(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
16 July 2009 (16.07.2009)

PCT

(10) International Publication Number
WO 2009/089144 A1

(51) International Patent Classification:
A01N 37/00 (2006.01) *A61K 31/19* (2006.01)

(21) International Application Number:
PCT/US2009/030095

(22) International Filing Date: 5 January 2009 (05.01.2009)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/018,962 4 January 2008 (04.01.2008) US

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declaration under Rule 4.17:
— *of inventorship (Rule 4.17(iv))*

Published:
— *with international search report*

(54) Title: KETONE BODIES AND KETONE BODY ESTERS AS BLOOD LIPID LOWERING AGENTS

(57) Abstract: The subject disclosure provides compositions for reducing serum cholesterol and/or triglyceride levels in subjects. These compositions can comprise racemic β-hydroxybutyrate or D-β-hydroxybutyrate, optionally in the acid form, physiologically compatible salts of racemic β-hydroxybutyrate or D-β-hydroxybutyrate, esters of D-β-hydroxybutyrate, oligomers of D-β-hydroxybutyrate containing from 2 to 20 or more monomeric units in either linear or cyclic form, racemic 1,3 butandiol or R- 1,3 butandiol alone and can be, optionally, administered in conjunction with a low fat diet to a subject. Alternatively, compositions comprising racemic β-hydroxybutyrate or D-β-hydroxybutyrate, optionally in the acid form, physiologically compatible salts of racemic β-hydroxybutyrate or D-β-hydroxybutyrate, esters of D-β-hydroxybutyrate, oligomers of D-β-hydroxybutyrate containing from 2 to 20 or more monomeric units in either linear or cyclic form, racemic 1,3 butandiol, R- 1,3 butandiol or combinations thereof can be formulated as nutritional supplements (also referred to as nutritional compositions) or incorporated into therapeutic compositions containing a) anti- hypertensive agents; b) anti-inflammatory agents; c) glucose lowering agents; or d) anti- lipemic agents) which are administered to a subject, optionally in combination with a low fat diet, in order to cause a reduction or lowering of: serum cholesterol levels; triglyceride levels; serum glucose levels, serum homocysteine levels, inflammatory proteins (e.g., C reactive protein) and/or hypertension in treated subjects. Alternatively, compositions disclosed herein can be administered alone, or in combination with other therapeutic agents to prevent or reverse vascular disease.

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DESCRIPTION

KETONE BODIES AND KETONE BODY ESTERS AS BLOOD LIPID LOWERING AGENTS

CROSS-REFERENCE TO RELATED APPLICATION

This application claims the benefit of U.S. Provisional Application Serial No. 61/018,962, filed January 4, 2008, the disclosure of which is hereby incorporated by reference in its entirety, including all figures, tables and amino acid or nucleic acid sequences.

BACKGROUND OF THE INVENTION

Vascular insufficiency, secondary to occlusive processes in the vasculature, constitutes a disease phenotype of wide applicability in a number of common disease states including among others: coronary insufficiency, cerebrovascular insufficiency, peripheral vascular insufficiency and impaired kidney perfusion. Among the major known predisposing factors causing narrowing of vasculature are: 1) elevated serum cholesterol, 2) elevated serum triglycerides, 3) elevated serum glucose, 4) elevated serum homocysteine, 5) certain inflammatory processes and 6) hypertension.

Ketone bodies cannot be utilized by liver, hence they can not be used to synthesize either triglycerides or cholesterol. Triglycerides and cholesterol are synthesized either from carbohydrates or lipids, which provide acetyl CoA, and thence respectively malonyl CoA or HMG CoA for the two synthetic pathways. The major source of blood cholesterol and triglyceride comes from liver where it is excreted into the blood as VLDL, the fatty acids of which are removed by various tissues to leave LDL in the blood.

The inventors of the subject patent application have found that feeding a subject a diet comprising, in part, esters or oligomers of the ketone body D-β-hydroxybutyrate and lowered dietary fat can reverse a number of the known predisposing factors leading to vascular diseases.

BRIEF SUMMARY OF THE INVENTION

The subject disclosure provides compositions for reducing serum cholesterol and/or triglyceride levels in subjects. These compositions can comprise racemic β-hydroxybutyrate

or D-β-hydroxybutyrate (optionally in the acid form), physiologically compatible salts of racemic β-hydroxybutyrate or D-β-hydroxybutyrate (*e.g.*, sodium, potassium, calcium or magnesium salts), esters of D-β-hydroxybutyrate, oligomers of D-β-hydroxybutyrate containing from 2 to 20 (or more) monomeric units in either linear or cyclic form, racemic 1,3 butandiol, R-1,3 butandiol or any combination thereof alone and can be, optionally, administered in conjunction with a low fat diet to a subject. Alternatively, compositions comprising racemic β-hydroxybutyrate or D-β-hydroxybutyrate (optionally in the acid form), physiologically compatible salts of racemic β-hydroxybutyrate or D-β-hydroxybutyrate (*e.g.*, sodium, potassium, calcium or magnesium salts), esters of D-β-hydroxybutyrate, oligomers of D-β-hydroxybutyrate containing from 2 to 20 (or more) monomeric units in either linear or cyclic form, racemic 1,3 butandiol, R-1,3 butandiol or any combination thereof can be formulated as nutritional supplements (also referred to as nutritional compositions) or incorporated into therapeutic compositions (compositions combining racemic β-hydroxybutyrate or D-β-hydroxybutyrate (optionally in the acid form), physiologically compatible salts of racemic β-hydroxybutyrate or D-β-hydroxybutyrate (*e.g.*, sodium, potassium, calcium or magnesium salts), esters of D-β-hydroxybutyrate, oligomers of D-β-hydroxybutyrate containing from 2 to 20 (or more) monomeric units in either linear or cyclic form, racemic 1,3 butandiol, R-1,3 butandiol or any combination thereof and a) anti-hypertensive agents; b) anti-inflammatory agents; c) glucose lowering agents; or d) anti-lipemic agents) which are administered to a subject, optionally in combination with a low fat diet, in order to cause a reduction or lowering of: serum cholesterol levels; triglyceride levels; serum glucose levels, serum homocysteine levels, inflammatory proteins (e.g., C reactive protein) and/or hypertension in treated subjects. Alternatively, racemic β-hydroxybutyrate or D-β-hydroxybutyrate (optionally in the acid form), physiologically compatible salts of racemic β-hydroxybutyrate or D-β-hydroxybutyrate (*e.g.*, sodium, potassium, calcium or magnesium salts), esters of D-β-hydroxybutyrate, oligomers of D-β-hydroxybutyrate containing from 2 to 20 (or more) monomeric units in either linear or cyclic form, racemic 1,3 butandiol, R-1,3 butandiol or any combination thereof can be administered alone, or in combination with other therapeutic agents to prevent or reverse vascular disease.

BRIEF DESCRIPTION OF THE TABLES

Table 1 provides details related to the diets fed to experimental animals.

