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Therapy and clinical trials

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Ezetimibe, which is the first selective inhibitor of cholesterol absorption and appears to work through the Niemann-Pick C1-like 1 protein, has been approved by the US Food and Drug Administration for treatment of dyslipidemia. This drug is now available for use as monotherapy or in combination with other agents. Negredo *et al.* [1**] recently made a useful contribution to the literature on treatment of HIV-infected patients with antiretroviral associated dyslipidemia. In their 24-week study they evaluated the effect of ezetimibe in HIV-infected patients with poorly controlled anti-retroviral associated dyslipidemia (i.e. failure to achieve the LDL-cholesterol goal of <130 mg/dl) despite use of 20 mg/day pravastatin. The investigators found that addition of ezetimibe 10 mg/day to the regimen resulted in substantial reductions in total cholesterol and LDL-cholesterol. Also, they found a significant increase in HDL-cholesterol and apolipoprotein A-I. There were no significant effects on triglycerides, apolipoprotein B, homocysteine, or C-reactive protein (CRP) levels, however. In view of the substantial reduction in LDL-cholesterol, it is unclear why a significant reduction in apolipoprotein B was not achieved. In terms of anti-retroviral therapy, the patients were receiving either a protease inhibitor or a non-nucleoside reverse transcriptase inhibitor. In both groups of patients a similar reduction in LDL-cholesterol was observed, and 61.5% of patients achieved the target LDL-cholesterol of under 130 mg/dl. It is important to note that no patient discontinued therapy because of intolerance or suffered adverse effects such as increased liver enzymes (transaminases) or creatine kinase increases. Furthermore, no differences in lopinavir or nevirapine concentrations were observed during ezetimibe therapy. Although it is small in size ($n = 19$), the study demonstrates that control of dyslipidemia in HIV-infected patients receiving pravastatin can be enhanced by ezetimibe therapy; it therefore represents a step forward in the management of these patients.

In the VYTAL (Vytorin versus Atorvastatin in Patients with Type 2 Diabetes Mellitus and Hypercholesterolemia) study, Goldberg *et al.* [2**] compared the usual starting doses of ezetimibe/simvastatin (10/20 mg/day) with those of atorvastatin (10 or 20 mg/day), and the next highest doses of these agents (ezetimibe/simvastatin 10/40 mg/day versus atorvastatin 40 mg/day) over 6 weeks. In their double-blind multicenter study, the investigators demonstrated a significantly greater mean reduction in LDL-cholesterol levels with ezetimibe/simvastatin 10/20 mg/day (53.6%) than with atorvastatin 10 mg/day (38.3%) or 20 mg/day (44.6%). Also, they found that ezetimibe/simvastatin 10/40 mg/day yielded a greater reduction in LDL-cholesterol (57.6%) than did atorvastatin 40 mg/day (50.9%). The combination therapy at both doses was superior to atorvastatin with respect to the increase in HDL-cholesterol levels and decrease in non-HDL-cholesterol levels. With regard to plasma triglycerides and high-sensitivity CRP levels, however, the reduction in levels was significant only for the 10/20 mg/day dose of ezetimibe/simvastatin. Although only the 10/20 mg dose of ezetimibe/simvastatin was superior to atorvastatin in terms of reducing LDL-cholesterol to below 100 mg/dl,

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ezetimibe/simvastatin at all doses was superior to atorvastatin in achieving LDL-cholesterol levels below 70 mg/dl. Importantly, no serious adverse reactions were reported for either regimen. Diabetes is considered a cardiovascular risk equivalent, and therefore this study suggests that ezetimibe/simvastatin at the doses studied should be seriously considered as first-line therapy for patients. The American Diabetes Association (ADA) recommends a 30–40% reduction in LDL-cholesterol, and combination therapy with ezetimibe and simvastatin reduces LDL-cholesterol by more than 50% from baseline at the starting dose.

To summarize, these studies reported by Negredo *et al.* [1**] and Goldberg *et al.* [2**] suggest that ezetimibe is a welcome additional therapeutic option in patients with AIDS who do not attain their LDL-cholesterol goal, and that the ezetimibe/simvastatin combination should be considered first-line therapy in patients with diabetes, especially those with cardiovascular disease.

