

Combination Therapy in The Management of Diabetic Dyslipidemia

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Ischemic cardiovascular and cerebrovascular events are leading causes of morbidity and mortality the world over. Deranged lipid levels are important causal factor in the development of ischemic disease. According to data from the Framingham Heart Study, persons with total cholesterol levels above 260 mg/dl had a 33% risk of death versus 15% in persons with levels below 180 mg/dl over a period of 30 years.

The new NCEP ATP II guidelines call for more aggressive management of hypercholesterolemia. Although LDL-C is the primary target of anti-hyperlipidemic therapy, effective treatment of dyslipidemia also involves targeting non-HDL cholesterol and, by extension, treatment of elevated TG and low HDL-C levels. A number of therapeutic interventions including lifestyle changes and pharmacologic agents are available that can be used in combination therapy to treat dyslipidemia.

Statins are highly effective LDL-C lowering agents that reduce the incidence of cardiovascular events. In the Heart Protection Study (HPS), the Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) trial and the Scandinavian Simvastatin Survival Study (4S), statin therapy was accompanied by reduction in CHD mortality (approximately by 17%, 24% and 42%, respectively). The Cholesterol and Recurrent Events (CARE) study reported a 24% reduction in fatal and non-fatal coronary events. In individuals at moderate to high risk for an initial CAD event, there were reductions in fatal and non-fatal coronary events of 31% in WOSCOPS and 40% in AFCAPS / TexCAPS.

Despite these benefits, many statin-treated patients still have an initial or recurrent CHD event in spite of reductions in LDL-C. It is possible that more aggressive LDL lowering and correction of abnormalities in other lipoprotein subclasses will be accompanied by a larger reductions in CHD events.

NCEP/ATP committee has now provided a secondary target for lipid management, namely non-HDL cholesterol. This target was chosen because apoB lipoprotein B-100 levels are a somewhat more sensitive predictor of risk in all patients than LDL levels.

The apo B-100 identifies multiple atherogenic particles beyond LDL alone. A calculation of non-HDL-C (total cholesterol minus HDL) provides an excellent surrogate for apo B-100 and is easy to calculate based on a standard lipid profile.

Several additional classes of pharmacologic agents are available that favourably affect lipoprotein metabolism, including statins, bile acid resins, nicotinic acid, cholesterol absorption inhibitors, fibric acid and fish oil. Combination therapy with these agents enhances their effect on lipoproteins but often requires close monitoring to avoid toxicity. Use of a standard protocol can guide treatment and promote monitoring of essential laboratory tests.

In summary, combination therapy can be extremely effective for both control of combined dyslipidemia as well as in patients who have refractory elevations in their LDL levels. The order of priorities for the therapeutic targets should be to treat the LDL to goal first, with statin therapy being the cornerstone of treatment in most patients. If after the LDL goal has been achieved and the patient has a TG level of ≥ 200 mg/dl, the non-LDL cholesterol is calculated and the target for this is defined as 30 points over the LDL target. In patients who have elevated non-HDL cholesterol, the options include increasing the statin to drive the LDL lower or to consider combination therapy, usually with niacin or a fibrate, to lower TG and increase the HDL. In patients who have primarily LDL elevation, but who do not achieve their goal at maximal doses of statins or who can not tolerate maximal doses of statins, the addition of bile acid resins is effective in potentiating LDL lowering, and newer agents such as ezetimibe and rosuvastatin promise to be extremely useful.

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