Table 2 relates to plasma metabolite levels in non-fasting rats fed one of three diets for 7 or 66 days. The ketone diet doubled the plasma β-hydroxybutyrate concentrations at both 7 and 66 days. Total cholesterol levels were significantly lower in ketone-fed rats compared with rats fed a Western diet. After 66 days on the diets, plasma HDL and LDL levels were significantly lower, and the HDL/LDL ratios tended to be higher, in the ketone fed rats compared with the Western-diet fed rats. The triacylglycerol levels were significantly lower in the rats fed the ketone diet, compared with rats fed the Western diet. There were no effects of diet on plasma free fatty acid levels, but the rats fed the ketone diet for 66 days had lower plasma glucose levels.

Table 3 provides a listing of combination therapies used for the treatment of hypertension.

DETAILED DESCRIPTION OF THE INVENTION

The subject disclosure provides compositions for reducing serum cholesterol and/or triglyceride levels in subjects. These compositions can comprise racemic β-hydroxybutyrate or D-β-hydroxybutyrate (optionally in the acid form), physiologically compatible salts of racemic β-hydroxybutyrate or D-β-hydroxybutyrate (*e.g.*, sodium, potassium, calcium or magnesium salts), esters of D-β-hydroxybutyrate, oligomers of D-β-hydroxybutyrate containing from 2 to 20 (or more) monomeric units in either linear or cyclic form, racemic 1,3 butandiol, R-1,3 butandiol, or any combination thereof alone. Alternatively, compositions comprising racemic β-hydroxybutyrate or D-β-hydroxybutyrate (optionally in the acid form), physiologically compatible salts of racemic β-hydroxybutyrate or D-β-hydroxybutyrate (*e.g.*, sodium, potassium, calcium or magnesium salts), esters of D-β-hydroxybutyrate, oligomers of D-β-hydroxybutyrate containing from 2 to 20 (or more) monomeric units in either linear or cyclic form, racemic 1,3 butandiol, R-1,3 butandiol, or any combination thereof can be formulated as nutritional supplements (also referred to as nutritional compositions) or incorporated into therapeutic compositions (compositions combining racemic β-hydroxybutyrate or D-β-hydroxybutyrate (optionally in the acid form), physiologically compatible salts of racemic β-hydroxybutyrate or D-β-hydroxybutyrate (*e.g.*, sodium, potassium, calcium or magnesium salts), esters of D-β-hydroxybutyrate, oligomers of D-β-hydroxybutyrate containing from 2 to 20 (or more) monomeric units in either linear or cyclic form, racemic 1,3 butandiol, R-1,3 butandiol, or any combination thereof and a) anti-

hypertensive agents; b) anti-inflammatory agents; c) glucose lowering agents; or d) anti-lipemic agents) which are administered to a subject in order to cause a reduction or lowering of: serum cholesterol levels; triglyceride levels; serum glucose levels, serum homocysteine levels, inflammatory proteins (e.g., C reactive protein) and/or hypertension in treated subjects. Alternatively, racemic β-hydroxybutyrate or D-β-hydroxybutyrate (optionally in the acid form), physiologically compatible salts of racemic β-hydroxybutyrate or D-β-hydroxybutyrate (*e.g.*, sodium, potassium, calcium or magnesium salts), esters of D-β-hydroxybutyrate, oligomers of D-β-hydroxybutyrate containing from 2 to 20 (or more) monomeric units in either linear or cyclic form, racemic 1,3 butandiol, R-1,3 butandiol, or any combination thereof can be administered alone in a normal diet, or in combination with other therapeutic agents to prevent or reverse vascular disease. In any of these embodiments, the compositions can be administered to a subject in combination with a low fat diet.

The subject application provides compositions comprising racemic β-hydroxybutyrate or D-β-hydroxybutyrate (optionally in the acid form), physiologically compatible salts of racemic β-hydroxybutyrate or D-β-hydroxybutyrate (*e.g.*, sodium, potassium, calcium or magnesium salts), esters of D-β-hydroxybutyrate, oligomers of D-β-hydroxybutyrate containing from 2 to 20 (or more) monomeric units in either linear or cyclic form, racemic 1,3 butandiol, R-1,3 butandiol, or any combination thereof in combination with:

a) anti-lipemic agents;

b) anti-hypertensive agents (including those combination treatments set forth in the table entitled "Combination Drugs for Treatment of Hypertension" [Table 3]);

c) glucose lowering agents; or

d) anti-inflammatory agents.

Non-limiting examples of anti-hypertensive agents that can be used in the formulation of compositions according to the subject invention include, and are not limited to, captopril (CAPOTEN), benazepril (LOTENSIN), enalapril (VASOTEC), lisinopril (PRINIVIL, ZESTRIL) fosinopril (MONOPRIL), ramipril (ALTACE), perindopril (ACEON), quinapril (ACCUPRIL), moexipril (UNIVASC), trandolapril (MAVIK), candesartan (ATACAND), eprosartan (TEVETAN), irbesartan (AVAPRO), telmisartan (MYCARDIS), valsartan (DIOVAN), losartan (COZAAR), atenolol (TENORMIN), propranolol (INDERAL), metoprolol (TOPROL), nadolol (CORGARD), betaxolol (KERLONE), acebutolol (SECTRAL), pindolol (VISKEN), bisoprolol (ZEBETA), hydrochlorothiazide

(HYDRODIURIL), furosemide (LASIX), torsemide (DEMADEX), the combination of triamterene and hydrochlorothiazide (DYAZIDE), metolazone (ZAROXOLYN), ethacrynic acid, nisoldipine (SULAR), nifedipine (ADALAT, PROCARDIA), nicardipine (CARDENE), bepridil (VASCOR), isradipine (DYNACIRC), nimodipine (NIMOTOP), felodipine (PLENDIL), amlodipine (NORVASC), diltiazem (CARDIZEM), verapamil (CALAN, ISOPTIN), terazosin (HYTRIN), doxazosin (CARDURA), tamsulosin (FLOMAX), alfuzosin (UROXATRAL) or clonidine (CATAPRES) and the combination therapies disclosed in the table below (entitled "Combination Drugs for Treatment of Hypertension" (Table 3)). These agents are formulated with racemic β-hydroxybutyrate or D-β-hydroxybutyrate (optionally in the acid form), physiologically compatible salts of racemic β-hydroxybutyrate or D-β-hydroxybutyrate (*e.g.*, sodium, potassium, calcium or magnesium salts), esters of D-β-hydroxybutyrate, oligomers of D-β-hydroxybutyrate containing from 2 to 20 (or more) monomeric units in either linear or cyclic form, racemic 1,3 butandiol, R-1,3 butandiol, or any combination thereof to provide compositions useful for the reduction or lowering hypertension in treated subjects. These compositions can also be used to prevent or reverse vascular disease in a subject.

With respect to glucose lowering agents, there are four major classes of oral glucose lowering agents. These include the biguanides (e.g., metformin), sulfonylureas (e.g., glyburide), thiazolidinediones and alpha-glucosidase inhibitors. Thus, the subject invention also provides compositions comprising D-β-hydroxybutyrate and esters or precursors thereof in combination with biguanides (*e.g.*, metformin), sulfonylureas (*e.g.*, glyburide), thiazolidinediones and/or alpha-glucosidase inhibitors that are useful for lowering blood glucose levels in a subject.

