated CRP in persons with metabolic syndrome (21). New data on non-HDL, apoA1 and -B100, standard lipid measures, and CRP show that there is low correlation of CRP with lipid measures and that non-HDL cholesterol has a very high correlation with apoB, with all of these parameters being good CVD risk predictors. In the PROVE IT (Pravastatin or Atorvastatin Evaluation and Infection Therapy) study, 4,162 persons with myocardial infarction or ACS were treated with the two agents. Atorvastatin (80 mg daily) reduced LDL cholesterol to 62 mg/dl, while pravastatin (40 mg daily) reduced LDL to 95 mg/dl, with 28% lower mortality with more aggressive treatment (22). In this study, LDL cholesterol levels <70 vs. ≥70 mg/dl and CRP levels <2 vs. ≥2 mg/l were additive in risk prediction, with patients treated with statins who achieve low CRP having better outcome than those whose CRP level remains elevated, regardless of the degree of lowering of LDL cholesterol. Ridker pointed out interesting studies suggesting that polymorphisms in CRP may be related to the effect of statins in lowering this marker, as well as to the risk of a given person, echoing Krauss’s recommendation that CRP should be added to the Framingham score, to the metabolic syndrome definition, and, perhaps, to LDL cholesterol measurement in treatment of persons with dyslipidemia. A number of genes are over- or underexpressed in metabolic syndrome, including some 100 genes related to inflammatory processes (23).

Steven E. Nissen (Cleveland, OH) reviewed cardiovascular biomarkers and coronary artery disease progression, addressing the link between LDL, CRP, and atherosclerosis. “The angiogram just gives us a silhouette of the vascular lumen,” he said, showing that the use of IVUS with a rotating ultrasound transducer gives a fuller understanding of atherosclerotic burden. The Glagov coronary remodeling hypothesis suggested that lumen narrowing occurs only late in the course of the disease, with well over 90% of the atheroma mass not narrowing the lumen, and those lesions narrowing the lumen actually responsible for little of the burden of CVD (24). Given the relatively linear relationship between LDL reduction and angiographic progression, but the evidence that even at LDL cholesterol levels around 100 mg/dl there was still some degree of progression, Nissen reviewed the REVERSAL (Reversal of Atherosclerosis with Aggressive Lipid Lowering) study, in which 502 persons were treated with 40 mg pravastatin versus 80 mg atorvastatin daily, with precise 1-mm ultrasound slices to assess the total atheroma volume before and following 18 months of treatment showing 2.7% progression vs. 0.4% regression of atheroma volume accompanying the decrease in mean LDL from 150 to 110 vs. 79 mg/dl (25). As expected, LDL change was linearly related to atherosclerosis progression. There was, however, a higher progression rate with pravastatin than with atorvastatin that was not explained by the difference in LDL lowering. CRP emerged as an important difference between the two agents, with pravastatin lowering CRP 5.2% and atorvastatin lowering CRP 36.4%, and there was a linear relationship between the suppression of CRP and atherosclerosis progression, with both parameters required to explain the difference between the two agents.

Peter Ganz (Boston, MA) gave further information about the anti-inflammatory effects of statins, asking whether these effects are “cholesterol independent,” and commenting that the term “pleiotropic” simply refers to effects of statins on many tissues including macrophages. In REVERSAL, the magnitude of CRP change was essentially independent of the LDL change. There is evidence that the early benefit of statin treatment in ACS is independent of LDL lowering. In a primate study comparing pravastatin and simvastatin, with high cholesterol feeding to prevent cholesterol lowering, there was a cholesterol-independent reduction in inflammation in atheroma (26). Comparison of ezetimibe versus simvastatin showed endothelial function benefit only with the latter (27). In the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) study, the degree of clinical benefit was independent of the change in LDL (28). Ganz reviewed the cholesterol biosynthetic pathway, noting that a number of products have biological activity, particularly geranylgeranyl diphosphate, which leads to Rho activation, causing inflammation, decreased eNOS, vasoconstriction, and prothrombotic effects. Inhibition of Rho kinase reduces neointima formation after balloon injury in animal models. Simvastatin decreases cerebral infarct size following middle cerebral artery occlusion in a mouse model, without reduction in serum cholesterol, by a pathway involving Rho inhibition and eNOS, with administration of geranylgeranyl diphosphate counteracting the effect (29). Atorvastatin (10 mg daily) inhibits Rho kinase activity in leukocytes of persons with atherosclerosis, correlating with CRP, platelet eNOS, and changes in LDL cholesterol,
so that different statins may differ in hepatic versus extrahepatic effects, with different durations of action and tissue distributions having different effects on LDL levels versus inflammation.

