Invited commentary

Achieving optimal lipid goals in the metabolic syndrome: A global health problem

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The metabolic syndrome is defined by a constellation of cardiometabolic risk factors that include abdominal obesity, elevated blood sugar, high blood pressure, low high-density lipoprotein (HDL) cholesterol and elevated triglycerides. The metabolic syndrome is diagnosed when 3 of these 5 risk factors are present [1]. Underlying these metabolic risk factors is adipose tissue dysfunction and insulin resistance which leads to an increase in circulating free fatty acids (FFA). Increased FFA delivery to the liver increases hepatic secretion and triglyceride enrichment of very-low-density lipoprotein (VLDL) cholesterol. Incomplete lipolysis of VLDL particles leads to an accumulation of triglyceride-rich remnant lipoproteins and triglyceride enrichment of HDL cholesterol via cholesteryl ester transfer protein (CETP) results in smaller HDL particles and low levels of HDL cholesterol [2]. Although low-density lipoprotein (LDL) cholesterol is not specifically part of the metabolic syndrome, individuals with the metabolic syndrome have a high concentration of small dense LDL cholesterol particles. The atherogenic dyslipidemia associated with the metabolic syndrome is an important risk factor for atherosclerosis and cardiovascular (CV) disease. The presence of the metabolic syndrome is associated with a 2-fold increased risk of CV disease and a 5-fold increased risk of diabetes [3].

The prevalence of the metabolic syndrome worldwide is on the rise. This is due to an increase in the rates of obesity in both adults and children, especially in developing countries [4]. Most deaths related to the metabolic syndrome are attributable to CV disease and this is mediated in large part by the hypertension and dyslipidemia associated with the metabolic syndrome. First-line management of the metabolic syndrome is lifestyle intervention; however when lifestyle changes alone are unsuccessful, pharmacologic therapy to target the high blood pressure and dyslipidemia associated with the metabolic syndrome is recommended. Statins are the drug of choice to target the dyslipidemia associated with the metabolic syndrome and are effective in lowering not only LDL cholesterol, but also lower triglyceride-rich remnant lipoproteins and have favorable effects on the size and concentration of LDL cholesterol particles [5]. Post-hoc analyses from several clinical outcome studies have shown that statin therapy reduces major CV event in patients with the metabolic syndrome [6,7] and subgroup analyses from other clinical trials suggest that fibrates, niacin and omega-3 fatty acids may further reduce CV risk in statin treated patients with high triglycerides and low HDL cholesterol [8–10]. Although the new ACC/AHA cholesterol lowering guidelines [11] do not specifically address the metabolic syndrome nor set cholesterol goals for treatment, most individuals who have the metabolic syndrome will have a high CV risk score or other indications that would warrant statin therapy. The National Lipid Association [12] and several international societies [13,14] also recommend lipid-lowering therapy for individuals with the metabolic syndrome and in contrast to the ACC/AHA cholesterol guidelines have set both LDL and non-HDL cholesterol goals for these patients. The question then is how successful have we been as clinicians in treating the dyslipidemia associated with the metabolic syndrome?

In this issue of Atherosclerosis, Wang and colleagues [15] help answer this question. They evaluated the use of lipid-lowering drugs and lipid goal attainment in patients with the metabolic syndrome from the large observational Dyslipidemia International Study of China (DYSIS-China). In this large study of 25,697 patients of varying CV risk, over one-third had the metabolic syndrome. Among these patients 37% had coronary heart disease and 57% had type 2 diabetes. Patients with the metabolic syndrome were less likely to achieve their LDL and non-HDL cholesterol goals compared to patients without the metabolic syndrome. LDL cholesterol goal attainment was achieved in 47% of patients with the metabolic syndrome compared to 69% in those without the metabolic syndrome (p < 0.001). Non-HDL cholesterol goals were achieved in 51% of patients with the metabolic syndrome compared to 72% in those without the metabolic syndrome (p < 0.001). The higher the CV risk
the less likely that the LDL cholesterol goal was attained. Among very high-risk individuals only 26% achieved their LDL cholesterol goal and 42% their non-HDL cholesterol goal. CV disease, diabetes, and systolic hypertension were some of the factors associated with failure to achieve optimal lipid goals. Almost all patients were on statin therapy, though the use of non-statins or combination lipid-lowering therapy was low as was the use of high potency statins. Among patients with the metabolic syndrome only 35% were treated with atorvastatin and 8% with rosuvastatin. The authors concluded that clinicians should consider more intense lipid-lowering therapy with combination lipid-lowering drugs in patients with the metabolic syndrome to better target their lipid goals and further reduce CV risk. These findings are not a surprise and are consistent with other studies that have shown that most high-risk patients do not achieve their optimal LDL and non-HDL cholesterol goals in clinical practice [16,17].