The subject invention also provides compositions comprising racemic β-hydroxybutyrate or D-β-hydroxybutyrate (optionally in the acid form), physiologically compatible salts of racemic β-hydroxybutyrate or D-β-hydroxybutyrate (*e.g.*, sodium, potassium, calcium or magnesium salts), esters of D-β-hydroxybutyrate, oligomers of D-β-hydroxybutyrate containing from 2 to 20 (or more) monomeric units in either linear or cyclic form, racemic 1,3 butandiol, R-1,3 butandiol, or any combination thereof in combination with anti-lipemic agents (e.g., probucol, niacin, omega 3 ethyl esters or omega 3 fatty acids), bile acid sequesterants (e.g., cholestyramine, cholestyramine-sucrose, cholestyramine-aspartame, colesevelam or colestipol), cholesterol absorption inhibitors (e.g., ezetimibe or ezetimibe-

simvastatin) , fibric acid derivatives (e.g., fenofibrates or gemfibrozil), and/or HMG-CoA reductase inhibitors (amlodipine-atorvastatin, atorvastatin, fluvastatin, lovastatin, niacin-lovastatin, pravastatin, rosuvastatin, simvastatin). Such compositions can be used to reduce or lower serum cholesterol levels or triglyceride levels in a subject.

Compositions comprising anti-inflammatory agents and racemic β-hydroxybutyrate or D-β-hydroxybutyrate (optionally in the acid form), physiologically compatible salts of racemic β-hydroxybutyrate or D-β-hydroxybutyrate (*e.g.*, sodium, potassium, calcium or magnesium salts), esters of D-β-hydroxybutyrate, oligomers of D-β-hydroxybutyrate containing from 2 to 20 (or more) monomeric units in either linear or cyclic form, racemic 1,3 butandiol, R-1,3 butandiol, or any combination thereof are also provided by the subject application. Anti-inflammatory agents include, but are not limited to: aspirin, salsalate, diflunisal, ibuprofen, ketoprofen, nabumetone, piroxicam, naproxen, diclofenac, indomethacin, sulindac, tolmetin, etodolac, ketorolac, oxaprozin or celecoxib. Thus, the subject invention also provides for the treatment of inflammation comprising the administration of compositions comprising racemic β-hydroxybutyrate or D-β-hydroxybutyrate (optionally in the acid form), physiologically compatible salts of racemic β-hydroxybutyrate or D-β-hydroxybutyrate (*e.g.*, sodium, potassium, calcium or magnesium salts), esters of D-β-hydroxybutyrate, oligomers of D-β-hydroxybutyrate containing from 2 to 20 (or more) monomeric units in either linear or cyclic form, racemic 1,3 butandiol, R-1,3 butandiol, or any combination thereof alone, or in combination with anti-inflammatory agents.

The subject invention also provides for the use of the aforementioned compositions comprising racemic β-hydroxybutyrate or D-β-hydroxybutyrate (optionally in the acid form), physiologically compatible salts of racemic β-hydroxybutyrate or D-β-hydroxybutyrate (*e.g.*, sodium, potassium, calcium or magnesium salts), esters of D-β-hydroxybutyrate, oligomers of D-β-hydroxybutyrate containing from 2 to 20 (or more) monomeric units in either linear or cyclic form, racemic 1,3 butandiol, R-1,3 butandiol, or any combination thereof for the preparation of a medicament for lowering or reducing serum cholesterol; triglyceride levels; serum glucose levels, serum homocysteine levels, inflammatory proteins (e.g., C reactive protein) and/or hypertension in a subject. The use described in this paragraph can optionally comprise the administration of the aforementioned compositions to a subject in conjunction with the administration of a low fat diet to a subject.

Thus, in one embodiment of the invention, a use of a composition, as described above, comprising racemic β-hydroxybutyrate or D-β-hydroxybutyrate (optionally in the acid form), physiologically compatible salts of racemic β-hydroxybutyrate or D-β-hydroxybutyrate (*e.g.*, sodium, potassium, calcium or magnesium salts), esters of D-β-hydroxybutyrate, oligomers of D-β-hydroxybutyrate containing from 2 to 20 (or more) monomeric units in either linear or cyclic form, racemic 1,3 butandiol, R-1,3 butandiol, or any combination thereof(alone or in combination with other agents (e.g., a) anti-lipemic agents; b) anti-hypertensive agents (including those combination treatments set forth in Table 3, entitled "Combination Drugs for Treatment of Hypertension"); c) glucose lowering agents; or d) anti-inflammatory agents)) to lower or reduce serum cholesterol levels; triglyceride levels; serum glucose levels, serum homocysteine levels, inflammatory proteins (e.g., C reactive protein) and/or hypertension in a subject is provided. These compositions can be administered to a subject orally (e.g., in the form of the diet of the subject (a nutritional composition for example) or via the administration of therapeutic compositions comprising racemic β-hydroxybutyrate or D-β-hydroxybutyrate (optionally in the acid form), physiologically compatible salts of racemic β-hydroxybutyrate or D-β-hydroxybutyrate (*e.g.*, sodium, potassium, calcium or magnesium salts), esters of D-β-hydroxybutyrate, oligomers of D-β-hydroxybutyrate containing from 2 to 20 (or more) monomeric units in either linear or cyclic form, racemic 1,3 butandiol, R-1,3 butandiol, or any combination thereof), parenterally, via injection or rectally. Again, the compositions described herein can be administered alone or in conjunction with a low fat diet to the subject.

In certain preferred embodiments, the methods of the subject application comprise the oral administration of compositions comprising racemic β-hydroxybutyrate or D-β-hydroxybutyrate (optionally in the acid form), physiologically compatible salts of racemic β-hydroxybutyrate or D-β-hydroxybutyrate (*e.g.*, sodium, potassium, calcium or magnesium salts), esters of D-β-hydroxybutyrate, oligomers of D-β-hydroxybutyrate containing from 2 to 20 (or more) monomeric units in either linear or cyclic form, racemic 1,3 butandiol, R-1,3 butandiol, or any combination thereof. These orally administered compositions have the benefit of lowering serum cholesterol, triglyceride and/or glucose levels in a subject, including those instances where the compositions are orally administered as a part of a low fat diet to the subject. For the purposes of this invention, the term "subject" is directed to mammals and, in certain embodiments, humans. "Administering" "administered" or

"administer" is defined as the introduction of the disclosed compositions into a subject via oral, nasal, ocular, rectal, vaginal and parenteral routes.