Fibrates. Anthony C. Keech (Sydney, Australia) described the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) trial (www.thefieldtrial.org) of 9,795 persons with diabetes randomized to fenofibrate versus placebo (30). The study closed in May 2005, and results will be available at the end of 2005. Seventy percent of those screened were entered in the study, suggesting that it will be representative of persons with diabetes. One-quarter of participants had a history of CVD, and three-quarters fulfilled the criteria for metabolic syndrome. Statin therapy, allowed where clinically warranted, was given to ~25% of patients. Baseline triglyceride was ~150, HDL 40, and LDL 120 mg/dl, with LDL decreasing 10%, apoB 14%, fibrinogen 11%, and triglycerides 25%, while HDL increased 7% during the initial 6 weeks of treatment. Creatinine increased 13%, an effect thought not related to a decrease in GFR, with intriguing recent evidence that fenofibrate decreases microalbuminuria.

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Peter Libby (Boston, MA) discussed the mechanisms of action and particular benefits of PPAR-α agonists in persons with type 2 diabetes and metabolic syndrome, describing diabetes as “not just a disease of glucose but... a vascular disease.” Atherosclerosis is an inflammatory process in all its stages, with diabetes linked to both inflammation and atherogenesis. The adipocyte is not only the source of substrate for lipid synthesis but also produces multiple factors, such as TNF-α, that increase vascular inflammation; there is also an inflammatory infiltrate in adipocytes that leads to further production of inflammatory mediators. Approaches to treatment include lifestyle measures, with decreased caloric intake and increased physical activity highly desirable although often not attained. Fibrates offer an additional approach. These agents have antiatherogenic properties, with the diabetic/insulin-resistant dyslipidemia pattern showing the greatest improvement in outcome only partially accounted for by their effects on lipids (31). Addressing potential mechanisms of the lipid-independent effect, Libby noted that PPAR-α is a nuclear receptor usually activated by fatty acids, which partition across the cell membrane into the nucleus, changing the configuration of PPAR-α in such a way as to bind retinoic X receptor with retinoic acid, with the activated heterodimer regulating a cassette of genes involved in HDL and fatty acid metabolism. There is evidence that human endothelial cells express PPAR-α and that fenofibrate inhibits TNF-α–induced vascular cell adhesion molecule-1 expression in a dose-dependent fashion (32) and inhibits leukocyte adherence to an activated endothelial monolayer. The potent procoagulant tissue factor is present in atherosclerotic lesions, and PPAR-α activators inhibit lipopolysaccharide-induced monocyte tissue factor activity. Another limb of the inflammatory system involved in atherosclerosis is the T-cell, which expresses both PPAR-α and -γ, with fenofibrate decreasing T-cell activation (33). Thus, fibrates increase HDL, decrease chylomicron and VLDL particle formation, and have direct anti-inflammatory effects. An additional non-lipid-dependent benefit shown for fenofibrate is increased expression of the cholesterol transporter ABCA1 (34). Another potential mechanism of benefit has been shown in a mouse model of angiotensin II–dependent hypertension, with fenofibrate prevention by inducing CYP 4A, leading to increased renal production of the vasodilator 10-HETE (35).

