UPDATE IN CARDIOLOGY

Update on Evidence-Based Diagnosis and Management of Mixed Dyslipidemias

ARTURO MEDINA-RUIZ, MD

This article summarizes the principal publications and those evidence-based clinical trials on dyslipidemias, including their main findings and recommendations for practicing cardiologists and clinicians.

Emphasis is given to the confirmed data regarding the pathophysiology as well as the diagnoses of dyslipidemias, and the established therapeutic approaches validated in multiple well supervised control trials. The basic recommendations provided by the American Heart Association and the American College of Cardiology are presented as well as a brief description of the objectives, findings and results of the most recognized control trials, particularly those whose results have been published from 2000 to 2008.

The importance of aggressive therapy to reach target lipids goals other than LDL-cholesterol in mixed dyslipidemias with combination therapy is strongly pointed out and emphasized.

Key words: Dyslipidemias, Cardiovascular Dysmetabolic Syndrome, Clustering, Biomarker, Combination therapy

Mixed dyslipidemias is the name given to the presence of abnormal serum levels of more than one lipid fraction, particularly abnormal levels of triglycerides (TGL) and low density lipoprotein (LDL) cholesterol. The importance of this combination resides in the increased risk of coronary artery disease (CAD) associated to it.

Patients with mixed dyslipidemias are at high risk of developing coronary artery disease (1). Diabetic dyspilidemias, characterized by a triad of high triglycerides (TGL), low high density lipoproteins (HDL), and a high number of atherogenic small dense low density lipoprotein (LDL) particles, significantly increase the risk of coronary events (2). A cluster of cardiovascular risk factors, such as hypertension, abnormal glucose metabolism, obesity, and lipid abnormalities, have been given many names including Syndrome X, insulin resistance syndrome, the deadly quartet, the metabolic syndrome and the cardiovascular dysmetabolic syndrome (CVDS). The high prevalence of this condition is of utmost importance due to its association with a high risk of developing both cardiovascular disease and type 2 diabetes mellitus. The prevalence is higher in Hispanics than in Caucasians or Afro-Americans.

Professor of Medicine, from the Section of Cardiology, Department of Medicine, Medical Sciences Campus, University of Puerto Rico, San Juan, Puerto Rico

Address correspondence to: Arturo Medina Ruíz, MD, Section of Cardiology, Department of Medicine, UPR School of Medicine, PO Box 365067, San Juan, PR 00936-5067. Tel: (787) 781-6822 • Fax: (787) 754-1739 • E-mail: amrmd@yahoo.com

There is consensus as to several factors that need to be present for the diagnosis of CVDS: obesity, high levels of triglycerides, HDL cholesterol, fasting plasma glucose, blood pressure, and microalbuminuria. There is a significant variability in the definition by different entities, including the World Health Organization (WHO), the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III), and the International Diabetic Federation (IDF). Regardless of the lack of consensus in the definition of this syndrome, the truth is that its prevalence and association to cardiovascular disease makes early diagnosis and proper treatment important (3). It is estimated that 25% of the US population meets these diagnostic criteria. The National Heath and Nutrition Examination Survey shows that the CVDS has increased by 25% in the last decade, parallel to the increase in the prevalence of obesity and diabetes. The prevalence also increases with age, being six times more common in adults over 50 years of age as compared to younger adults between 20 to 29 years of age. The increased prevalence may be related to obesity, a sedentary lifestyle, as well as a higher prevalence of several other criteria for the diagnosis of the CVDS, such as hypertension and diabetes in the older age group.

There is a well-documented genetic predisposition to developing this condition (4). However, the CVDS in epidemic proportions is not only due to genes, but rather to the ethnic groups habits, physical activity and environmental factors that lead to obesity, hypertension, and lipid disorders. Excessive body fat is a major risk factor for insulin resistance, considered by many as the underlying disease mechanism for this syndrome. When

the deposits of body fat increase, the turnover of free fatty acids also increases, acting as a potent inhibitor of the action of insulin at the cellular level. Adipose tissue release of free fatty acids drives the production of triglycerides in the liver, increasing plasma triglycerides levels. Obesity also promotes insulin resistance by inducing a leptin-resistance state, increasing the levels of leptin, a potential inhibitor of the insulin receptor at the cellular level.