Compositions comprising racemic β-hydroxybutyrate or D-β-hydroxybutyrate (optionally in the acid form), physiologically compatible salts of racemic β-hydroxybutyrate or D-β-hydroxybutyrate (*e.g.*, sodium, potassium, calcium or magnesium salts), esters of D-β-hydroxybutyrate, oligomers of D-β-hydroxybutyrate containing from 2 to 20 (or more) monomeric units in either linear or cyclic form, racemic 1,3 butandiol, R-1,3 butandiol, or any combination thereof may be administered alone (e.g., a composition comprising racemic β-hydroxybutyrate or D-β-hydroxybutyrate (optionally in the acid form), physiologically compatible salts of racemic β-hydroxybutyrate or D-β-hydroxybutyrate (*e.g.*, sodium, potassium, calcium or magnesium salts), esters of D-β-hydroxybutyrate, oligomers of D-β-hydroxybutyrate containing from 2 to 20 (or more) monomeric units in either linear or cyclic form, racemic 1,3 butandiol, R-1,3 butandiol, or any combination thereof and lacking any other therapeutic ingredient) or in combination with other agents (e.g., a) anti-lipemic agents; b) anti-hypertensive agents (including those combination treatments set forth in Table 3, entitled "Combination Drugs for Treatment of Hypertension"); c) glucose lowering agents; or d) anti-inflammatory agents) via any route of administration and, optionally, in conjunction with the administration or intake of a low fat diet by the subject. These routes of administration include, and are not limited to, subcutaneous (SQ), intramuscular (IM), intravenous (IV), intraperitoneal (IP), intradermal (ID), via the nasal, ocular or oral mucosa (IN), or orally (PO). When the compositions disclosed herein are administered orally, the compositions can be provided to the subject in the form of the diet eaten by the subject or in pills or other unit dose forms. A unit dose form can be a packaged preparation, such as packeted tablets, capsules, and powders in paper or plastic containers or in vials or ampoules. Also, the unit dosage can be a liquid based preparation or formulated to be incorporated into solid food products, chewing gum, or lozenge. As described herein, the phrase "in combination" is to be interpreted as the administration of compositions comprising racemic β-hydroxybutyrate or D-β-hydroxybutyrate (optionally in the acid form), physiologically compatible salts of racemic β-hydroxybutyrate or D-β-hydroxybutyrate (*e.g.*, sodium, potassium, calcium or magnesium salts), esters of D-β-hydroxybutyrate, oligomers of D-β-hydroxybutyrate containing from 2 to 20 (or more) monomeric units in either linear or cyclic form, racemic 1,3 butandiol, R-1,3 butandiol, or any combination thereof with other agents

either together (in a single composition), separately (*i.e.*, a first composition comprising racemic β-hydroxybutyrate or D-β-hydroxybutyrate (optionally in the acid form), physiologically compatible salts of racemic β-hydroxybutyrate or D-β-hydroxybutyrate (*e.g.*, sodium, potassium, calcium or magnesium salts), esters of D-β-hydroxybutyrate, oligomers of D-β-hydroxybutyrate containing from 2 to 20 (or more) monomeric units in either linear or cyclic form, racemic 1,3 butandiol, R-1,3 butandiol, or any combination thereof and a second composition comprising another agent (e.g., a) anti-lipemic agents; b) anti-hypertensive agents (including those combination treatments set forth in the table entitled "Combination Drugs for Treatment of Hypertension" [Table 3]); c) glucose lowering agents; or d) anti-inflammatory agents)) or sequentially. For the sequential administration of a first and second composition to be considered a combination therapy (e.g., "in combination"), the first and second compositions must be administered separated by a time interval that still permits the first composition to be used during a treatment cycle of the second composition, or that permits the first composition to show enhanced activity, particularly activity, when compared with the single components alone. In the context of this invention, the term "activity" relates to an ability to lower serum cholesterol levels; triglyceride levels; serum glucose levels, blood sugar levels, serum homocysteine levels, inflammatory proteins, inflammation or blood pressure/hypertension.

Racemic β-hydroxybutyrate or D-β-hydroxybutyrate (optionally in the acid form), physiologically compatible salts of racemic β-hydroxybutyrate or D-β-hydroxybutyrate (*e.g.*, sodium, potassium, calcium or magnesium salts), esters of D-β-hydroxybutyrate, oligomers of D-β-hydroxybutyrate containing from 2 to 20 (or more) monomeric units in either linear or cyclic form, racemic 1,3 butandiol, R-1,3 butandiol, or any combination thereof are administered to an individual in an amount that results in blood concentrations of between 0.1 to 25 mM of D-β-hydroxybutyrate plus acetoacetate, or preferably between 0.4 to 10 mM or most preferred between 0.6 and 3 mM blood levels of D-β-hydroxybutyrate plus acetoacetate. Alternatively, the methods may recite the levels of racemic β-hydroxybutyrate or D-β-hydroxybutyrate (optionally in the acid form), physiologically compatible salts of racemic β-hydroxybutyrate or D-β-hydroxybutyrate (*e.g.*, sodium, potassium, calcium or magnesium salts), esters of D-β-hydroxybutyrate, oligomers of D-β-hydroxybutyrate containing from 2 to 20 (or more) monomeric units in either linear or cyclic form, racemic 1,3 butandiol, R-1,3 butandiol, or any combination thereof that are to be administered to an individual in terms of

percentages. Thus, racemic β-hydroxybutyrate or D-β-hydroxybutyrate (optionally in the acid form), physiologically compatible salts of racemic β-hydroxybutyrate or D-β-hydroxybutyrate (*e.g.*, sodium, potassium, calcium or magnesium salts), esters of D-β-hydroxybutyrate, oligomers of D-β-hydroxybutyrate containing from 2 to 20 (or more) monomeric units in either linear or cyclic form, racemic 1,3 butandiol, R-1,3 butandiol, or any combination thereof can be administered in amounts that range from 2-100% of the diet of an individual, or preferably 5-70% of the diet of an individual, or most preferred 5-30% of the diet of the individual. These percentages refer to the total caloric intake of the individual. Additionally, any combination of racemic β-hydroxybutyrate or D-β-hydroxybutyrate (optionally in the acid form), physiologically compatible salts of racemic β-hydroxybutyrate or D-β-hydroxybutyrate (*e.g.*, sodium, potassium, calcium or magnesium salts), esters of D-β-hydroxybutyrate, oligomers of D-β-hydroxybutyrate containing from 2 to 20 (or more) monomeric units in either linear or cyclic form, racemic 1,3 butandiol or R-1,3 butandiol can be administered to an individual in accordance with the aforementioned methods.

EXAMPLES

Animals were fed diets comprising the various components as set forth in Table 1. The animals were then tested to determine total cholesterol levels, low density lipoprotein levels, high density lipoprotein levels, triacylglycerol levels, free fatty acid levels and plasma glucose levels. **Table 2** relates to plasma metabolite levels in non-fasting rats fed one of three diets for 7 or 66 days. The ketone diet doubled the plasma β-hydroxybutyrate concentrations at both 7 and 66 days. Total cholesterol levels were significantly lower in ketone-fed rats compared with rats fed a Western diet. After 66 days on the diets, plasma HDL and LDL levels were significantly lower, and the HDL/LDL ratios tended to be higher, in the ketone fed rats compared with the Western-diet fed rats. The triacylglycerol levels were significantly lower in the rats fed the ketone diet, compared with rats fed the Western diet. There were no effects of diet on plasma free fatty acid levels, but the rats fed the ketone diet for 66 days had lower plasma glucose levels.