The metabolic syndrome confers a twofold increased risk for cardiovascular disease and a fivefold increased risk for diabetes. Boulon *et al.* [3**] evaluated the prevalence and characteristics of the metabolic syndrome in patients who have suffered an acute coronary syndrome. They also examined the effect of intensive risk factor management on mortality associated with the metabolic syndrome, as defined by both the National Cholesterol Education Program Adult Treatment Panel III (ATP-III) and the International Diabetes Federation (IDF) criteria. The percentage of patients with atherosclerosis was greater in the group with metabolic syndrome as defined by the ATP-III. During the follow-up period, there was an increase in total mortality in the metabolic syndrome group compared with the group without metabolic syndrome, as assessed using the IDF criteria. Thus, the investigators demonstrated that metabolic syndrome is highly prevalent following acute coronary syndrome, and this is especially true in young patients regardless of the criteria used (ATP-III or IDF). Based on the IDF definition, more than 33% of young patients who have suffered an acute coronary syndrome presented with metabolic syndrome, indicating that the IDF definition is effective at predicting risk for coronary artery disease. Use of the new cutoff of fasting glucose (100 mg/dl) in the ATP-III definition of metabolic syndrome might have improved prediction of risk for coronary artery disease, however. The ATP-III definition of metabolic syndrome appears to predict the extent of atherosclerosis better in patients with angiographically documented coronary artery disease. What is more important is that, regardless of definition used, patients with metabolic syndrome who underwent risk factor management exhibited no increase in cardiovascular death or events. It would be interesting to have some measure of insulin sensitivity, such as the homeostasis model assessment of insulin resistance or the quantitative insulin-sensitivity check index, to assess patients at follow up. Furthermore, metabolic syndrome prevalence at follow up could not be calculated because the investigators did not have data on waist circumference, which would have been ideal. Furthermore, although high-sensitivity CRP was assessed at 3 months, these values were not provided at follow up. Provision of these data would have been ideal because high-sensitivity CRP is an excellent biomarker for assessing response to intensive risk factor management in patients with acute coronary syndromes.

Young obese children may present with metabolic syndrome. Among the various adipokines, adiponectin appears to possess antiatherogenic and anti-inflammatory properties and may protect against cardiovascular disease. Gilardini *et al.* [4**] evaluated the utility of adiponectin as a biomarker of metabolic syndrome in obese children and adolescent persons. The reported that, when adjusted for all other variables, hypoadiponectinemia was independently associated with greater risk for metabolic syndrome ($P < .001$) and concluded that it is the best predictor of metabolic syndrome. In a study of 162 obese children and adolescent persons, they examined other potential biomarkers such as levels of plasminogen activator inhibitor (PAI)-1, interleukin-18, CRP, and fibrinogen. After adjusting for body mass index, high levels of PAI-1

and interleukin-18 and low levels of adiponectin were significantly more common in patients with metabolic syndrome than in those without metabolic syndrome. Because CRP levels correlate strongly with obesity, the investigators failed to identify significant differences in this marker between patients with and those without metabolic syndrome, possibly because of the levels being elevated in obese individuals. Although they propose that a cutoff of adiponectin of 8 µg/ml was the best predictor of metabolic syndrome, their population consisted of obese individuals who already had low levels of adiponectin, and their sample size was probably too small to allow them to establish appropriate cutoff values. Furthermore, they did not correlate adiponectin with insulin sensitivity using the clamp method (the 'gold standard') and failed to determine levels of high-molecular-weight adiponectin in their cohort, which appears to be more biologically relevant. In conclusion, there is no doubt that, with the increasing prevalence of metabolic syndrome and its associated co-morbidities, there is a need for a suitable biomarker. Metabolic syndrome is a chronic, low-grade inflammatory state. Thus, it is encouraging that low circulating levels of adiponectin can be used in risk assessment models, and this marker should ultimately be compared with others such as CRP and PAI-1 and correlated with indices of insulin resistance.