Obesity has been associated to an inflammatory state by increasing the production of pro-inflammatory cytokines by adipose tissue. Markers of inflammation such as C-reactive protein may cause insulin resistance as well, making inflammation both cause and consequence of impaired insulin sensitivity. Other risk factors independent to obesity are a sedentary lifestyle and a high consumption of refined carbohydrates and saturated fats. Changes in the level of physical activity and diet have shown to improve all of the components of the CVDS.

Each one of the components of the CVDS is an independent risk factor for cardiovascular disease. The clustering of risk factors in the CVDS increases the risk of cardiovascular events by two to four-folds, and increases the risk of developing type 2 diabetes mellitus by eight-folds.

The management of choice for the CVDS is lifestyle changes. However, this is "easier said than done". It takes motivation, tools to facilitate the change, and also tools to facilitate the maintenance of a healthy behavior. Exercise programs and nutritional recommendations are of utmost importance. Patients must understand that focusing on dietary changes and an active lifestyle is by far more important that focusing on the amount of weight loss.

At Mayo Clinic in Rochester, the Cardiometabolic Program is a six-week course that includes a DVD that specifies the risks of the CVDS and the lifestyle changes to modify them; exercise prescription, cooking demonstrations, and extensive educational material on behavioral changes, nutrition, and exercise.

In spite of the patient's motivation in lifestyle changes, some components of the CVDS may need pharmacotherapy. Blood pressure needs proper control and may need antihypertensive therapy. The management of dyslipidemia should be guided by the underlying risk or presence of cardiovascular disease. The focus should be on maintaining low density lipoprotein (LDL) at target values. Although statins are the first step in the treatment, patients remain at high risk for coronary heart disease and cardiovascular events due to the fact that elevated triglycerides and low HDL cholesterol levels are not adequately treated by statins. Although several therapies may be added to statins to further manage dyslipidemia, outcomes data lack information about the use of most of these agents along with a statin. Although fibrates, niacin and omega-3 fatty acids independently reduce cardiovascular risk and are an approved therapy for hypertriglyceridemia, no completed trials have examined the addition of these agents to statins in patients with mixed dyslipedimias.

According to the NECP ATP III, elevated triglycerides are a biomarker for increased risk of coronary heart disease. In 2007, the American Diabetic Association (ADA) and the American Heart Association (AHA) issued a joint scientific statement for the primary prevention of CVD in patients with diabetes. They recommend that LDL cholesterol be the primary target of therapy with a goal of <100 mg/dL. If triglycerides levels are ≥500 mg/dL, they become the priority in the management of dyslipidemia.

Several studies have shown that elevated triglycerides levels are associated with a high risk of the CHD. The Prospective Cardiovascular Munster Study (PROCAM) published by Dr. Gerd Assman in the American Journal of Cardiology in 1992 (5), and more recently a meta-analysis of 29 western prospective studies published by N. Sarwar in Circulation in 2007 (6), show evidence that the CHD risk biomarker stems from the increases of cholesterol enriched atherogenic remnant particles, IDL and LDL, by-products of the hydrolysis of triglyceride-rich lipoproteins, VLDL, and chylomicrons.

Lipoproteins with a high triglyceride content are very low density lipoproteins (VLDL) secreted by the liver, and chylomicrons produced in the gut from dietary fat. Niacin has two related mechanisms by which it reduces triglycerides levels. It blocks the release of free fatty acids from adipose tissue, the mechanism that drives the production of triglycerides in the liver.

Fibrates inhibit the secretion of triglycerides by the liver and stimulate the clearance of triglycerides by activating lipoprotein lipase, both mechanisms reduce the blood triglycerides levels.

Omega-3 fatty acids inhibit the release of triglycerides from the liver by a different mechanism from fibrates. Similarly to fibrates, they also stimulate lipoprotein lipase activity, increasing the clearance of triglycerides. This fish oil extract may increase the endogenous activity of lipoprotein lipase by 60% and that of hepatic lipase by 70% in healthy humans. The omega-3 fatty acids also increase the gene expression of lipoprotein lipase in adipose tissue, increasing lipoprotein lipase in plasma.