Combination therapy. Christie Ballantyne (Houston, TX) discussed tactics to be used in combination therapy for lipid disorders, usually based on a statin with addition of niacin, fibrates, ω-3 unsaturated fatty acids, ezetimibe, and PPAR-γ agonists. Future approaches include combination statin plus CETP inhibitor combination PPAR-α/γ agents, increasing reverse cholesterol transport with synthetic HDL or with apoA1 mimetics, and rimonabant. Niacin-statin combination treatment raises HDL >30%, fenofibrate-statin combination increases HDL 12–20%, and gemfibrozil-statin combinations are now infrequently used because of safety considerations. Benefits include better triglyceride lowering and HDL raising, as well as a modest additional decrease in LDL cholesterol, reductions in lipoprotein(a) with niacin, increases in LDL particle size, decreases in fibrinogen with fibrates, and decreased CRP and inflammation, although arguments against these approaches include increased cost and complexity, increased myositis risk with fibrate, increased hepatitis risk with sustained-release niacin, potential for other drug interactions, and lack of outcome data. A prescription ω-3 formulation will become available, with evidence of a trend to better CRP reduction when administered in combination with a statin. Ezetimibe did not further reduce CRP or triglyceride when given with fenofibrate but does appear to give additional CRP as well as LDL reduction when given in combination with a statin. The combination PPAR-α/γ agents tese-siltazair and muragliltazair show greater triglyceride lowering and HDL raising than pioglitazone and may prove advantageous. Thus, as combination therapy is well accepted in the treatment of hypertension, combinations may be of benefit in lipid treatment, particularly with development of “two in one pill” approaches.

Peter H. Jones (Houston, TX) discussed approaches to assessing the efficacy and safety of fibrate-statins combination therapies in the management of high-risk mixed dyslipidemia patients, noting the evidence of benefit of fibrate monotherapy in persons with diabetes and in those with metabolic syndrome. The National Cholesterol Education Program guidelines focus on LDL cholesterol but suggest that “for high risk patients who have elevated triglyceride or low LDL addition of a fibrate or niacin to LDL-lowering therapy can be considered” (36). The American Diabetes Association guidelines also give priority to LDL lowering, with niacin or fibrates for HDL raising and fibrates or niacin for triglyceride lowering also recommended (37). Combination statin-fibrate treatment lowers both LDL and triglyceride and raises HDL cholesterol, decreasing non-HDL cholesterol and increasing LDL particle size, with fenofibrate decreasing fibrinogen and uric acid (13), although with increased cost and with possible increased risk of adverse effects. In a study of persons with mixed dyslipidemia receiving simvastatin, addition of fenofibrate lowered triglyceride and VLDL, with further decrease in LDL and increase in HDL cholesterol (38). Jones contrasted the risk of adverse effect with high-dose simvastatin in the Heart Protection Study, which showed ~12 cases of liver or muscle toxicity per 10,000 persons, 211 nonfatal myocardial infarctions, 137 strokes, 259 revascularizations, and 117 coronary deaths prevented per 10,000 persons with this agent (39). Possible mechanisms of toxicity may involve the monomeric GTP-binding proteins Rho and Ras. Combination statin-fibrate use is probably best with lower doses of statins and should be avoided in persons with renal insuf-
ciency; in persons with concomitant cyclosporine, ketoconazole, erythromycin, protease inhibitor, or amiodarone treatment; or in elderly women.

Michael H. Davidson (Chicago, IL) discussed safety considerations for combination therapy for patients with metabolic syndrome, noting that the majority of persons optimally treated with statins will still have events. All statins at doses beyond the maximal recommended level cause muscle toxicity, which also is seen with increased age, in females, with decreased weight, and with renal insufficiency. Blood statin levels are elevated in persons with rhabdomyolysis, supporting this argument. Ezetimibe has no impact on statin drug levels and does not increase myopathy. No increase in statin blood levels are seen with niacin administration, although there is the possibility that high niacin doses may cause liver toxicity with development of myopathy, suggesting that lower doses should be used in combination therapy. Forty-four percent of rhabdomyolysis occurs in persons receiving statins with fibrates. Combined administration of gemfibrozil with a statin is associated with 5- to 15-fold increased risk of rhabdomyolysis (40,41), but fenofibrate has a different safety profile. It appears that gemfibrozil, but not fenofibrate or bezafibrate, interferes with glucuronidation, a secondary pathway for statin elimination. There is also evidence that gemfibrozil may increase glucose, an effect not seen with other fibrates.

References


29. FIELD Study Investigators: The need for a large-scale trial of fibrate therapy in diabetes: the rationale and design of the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study. Cardiovasc Diabetol 3:9, 2004