Table 1. Diet macronutrient composition. All diets contained the same energy (kcal/g), but had different macronutrients.

Diet	Energy	Fat	Protein	Carbohydrate	Ketone
	(kcal/g)		(%kcal)		
Western	1.76	34	27	39	0
Carbohydrate	1.76	4	26	70	0
Ketone	1.76	4	27	39	30

Table 2. Non-fasting rat plasma metabolite levels measured after feeding a Western, high carbohydrate or ketone diet for 7 (upper section) or 66 ± 3 days (lower section).

Plasma metabolites after 7 days on diet	**Western diet (n = 10)**	**Ketone diet (n = 10)**
β-Hydroxybutyrate (mM)	0.41 ± 0.03	0.85 ± 0.10***
Cholesterol (mM)	1.9 ± 0.1	1.2 ± 0.1***
Triacylglycerol (mM)	1.95 ± 0.15	0.79 ± 0.11**
Free fatty acids (mM)	0.11 ± 0.01	0.15 ± 0.02
Glucose (mM)	15 ± 1	14 ± 1

Plasma metabolites after 66 days on diet	Western diet (n = 10)	Carbohydrate diet (n = 10)	Ketone diet (n = 10)
β-Hydroxybutyrate (mM)	0.48 ± 0.06	0.59 ± 0.14	0.91 ± 0.20*
Cholesterol (mM)	2.3 ± 0.2	1.6 ± 0.2	1.1 ± 0.1***
HDL (mM)	0.69 ± 0.03	0.47 ± 0.04***	0.33 ± 0.05***
LDL (mM)	0.22 ± 0.03	0.13 ± 0.03*	0.09 ± 0.02***
HDL/LDL	3.4 ± 0.3	4.2 ± 0.6	4.4 ± 0.5
Triacylglycerol (mM)	1.11 ± 0.13	0.92 ± 0.09	0.67 ± 0.11***
Free fatty acids (mM)	0.23 ± 0.09	0.23 ± 0.03	0.26 ± 0.04
Glucose (mM)	12.8 ± 0.42	14.9 ± 2.1	8.6 ± 1.1**

*P < 0.05; **$P < 0.01$; ***$P < 0.001$ vs. Western diet.

Table 3. Combination Drugs for Treatment of Hypertension

amiloride and hydrochlorothiazide
spironolactone and hydrochlorothiazide
triamterene and hydrochlorothiazide
triamterene and hydrochlorothiazide
atenolol and chlorthalidone
bisoprolol and hydrochlorothiazide
metoprolol and hydrochlorothiazide
nadolol and bendroflumethazide
propranolol and hydrochlorothiazide
propranolol and hydrochlorothiazide
timolol and hydrochlorothiazide
benazepril and hydrochlorothiazide
captopril and hydrochlorothiazide
enalapril and hydrochlorothiazide
lisinopril and hydrochlorothiazide
lisinopril and hydrochlorothiazide
moexipril and hydrochlorothiazide
losartan and hydrochlorothiazide
valsartan and hydrochlorothiazide
amlodipine and benazepril
diltiazem and enalapril
felodipine and enalapril
verapamil and trandolapril
clonidine and chlorthalidone
hydralazine and hydrochlorothiazide
methyldopa and hydrochlorothiazide
prazosin and polythiazide

CLAIMS

We claim:

1. A method for reducing or lowering a biological parameter comprising the administration of a composition comprising racemic β-hydroxybutyrate or D-β-hydroxybutyrate, optionally in the acid form, physiologically compatible salts of racemic β-hydroxybutyrate or D-β-hydroxybutyrate, esters of D-β-hydroxybutyrate, oligomers of D-β-hydroxybutyrate containing from 2 to 20 or more monomeric units in either linear or cyclic form, racemic 1,3 butandiol, R-1,3 butandiol, or combinations thereof alone, or in combination with an additional therapeutic agent, to a subject so as to raise blood D-β-hydroxybutyrate plus acetoacetate from between 0.1 to 20 mM, between 0.5 and 10 mM or between 1 to 3 mM.

2. The method according to claim 1, wherein said composition comprising racemic β-hydroxybutyrate or D-β-hydroxybutyrate, optionally in the acid form, physiologically compatible salts of racemic β-hydroxybutyrate or D-β-hydroxybutyrate, esters of D-β-hydroxybutyrate, oligomers of D-β-hydroxybutyrate containing from 2 to 20 or more monomeric units in either linear or cyclic form, racemic 1,3 butandiol, R-1,3 butandiol or combinations thereof alone is administered in the form of the subject's diet.

3. The method according to claim 1, wherein said method comprises the administration of a first composition comprising racemic β-hydroxybutyrate or D-β-hydroxybutyrate, optionally in the acid form, physiologically compatible salts of racemic β-hydroxybutyrate or D-β-hydroxybutyrate, esters of D-β-hydroxybutyrate, oligomers of D-β-hydroxybutyrate containing from 2 to 20 or more monomeric units in either linear or cyclic form, racemic 1,3 butandiol, R-1,3 butandiol, or combinations thereof in combination with a second composition comprising a therapeutic agent, wherein said first and second compositions are administered separately, sequentially or together and each composition is in unit dosage form.

4. The method according to claim 3, wherein said therapeutic agent is selected from glucose/blood sugar lowering agents, lipid lowering(anti-lipemic) agents, blood pressure lowering agents (anti-inflammatory agents), or agents that reduce inflammation (anti-inflammatory agents).

5. The method according to claim 1 or 3 or 4, wherein said therapeutic agent is selected from: captopril (CAPOTEN), benazepril (LOTENSIN), enalapril (VASOTEC), lisinopril (PRINIVIL, ZESTRIL) fosinopril (MONOPRIL), ramipril (ALTACE), perindopril (ACEON), quinapril (ACCUPRIL), moexipril (UNIVASC), trandolapril (MAVIK), candesartan (ATACAND), eprosartan (TEVETAN), irbesartan (AVAPRO), telmisartan (MYCARDIS), valsartan (DIOVAN), losartan (COZAAR), atenolol (TENORMIN), propranolol (INDERAL), metoprolol (TOPROL), nadolol (CORGARD), betaxolol (KERLONE), acebutolol (SECTRAL), pindolol (VISKEN), bisoprolol (ZEBETA), hydrochlorothiazide (HYDRODIURIL), furosemide (LASIX), torsemide (DEMADEX), the combination of triamterene and hydrochlorothiazide (DYAZIDE), metolazone (ZAROXOLYN), ethacrynic acid, nisoldipine (SULAR), nifedipine (ADALAT, PROCARDIA), nicardipine (CARDENE), bepridil (VASCOR), isradipine (DYNACIRC), nimodipine (NIMOTOP), felodipine (PLENDIL), amlodipine (NORVASC), diltiazem (CARDIZEM), verapamil (CALAN, ISOPTIN), terazosin (HYTRIN), doxazosin (CARDURA), tamsulosin (FLOMAX), alfuzosin (UROXATRAL), clonidine (CATAPRES), the combination therapies disclosed in the table entitled "Combination Drugs for Treatment of Hypertension, biguanides, sulfonylureas, thiazolidinediones, alpha-glucosidase inhibitors, probucol, niacin, omega 3 ethyl esters, omega 3 fatty acids, bile acid sequesterants, cholestyramine, cholestyramine-sucrose, cholestyramine-aspartame, colesevelam, colestipol, cholesterol absorption inhibitors, ezetimibe, ezetimibe-simvastatin, fibric acid derivatives, fenofibrates, gemfibrozil, HMG-CoA reductase inhibitors, amlodipine-atorvastatin, atorvastatin, fluvastatin, lovastatin, niacin-lovastatin, pravastatin, rosuvastatin, simvastatin, aspirin, salsalate, diflunisal, ibuprofen, ketoprofen, nabumetone, piroxicam, naproxen, diclofenac, indomethacin, sulindac, tolmetin, etodolac, ketorolac, oxaprozin or celecoxib.