Atherogenic lipoprotein phenotypes, like small, dense LDL particles originate from defective triglycerides metabolism. Prescription omega-3 fatty acids induce a significant elevation of lipoprotein lipase mRNA expression in adipose tissue and post-hepatic lipoprotein lipase, reducing plasma triglycerides, attenuating the

post-prandial triglycerides response, and decreasing small dense LDL cholesterol.

A physiologic elevation of LDL cholesterol occurs with both omega-3 fatty acids and fibrates as lipoprotein lipase metabolizes VLDL particles secreted by the liver, removing triglycerides, shrinking the molecule into intermediate-density lipoprotein (IDL) and low density lipoprotein (LDL).

Epidemiologic evidence supports the fact that triglyceride elevations are an independent risk biomarker for coronary artery disease. I already mentioned the study conducted by Assman (PROCAM) and Sarwar's meta-analysis. The Baltimore Coronary Observational Long-Term Study (COLTS) published in the Journal of the American College of Cardiology in 1998 (7) showed a statistically significant reduction of CHD event survival in patients with triglyceride levels of 100mg/dL compared to those with levels below 100mg/dL.

There are three coronary heart disease prevention trials with fibrates: The Helsinky Heart Study (8) published by Vesa Manninen in 1992, a primary prevention study using gemfibrozil, showed a three-fold increase in cardiovascular events in high risk diabetic patients with triglycerides levels over 200mg/dL and an LDL/HDL ratio over five treated with placebo. Those patients assigned to gemfibrozil showed a 62% reduction in the incidence of CHD events compared to placebo treated patients.

The VA-HIT(9), a secondary prevention study with gemfibrozil, published by Rubins and Robins in the New England Journal of Medicine in 1999, showed a statistically significant 24% reduction in CHD events with gemfibrozil versus placebo.

The FIELDS Study (10), published by Keech, Sims and Barter in Lancet in 2005 using fenofibrate, is difficult to evaluate because many patients started statin therapy during the trial. Nevertheless, the trial showed a statistically significant 24% reduction in non-fatal myocardial infarctions (MI). However, it did not achieve its primary end point on secondary prevention patients.

A sub-group analysis of the Coronary Drug Project (11), published by Canner in the American Journal of Cardiology in 2005, revealed a reduction in the incidence of non-fatal MI with high dose niacin (3 grams daily) vs placebo in diabetic patients.

In the Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROactive) (12), published by Dormandy in Lancet in 2005, pioglitazone, a PPAR gamma agonist, caused a statistically significant reduction in triglycerides levels, a statistically significant increase in HDL cholesterol levels, and a statistically significant reduction in LDL/HDL ratio versus placebo. It also caused a significant 16% reduction in the combined risk of death, MI, and stroke, and a 37% reduction in the occurrence of acute coronary syndrome (ACS).

The GISSI-Prevenzione Trial (13), published by the GISSI group in Lancet in 2001, studied post MI patients assigned to omega-3 fatty acids, vitamin E, both or neither. Vitamin E had no effect in any of the end points, but the fish oil was associated with a statistically significant reduction in all cause mortality, apparently as early as 90 days into the trial, driven by a statistically significant reduction in sudden cardiac death.

The JELIS Study(14), published by Yokoyama and others in Lancet 2007, is the first trial combining a statin and omega-3 fatty acid therapy in hypercholesterolemic patients. The primary end point was the incidence of major cardiovascular events. The primary end point was achieved in 2.8% of the patients treated with fish oil plus a statin as compared to 3.5% in patients treated with a statin alone, resulting in a 19% reduction in favor of the combination therapy.

Other ongoing studies are the ACCORD Trial (15) in type 2 diabetes mellitus patients with the addition of fenofibrate to simvastatin; and the AIM HIGH in patients with the CVDS randomized to simvastatin alone or combined with niacin.

The Combination of Prescription Omega-3 Plus Simvastatin Trial (16), published by Dr. Harold Bays and others in Clinical Therapeutics last year, evaluated a common scenario of patients who reached the LDL goals with statin therapy but persist with hypertriglyceridemia. Many of the patients met the CVDS diagnostic criteria. The outcomes showed a 7.9% reduction in non-HDL (total cholesterol-HDLcholesterol), a 29.5% reduction in triglycerides, and a 3.4% increase in HDL-cholesterol, all favoring the combination therapy versus placebo plus simvastatin.

