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(54) Title: METHOD FOR TREATING ATHEROSCLEROSIS WITH AN MPT INHIBITOR AND CHOLESTEROL LOWERING DRUGS

(57) Abstract

A method is provided for preventing or reducing the risk of onset of a cardiovascular event by administering an MTP inhibitor alone or in combination with another cholesterol lowering drug such as an HMG CoA reductase inhibitor such as pravastatin, to a patient who may or may not have one or more risk factors for a coronary and/or cerebrovascular event such as hypercholesterolemia.

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METHOD FOR TREATING ATHEROSCLEROSIS WITH AN MPT INHIBITOR AND CHOLESTEROL LOWERING DRUGS

Field of the Invention

The present invention relates to a method for preventing or reducing the risk of or onset of cardiovascular events employing an MTP inhibitor alone or in combination with another cholesterol lowering drug, for example, an HMG CoA reductase inhibitor, such as pravastatin.

Background of the Invention

Despite significant progress in reducing mortality due to atherosclerotic coronary artery disease (CAD) over the last several years, cardiovascular disease remains the major cause of death in most developed countries. The relation between CAD and elevated concentrations of serum total cholesterol, particularly low-density lipoprotein (LDL) cholesterol, is well documented.

It is well established that lipid disorders are important factors in the development of coronary heart disease (CHD), Schettler, G., "The role of diet and drugs in lowering serum cholesterol in the postmyocardial infarction patient," Cardiovasc. Drugs Ther., 1989, 2/6 (795-799).

Glatter, T.R., "Hyperlipidemia. What is 'normal', who should be treated and how," Postgrad. Med., 1984, 76/6 (49-59), states that "As the Coronary Primary Prevention Trial has recently shown, a 1% reduction in cholesterol level produces a 2% reduction in risk of myocardial infarction."

Goldstein, J.L., et al, "The LDL receptor defect in familial hypercholesterolemia. Implications for pathogenesis and therapy," Med. Clin. North Am., 1982, 66/2 (335-362) indicate that "familial hypercholesterolemia was

the first genetic disorder recognized to cause myocardial infarction. To this day, it remains the outstanding example of a single-gene mutation that causes both hypercholes-terolemia and coronary atherosclerosis."

Satler, L.F., et al, "Reduction in coronary heart disease: Clinical and anatomical considera-tions," Clin. Cardiol., 1989, 12/8 (422-426) disclose that "the higher the total plasma cholesterol and low density lipoprotein cholesterol (LDL-C), the greater the risk that coronary artery disease will develop. Recently, clinical trials including the Coronary Drug Project, the Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT), and the Helsinki Heart Study provided evidence that lowering cholesterol reduces the frequency of fatal and nonfatal coronary events." In addition, Satler et al disclose that other studies "demonstrated that lowering of cholesterol was associated with a decreased incidence of progression of coronary disease, as well as with the potential for reduction in the atherosclerotic plaque."

Wilhelmsen, L., "Practical guidelines for drug therapy after myocardial infarction," Drugs, 1989, 38/6 (1000-1007) discloses that it is advisable to correct blood lipid disturbances in effective management of the postinfarction patient.

Yamamoto, A., et al, "Clinical features of familial hypercholesterolemia," Arteriosclerosis, Jan.-Feb. 1989, 9 (1 Suppl.) p I66-74, disclose that "in addition to the low density lipoprotein (LDL) cholesterol level, higher triglyceride and lower high density lipoprotein (HDL) cholesterol levels correlate with an increased risk of ischemic heart disease.

Other references disclosing the relation between CAD and elevated concentrations of serum total cholesterol include

1. Canner P.L. et al, "Fifteen year mortality in Coronary Drug Project patients: long-term benefit with niacin", J. Am. Coll. Cardiol. 1986; 8:1245-1255.

2. Frick, M.H. et al, "Helsinki Heart Study: primary-prevention trial with gemfibrozil in middle-aged men with dyslipidemia. Safety of treatment, changes in risk factors, and incidence of coronary heart disease," N. Engl. J. Med. 1987; 317:1237-1245.

3. Kannel, W.B. et al, "Serum cholesterol, lipoproteins, and the risk of coronary heart disease: the Framingham Study," Ann. Intern. Med. 1971; 74:1-12.

4. "The Lipid Research Clinics Program. The Lipid Research Clinics Coronary Primary Prevention Trial results, I: reduction in incidence of coronary heart disease," JAMA 1984; 251-351-364.

5. Martin, M.J. et al, "Serum cholesterol, blood pressure, and mortality: implications from a cohort of 361,662 men," Lancet 1986; 2:933-936.

Efforts to further reduce the mortality rate from CAD should benefit from appropriate screening for, and treatment of, hypercholesterolemia. Primary hypercholesterolemia is initially treated with a low-cholesterol low-fat diet and lifestyle modification. If these measures are inadequate, lipid lowering drugs are then added. Agents currently available for the treatment of hypercholesterolemia include bile acid-binding resins, nicotinic acid, probucol, fibrates, and 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors. Pravastatin, a member of the latter class, in doses up to 40 mg/day, reduces serum LDL cholesterol an average of 32 to 34% and total cholesterol an average of 24 to 26% in patients with primary hypercholesterolemia. Hunninghake, D.B. et al, "Efficacy and safety of pravastatin in patients with primary hypercholesterolemia, I: a dose-response study." Atherosclerosis 1990; 85:81-89.

European Patent Application 0461548A2 discloses use of an HMG CoA reductase inhibitor for preventing a second heart attack.

Pending U.S. Application Serial No. 08/424,984 filed April 19, 1995, discloses use of an HMG CoA reductase

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