The strengths of this study are the large patient number and that the analysis was performed not just by the Chinese guidelines, but also by the American NCEP ATP III guidelines. The findings were similar irrespective of whether the American or Chinese guidelines were used. In the multinational L-TAP 2 survey only 30% of coronary heart disease patients achieved an optimal LDL cholesterol goal of <70 mg/dL [17]. The survey was conducted from 2006 to 2007 in over 10,000 patients from 9 countries and spanning 3 continents. Although it is somewhat difficult to compare L-TAP 2 with the current study by Wang and colleagues it appears that optimal lipid goal attainment in high-risk patients has not improved much since that survey was conducted. In the study by Wang and colleagues, what lifestyle interventions if any were performed and the doses of statins used were not reported? These are limitations of the study, however previous studies have shown that most high-risk patients are not prescribed a high intensity statin regimen. In a study of 9950 coronary artery disease patients in the United States, only 17% were on a high intensity statin regimen and 27% on combination lipid-lowering therapy [18]. Wang and colleagues found that the majority of metabolic syndrome patients fell into a very high or high-risk category and one explanation for why patients with the metabolic syndrome fail to achieve their optimal lipid goals is that they are assigned more aggressive lipid goals because of their higher risk.

So what are the clinical implications of the study by Wang and colleagues and how do we interpret their results in light of the current guidelines in cholesterol management? The study by Wang and colleagues highlights the fact that the metabolic syndrome and achieving optimal lipid goals in these patients are global health problems. We need a better understanding as to why patients with the metabolic syndrome are not achieving their optimal lipid goals and there are several possible reasons for this. Clinicians may underestimated the increased CV risk associated with the metabolic syndrome, patients may be intolerant to higher intensity statin drugs, and the lack of positive clinical outcome studies evaluating combination lipid-lowering therapy in high-risk patients may dissuade clinicians from using multiple lipid-lowering drugs in combination. Many patients with the metabolic syndrome will be considered high-risk and their LDL and non-HDL cholesterol goals may be difficult to achieve with statin therapy alone. Patient and physician awareness regarding the dyslipidemia and increased CV risk associated with the metabolic syndrome is needed. In patients with the metabolic syndrome, non-HDL cholesterol may be a better predictor of CV risk than LDL cholesterol. Among individuals with a discordantly high non-HDL compared to LDL cholesterol, CV risk may be underestimated when only LDL cholesterol is considered [19]. To this point the recent NLA cholesterol guidelines have placed non-HDL ahead of LDL cholesterol as a therapeutic target [12]. In addition clinical outcome studies of combination lipid-lowering therapy in patients with the metabolic syndrome who are inadequately treated with statin monotherapy are needed. However, even with a high intensity statin and combination lipid-lowering therapy many of these patients will not achieve their optimal lipid goals [20]. To improve lipid goal attainment and reduce CV risk worldwide we need to develop and implement better ways of addressing lifestyle changes to battle the increasing global rates of obesity and diabetes. Lifestyle changes can result in significant improvement in most components of the metabolic syndrome [21].

People in various parts of the world are more similar than different and we all share the propensity to develop atherosclerosis and CV disease, especially when lifestyle risk factors are not controlled. Pharmacologic therapy to treat the dyslipidemia associated with the metabolic syndrome will play an important role in reducing CV risk in these patients. However if we do not focus on real changes in lifestyle, as the world population grows larger so will their waistline and risk of CV disease.

Conflict of interest

Within the last 3 years I have received honorarium from Abbott, GSK, Astra Zeneca and Aegerion Pharmaceuticals.

References