6. The method according to any one of claims 1, 2, 3, 4 or 5, wherein the biological parameter is selected from serum cholesterol levels; triglyceride levels; serum

glucose levels, blood sugar levels, serum homocysteine levels, inflammatory proteins, inflammation or blood pressure/hypertension.

7. The method according to any one of claims 1, 2 or 6, wherein said method lowers or reduces serum cholesterol levels and comprises feeding a subject a diet containing racemic β-hydroxybutyrate or D-β-hydroxybutyrate, optionally in the acid form, physiologically compatible salts of racemic β-hydroxybutyrate or D-β-hydroxybutyrate, esters of D-β-hydroxybutyrate, oligomers of D-β-hydroxybutyrate containing from 2 to 20 or more monomeric units in either linear or cyclic form, racemic 1,3 butandiol, R-1,3 butandiol or combinations thereof.

8. The method according to any one of claims 1, 2 or 6, wherein said method lowers or reduces blood triglycerides and comprises feeding a subject a diet containing racemic β-hydroxybutyrate or D-β-hydroxybutyrate, optionally in the acid form, physiologically compatible salts of racemic β-hydroxybutyrate or D-β-hydroxybutyrate, esters of D-β-hydroxybutyrate, oligomers of D-β-hydroxybutyrate containing from 2 to 20 or more monomeric units in either linear or cyclic form, racemic 1,3 butandiol, R-1,3 butandiol or combinations thereof.

9. The method according to any one of claims 1, 2 or 6, wherein said method lowers or reduces blood sugar/glucose levels and comprises feeding a subject a diet containing racemic β-hydroxybutyrate or D-β-hydroxybutyrate, optionally in the acid form, physiologically compatible salts of racemic β-hydroxybutyrate or D-β-hydroxybutyrate, esters of D-β-hydroxybutyrate, oligomers of D-β-hydroxybutyrate containing from 2 to 20 or more monomeric units in either linear or cyclic form, racemic 1,3 butandiol, R-1,3 butandiol or combinations thereof.

10. The method according to any one of claims 1, 2 or 6, wherein said method lowers or reduces blood sugar in a diabetic subject without inducing insulin shock and comprises feeding a diabetic subject a diet containing racemic β-hydroxybutyrate or D-β-hydroxybutyrate, optionally in the acid form, physiologically compatible salts of racemic β-hydroxybutyrate or D-β-hydroxybutyrate, esters of D-β-hydroxybutyrate, oligomers of D-β-

hydroxybutyrate containing from 2 to 20 or more monomeric units in either linear or cyclic form, racemic 1,3 butandiol, R-1,3 butandiol or combinations thereof.

11. The method according to any one of claims 1, 2 or 6, wherein said method lowers or reduces elevated blood homocysteine and comprises feeding a subject a diet containing racemic β-hydroxybutyrate or D-β-hydroxybutyrate, optionally in the acid form, physiologically compatible salts of racemic β-hydroxybutyrate or D-β-hydroxybutyrate, esters of D-β-hydroxybutyrate, oligomers of D-β-hydroxybutyrate containing from 2 to 20 or more monomeric units in either linear or cyclic form, racemic 1,3 butandiol, R-1,3 butandiol or combinations thereof.

12. The method according to any one of claims 1, 2 or 6, wherein said method lowers or reduces serum C-reactive protein levels and comprises feeding a subject a diet containing racemic β-hydroxybutyrate or D-β-hydroxybutyrate, optionally in the acid form, physiologically compatible salts of racemic β-hydroxybutyrate or D-β-hydroxybutyrate, esters of D-β-hydroxybutyrate, oligomers of D-β-hydroxybutyrate containing from 2 to 20 or more monomeric units in either linear or cyclic form, racemic 1,3 butandiol, R-1,3 butandiol or combinations thereof.

13. The method according to any one of claims 1, 2 or 6, wherein said method lowers or reduces blood pressure levels in a subject and comprises feeding a subject a diet containing racemic β-hydroxybutyrate or D-β-hydroxybutyrate, optionally in the acid form, physiologically compatible salts of racemic β-hydroxybutyrate or D-β-hydroxybutyrate, esters of D-β-hydroxybutyrate, oligomers of D-β-hydroxybutyrate containing from 2 to 20 or more monomeric units in either linear or cyclic form, racemic 1,3 butandiol, R-1,3 butandiol or combinations thereof.

14. A method retarding the development of vascular disease comprising the administration of a composition comprising racemic β-hydroxybutyrate or D-β-hydroxybutyrate, optionally in the acid form, physiologically compatible salts of racemic β-hydroxybutyrate or D-β-hydroxybutyrate, esters of D-β-hydroxybutyrate, oligomers of D-β-hydroxybutyrate containing from 2 to 20 or more monomeric units in either linear or cyclic

form, racemic 1,3 butandiol, R-1,3 butandiol, or combinations thereof, or in combination with an additional therapeutic agent, to a subject.

15. The method according to claim 14, wherein said composition comprising racemic β-hydroxybutyrate or D-β-hydroxybutyrate, optionally in the acid form, physiologically compatible salts of racemic β-hydroxybutyrate or D-β-hydroxybutyrate, esters of D-β-hydroxybutyrate, oligomers of D-β-hydroxybutyrate containing from 2 to 20 or more monomeric units in either linear or cyclic form, racemic 1,3 butandiol, R-1,3 butandiol or combinations thereof alone is administered in the form of the subject's diet.

16. The method according to claim 14, wherein said method comprises the administration of a first composition comprising racemic β-hydroxybutyrate or D-β-hydroxybutyrate, optionally in the acid form, physiologically compatible salts of racemic β-hydroxybutyrate or D-β-hydroxybutyrate, esters of D-β-hydroxybutyrate, oligomers of D-β-hydroxybutyrate containing from 2 to 20 or more monomeric units in either linear or cyclic form, racemic 1,3 butandiol, R-1,3 butandiol or combinations thereof in combination with a second composition comprising a therapeutic agent, wherein said first and second compositions are administered separately, sequentially or together and each composition is in unit dosage form.