Recommended reading

Boulon C, Lafitte M, Richeboeuf V, *et al.* Prevalence of metabolic syndrome after acute coronary syndrome and its prognostic significance. *Am J Cardiol* 2006; 98:1429–1434. •• This study shows that metabolic syndrome is highly prevalent after an acute coronary syndrome, and that the IDF criteria are effective at predicting coronary artery disease risk in these patients. Furthermore, patients with metabolic syndrome who undergo risk factor management exhibit no increase in cardiovascular death or events.

Chapman CM, McQuillan BM, Beilby JP, *et al.* Interleukin-18 levels are not associated with subclinical carotid atherosclerosis in a community population. The Perth Carotid Ultrasound Disease Assessment Study (CUDAS). *Atherosclerosis* 2006; 189:414–419. • Interleukin-18 is a novel proinflammatory cytokine that plays a central role in innate and acquired immunity, making it a likely inflammatory candidate in atherosclerosis. In this cross-sectional community population, interleukin-18 levels were related to traditional risk factors and inflammatory markers, but they were not independently associated with subclinical carotid atherosclerosis.

Gilardini L, McTernan PG, Girola A, *et al.* Adiponectin is a candidate marker of metabolic syndrome in obese children and adolescents. *Atherosclerosis* 2006; 189:401–407. •• In this study of young obese children with metabolic syndrome, low levels of adiponectin were independently associated with greater risk for metabolic syndrome, and so adiponectin appears to be an ideal biomarker.

Goldberg RB, Guyton JR, Mazzone T, *et al.* Ezetimibe/Simvastatin vs Atorvastatin in Patients with Type 2 Diabetes Mellitus and Hypercholesterolemia: the VYTAL study. *Mayo Clin Proc* 2006; 81:1579–1588. •• In diabetic patients combining ezetimibe and simvastatin was a very potent therapeutic strategy in achieving LDL-cholesterol levels below 70 mg/dl. Furthermore, there were no major adverse reactions, and so this combination should be considered first-line therapy in diabetic patients with or without vascular disease. Also, combination achieved a significant increase in HDL-cholesterol and a decrease in non-HDL-cholesterol. These multiple effects on the lipid profile are clearly beneficial in the management of diabetic dyslipidemia.

Negredo E, Molto J, Puig J, *et al.* Ezetimibe, a promising lipid-lowering agent for the treatment of dyslipidemia in HIV-infected patients with poor response to statins. *AIDS* 2006; 20:2159–2164. •• This study demonstrates that control of dyslipidemia in HIV-infected patients

receiving pravastatin can be enhanced by ezetimibe therapy; it therefore represents a step forward in the management of these patients.

Neil HA, DeMicco DA, Luo D, *et al.*, CARDS Study Investigators. Analysis of efficacy and safety in patients aged 65–75 years at randomization: Collaborative Atorvastatin Diabetes Study (CARDS). *Diabetes Care* 2006; 29:2378–2384. •• This is a post-hoc analysis of the Collaborative Atorvastatin Diabetes Study that compared the efficacy and safety of atorvastatin between 1129 patients aged 65–75 years at randomization and 1709 younger patients. The overall safety profile of atorvastatin was similar between age groups. The results of the analysis strongly support the guidelines recommending statin treatment for all patients older than 40 years with type 2 diabetes, including the elderly, regardless of baseline LDL-cholesterol level.

Yoshida T, Yamagishi S, Nakamura K, *et al.* Telmisartan inhibits AGE-induced C-reactive protein production through downregulation of the receptor for AGE via peroxisome proliferator-activated receptor- γ activation. *Diabetologia* 2006; 49:3094–3099. • This in-vitro study conducted in the human hepatoma cell line demonstrated that telmisartan (a unique angiotensin II type 1 receptor blocker with peroxisome proliferator-activated receptor- γ modulating activity) suppresses production of reactive oxygen species and CRP synthesis, and decreases expression of RAGE (receptor for advanced glycation end-products) via peroxisome proliferator-activated receptor- γ activation in liver. It may play a protective role in vascular injury in diabetes.

Acknowledgements

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