Many of our patients with mixed dyslipidemias (diabetic dyslipidemias, CVDS), like in the COMBOS Trial (16), persisted with elevated triglycerides after achieving LDL goals with statin monotherapy. Adding triglyceride lowering drugs to a statin helps to achieve the next treatment goal, according to the NCEP-NTP III, lowering the non-HDL cholesterol that sums the cholesterol carried by atherogenic lipoproteins.

I must add a short comment about the new controversy, extensively covered in the lay and scientific media, precipitated by the results of the ENHANCE Study (17). The editorials by Greenland and Lloyd-Jones (18) and that of Brown and Taylor (19) criticizing the study, have generated a far reaching controversy. I certainly believe in the honest statements made by the American College of Cardiology and the American Heart Association recognizing that the results of the ENHANCE Study are

preliminary. Further research is needed to confirm or deny this medical information. Dr. Robert M. Guthrie, a renowned lipid researcher and educator from the Ohio State University, wrote in the January 2008 issue of Courtlandt Forum (20) and I quote:

> "the goal of cholesterol management is not the correction of lipid numbers but the reduction in heart attack and other cardiac endpoints. At this point, statins remain the cornerstone of therapy for hyperlipidemia. As you consider whether to institute combination therapy for further reduction of one or more of the lipid fractions, you should carefully study the information about the benefits, or lack thereof, of combination therapy".

The first landmark statin trial, Scandinavian Simvastatin Survival Study, 4S, published in 1994, proved relative risk reductions in morbidity and mortality due to coronary heart disease. Other early trials (WOSCOPS, CARE, AFCAPS/TexCAPS, LIPID) in primary and secondary prevention, with other statins confirmed the 4S results. Other statin trials in the early 2000's (MIRACL, HPS, PROSPER ALLHAT-LLT, ASCOT, CARDS, ALLIANCE, PROVE IT, A to Z) focus on high-risk groups (ACS, elderly, diabetes, hypertension) and comparisons beyond placebo: versus usual care (ALLIANCE, ALLHAT-LLT) or active comparator (PROVE IT, A to Z). More recent studies focus on the value of intensive statin therapy in high risk patients (TNT, IDEAL) and patients with prior stroke or transient ischemic attack without established CHD (SPARCL).

There has been a significant evolution of the guidelines for lipid lowering since those of the NCEP ATP I of 1988. Evidence-based updates precipitated by the studies mentioned, have been evolving year after year. AHA/ACC guidelines emphasize the importance of evidence based treatment decisions and recommend physicians to consider the use of medications proven in clinical trials (21).

The ACC and AHA have released clarifying statements in the ENHANCE trial (17), reiterating previous recommendations:

> "The study reinforces the need to adhere to current ACC/AHA guidelines which recommend statins to the maximally tolerated dose or to goal as first line treatment for patients with coronary artery disease" (22).
>
> "Statins are the only drug class for lowering cholesterol that currently has evidence that heart attacks are prevented" (23).

There are guidelines based on evidence from the clinical trials mentioned above for practically any patient scenario you may encounter in your practice. Combination pharmacotherapy maybe necessary in patients with mixed dyslipidemias that persist with elevated lipids fractions after achieving LDL goals with statin therapy. I reviewed for you the options available, based on completed clinical trials. Other ongoing trials may add further information to achieve the next treatment goal.

Resumen

Se presenta un repaso de las principales publicaciones, incluidos los estudios clínicos sobre las dislipidemias, de la literatura médica desde 1990 hasta el presente, con recomendaciones basadas en evidencia para el beneficio de los cardiólogos y los clínicos en general. Se enfatiza en la fisiopatología confirmada de las dislipidemias así como también en las modalidades terapéuticas establecidas y confirmadas en los estudios clínicos. Se presentan las recomendaciones del Colegio Americano de Cardiología y de la Asociación Americana del Corazón basadas en objetivos, hallazgos y resultados de los más importantes estudios clínicos de las últimas décadas. Se señala y se enfatiza la importancia del manejo agresivo para alcanzar las metas de otros lípidos, aparte del colesterol-LDL, en las dislipidemias mixtas con terapia combinada.

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