17. The method according to claim 16, wherein said therapeutic agent is selected from glucose/blood sugar lowering agents, lipid lowering(anti-lipemic) agents, blood pressure lowering agents (anti-inflammatory agents), or agents that reduce inflammation (anti-inflammatory agents).

18. The method according to claim 14 or 16 or 17, wherein said therapeutic agent is selected from: captopril (CAPOTEN), benazepril (LOTENSIN), enalapril (VASOTEC), lisinopril (PRINIVIL, ZESTRIL) fosinopril (MONOPRIL), ramipril (ALTACE), perindopril (ACEON), quinapril (ACCUPRIL), moexipril (UNIVASC), trandolapril (MAVIK), candesartan (ATACAND), eprosartan (TEVETAN), irbesartan (AVAPRO), telmisartan (MYCARDIS), valsartan (DIOVAN), losartan (COZAAR), atenolol (TENORMIN), propranolol (INDERAL), metoprolol (TOPROL), nadolol (CORGARD), betaxolol

(KERLONE), acebutolol (SECTRAL), pindolol (VISKEN), bisoprolol (ZEBETA), hydrochlorothiazide (HYDRODIURIL), furosemide (LASIX), torsemide (DEMADEX), the combination of triamterene and hydrochlorothiazide (DYAZIDE), metolazone (ZAROXOLYN), ethacrynic acid, nisoldipine (SULAR), nifedipine (ADALAT, PROCARDIA), nicardipine (CARDENE), bepridil (VASCOR), isradipine (DYNACIRC), nimodipine (NIMOTOP), felodipine (PLENDIL), amlodipine (NORVASC), diltiazem (CARDIZEM), verapamil (CALAN, ISOPTIN), terazosin (HYTRIN), doxazosin (CARDURA), tamsulosin (FLOMAX), alfuzosin (UROXATRAL), clonidine (CATAPRES), the combination therapies disclosed in the table entitled "Combination Drugs for Treatment of Hypertension, biguanides, sulfonylureas, thiazolidinediones, alpha-glucosidase inhibitors, probucol, niacin, omega 3 ethyl esters, omega 3 fatty acids, bile acid sequesterants, cholestyramine, cholestyramine-sucrose, cholestyramine-aspartame, colesevelam, colestipol, cholesterol absorption inhibitors, ezetimibe, ezetimibe-simvastatin, fibric acid derivatives, fenofibrates, gemfibrozil, HMG-CoA reductase inhibitors, amlodipine-atorvastatin, atorvastatin, fluvastatin, lovastatin, niacin-lovastatin, pravastatin, rosuvastatin, simvastatin, aspirin, salsalate, diflunisal, ibuprofen, ketoprofen, nabumetone, piroxicam, naproxen, diclofenac, indomethacin, sulindac, tolmetin, etodolac, ketorolac, oxaprozin or celecoxib.

19. A method for reversing vascular disease comprising the administration of a composition comprising racemic β-hydroxybutyrate or D-β-hydroxybutyrate, optionally in the acid form, physiologically compatible salts of racemic β-hydroxybutyrate or D-β-hydroxybutyrate, esters of D-β-hydroxybutyrate, oligomers of D-β-hydroxybutyrate containing from 2 to 20 or more monomeric units in either linear or cyclic form, racemic 1,3 butandiol, R-1,3 butandiol or combinations thereof alone, or in combination with an additional therapeutic agent, to a subject.

20. The method according to claim 19, wherein said composition comprising racemic β-hydroxybutyrate or D-β-hydroxybutyrate, optionally in the acid form, physiologically compatible salts of racemic β-hydroxybutyrate or D-β-hydroxybutyrate, esters of D-β-hydroxybutyrate, oligomers of D-β-hydroxybutyrate containing from 2 to 20 or more monomeric units in either linear or cyclic form, racemic 1,3 butandiol, R-1,3 butandiol or combinations thereof alone is administered in the form of the subject's diet.

21. The method according to claim 19, wherein said method comprises the administration of a first composition comprising racemic β-hydroxybutyrate or D-β-hydroxybutyrate, optionally in the acid form, physiologically compatible salts of racemic β-hydroxybutyrate or D-β-hydroxybutyrate, esters of D-β-hydroxybutyrate, oligomers of D-β-hydroxybutyrate containing from 2 to 20 or more monomeric units in either linear or cyclic form, racemic 1,3 butandiol, R-1,3 butandiol or combinations thereof in combination with a second composition comprising a therapeutic agent, wherein said first and second compositions are administered separately, sequentially or together and each composition is in unit dosage form.

22. The method according to claim 21, wherein said therapeutic agent is selected from glucose/blood sugar lowering agents, lipid lowering(anti-lipemic) agents, blood pressure lowering agents (anti-inflammatory agents), or agents that reduce inflammation (anti-inflammatory agents).

23. The method according to claim 19 or 21 or 22, wherein said therapeutic agent is selected from: captopril (CAPOTEN), benazepril (LOTENSIN), enalapril (VASOTEC), lisinopril (PRINIVIL, ZESTRIL) fosinopril (MONOPRIL), ramipril (ALTACE), perindopril (ACEON), quinapril (ACCUPRIL), moexipril (UNIVASC), trandolapril (MAVIK), candesartan (ATACAND), eprosartan (TEVETAN), irbesartan (AVAPRO), telmisartan (MYCARDIS), valsartan (DIOVAN), losartan (COZAAR), atenolol (TENORMIN), propranolol (INDERAL), metoprolol (TOPROL), nadolol (CORGARD), betaxolol (KERLONE), acebutolol (SECTRAL), pindolol (VISKEN), bisoprolol (ZEBETA), hydrochlorothiazide (HYDRODIURIL), furosemide (LASIX), torsemide (DEMADEX), the combination of triamterene and hydrochlorothiazide (DYAZIDE), metolazone (ZAROXOLYN), ethacrynic acid, nisoldipine (SULAR), nifedipine (ADALAT, PROCARDIA), nicardipine (CARDENE), bepridil (VASCOR), isradipine (DYNACIRC), nimodipine (NIMOTOP), felodipine (PLENDIL), amlodipine (NORVASC), diltiazem (CARDIZEM), verapamil (CALAN, ISOPTIN), terazosin (HYTRIN), doxazosin (CARDURA), tamsulosin (FLOMAX), alfuzosin (UROXATRAL), clonidine (CATAPRES), the combination therapies disclosed in the table entitled "Combination Drugs for Treatment

of Hypertension, biguanides, sulfonylureas, thiazolidinediones, alpha-glucosidase inhibitors, probucol, niacin, omega 3 ethyl esters, omega 3 fatty acids, bile acid sequesterants, cholestyramine, cholestyramine-sucrose, cholestyramine-aspartame, colesevelam, colestipol, cholesterol absorption inhibitors, ezetimibe, ezetimibe-simvastatin, fibric acid derivatives, fenofibrates, gemfibrozil, HMG-CoA reductase inhibitors, amlodipine-atorvastatin, atorvastatin, fluvastatin, lovastatin, niacin-lovastatin, pravastatin, rosuvastatin, simvastatin, aspirin, salsalate, diflunisal, ibuprofen, ketoprofen, nabumetone, piroxicam, naproxen, diclofenac, indomethacin, sulindac, tolmetin, etodolac, ketorolac, oxaprozin or celecoxib.

24. The method according to any one of claims 1-23, wherein the dietary intake of fat by said subject is reduced.

25. A composition comprising racemic β-hydroxybutyrate or D-β-hydroxybutyrate, optionally in the acid form, physiologically compatible salts of racemic β-hydroxybutyrate or D-β-hydroxybutyrate, esters of D-β-hydroxybutyrate, oligomers of D-β-hydroxybutyrate containing from 2 to 20 or more monomeric units in either linear or cyclic form, racemic 1,3 butandiol, R-1,3 butandiol or combinations thereof in combination with a therapeutic agent selected from:

a) anti-lipemic agents;

b) anti-hypertensive agents (including those combination treatments set forth in the table entitled "Combination Drugs for Treatment of Hypertension");

c) glucose lowering agents; or

d) anti-inflammatory agents.

26. The composition according to claim 25, wherein said composition comprises a single composition and said composition comprises racemic β-hydroxybutyrate or D-β-hydroxybutyrate, optionally in the acid form, physiologically compatible salts of racemic β-hydroxybutyrate or D-β-hydroxybutyrate, esters of D-β-hydroxybutyrate, oligomers of D-β-hydroxybutyrate containing from 2 to 20 or more monomeric units in either linear or cyclic form, racemic 1,3 butandiol, R-1,3 butandiol or combinations thereof and said therapeutic agent is selected from: captopril (CAPOTEN), benazepril (LOTENSIN), enalapril (VASOTEC), lisinopril (PRINIVIL, ZESTRIL) fosinopril (MONOPRIL), ramipril

(ALTACE), perindopril (ACEON), quinapril (ACCUPRIL), moexipril (UNIVASC), trandolapril (MAVIK), candesartan (ATACAND), eprosartan (TEVETAN), irbesartan (AVAPRO), telmisartan (MYCARDIS), valsartan (DIOVAN), losartan (COZAAR), atenolol (TENORMIN), propranolol (INDERAL), metoprolol (TOPROL), nadolol (CORGARD), betaxolol (KERLONE), acebutolol (SECTRAL), pindolol (VISKEN), bisoprolol (ZEBETA), hydrochlorothiazide (HYDRODIURIL), furosemide (LASIX), torsemide (DEMADEX), the combination of triamterene and hydrochlorothiazide (DYAZIDE), metolazone (ZAROXOLYN), ethacrynic acid, nisoldipine (SULAR), nifedipine (ADALAT, PROCARDIA), nicardipine (CARDENE), bepridil (VASCOR), isradipine (DYNACIRC), nimodipine (NIMOTOP), felodipine (PLENDIL), amlodipine (NORVASC), diltiazem (CARDIZEM), verapamil (CALAN, ISOPTIN), terazosin (HYTRIN), doxazosin (CARDURA), tamsulosin (FLOMAX), alfuzosin (UROXATRAL), clonidine (CATAPRES), the combination therapies disclosed in the table entitled "Combination Drugs for Treatment of Hypertension, biguanides, sulfonylureas, thiazolidinediones, alpha-glucosidase inhibitors, probucol, niacin, omega 3 ethyl esters, omega 3 fatty acids, bile acid sequesterants, cholestyramine, cholestyramine-sucrose, cholestyramine-aspartame, colesevelam, colestipol, cholesterol absorption inhibitors, ezetimibe, ezetimibe-simvastatin, fibric acid derivatives, fenofibrates, gemfibrozil, HMG-CoA reductase inhibitors, amlodipine-atorvastatin, atorvastatin, fluvastatin, lovastatin, niacin-lovastatin, pravastatin, rosuvastatin, simvastatin, aspirin, salsalate, diflunisal, ibuprofen, ketoprofen, nabumetone, piroxicam, naproxen, diclofenac, indomethacin, sulindac, tolmetin, etodolac, ketorolac, oxaprozin or celecoxib.

27. A composition for sequential or co-administration comprising two separate compositions, wherein said two separate compositions comprise a first composition comprising racemic β-hydroxybutyrate or D-β-hydroxybutyrate, optionally in the acid form, physiologically compatible salts of racemic β-hydroxybutyrate or D-β-hydroxybutyrate, esters of D-β-hydroxybutyrate, oligomers of D-β-hydroxybutyrate containing from 2 to 20 or more monomeric units in either linear or cyclic form, racemic 1,3 butandiol, R-1,3 butandiol or combinations thereof and a second composition comprising therapeutic agent selected from:

a) anti-lipemic agents;

b) anti-hypertensive agents (including those combination treatments set forth in the table entitled "Combination Drugs for Treatment of Hypertension");

c) glucose lowering agents; or

d) anti-inflammatory agents.

28. The composition according to claim 27, wherein said second composition comprises a single composition and said composition comprises a therapeutic agent selected from: captopril (CAPOTEN), benazepril (LOTENSIN), enalapril (VASOTEC), lisinopril (PRINIVIL, ZESTRIL) fosinopril (MONOPRIL), ramipril (ALTACE), perindopril (ACEON), quinapril (ACCUPRIL), moexipril (UNIVASC), trandolapril (MAVIK), candesartan (ATACAND), eprosartan (TEVETAN), irbesartan (AVAPRO), telmisartan (MYCARDIS), valsartan (DIOVAN), losartan (COZAAR), atenolol (TENORMIN), propranolol (INDERAL), metoprolol (TOPROL), nadolol (CORGARD), betaxolol (KERLONE), acebutolol (SECTRAL), pindolol (VISKEN), bisoprolol (ZEBETA), hydrochlorothiazide (HYDRODIURIL), furosemide (LASIX), torsemide (DEMADEX), the combination of triamterene and hydrochlorothiazide (DYAZIDE), metolazone (ZAROXOLYN), ethacrynic acid, nisoldipine (SULAR), nifedipine (ADALAT, PROCARDIA), nicardipine (CARDENE), bepridil (VASCOR), isradipine (DYNACIRC), nimodipine (NIMOTOP), felodipine (PLENDIL), amlodipine (NORVASC), diltiazem (CARDIZEM), verapamil (CALAN, ISOPTIN), terazosin (HYTRIN), doxazosin (CARDURA), tamsulosin (FLOMAX), alfuzosin (UROXATRAL), clonidine (CATAPRES), the combination therapies disclosed in the table entitled "Combination Drugs for Treatment of Hypertension, biguanides, sulfonylureas, thiazolidinediones, alpha-glucosidase inhibitors, probucol, niacin, omega 3 ethyl esters, omega 3 fatty acids, bile acid sequesterants, cholestyramine, cholestyramine-sucrose, cholestyramine-aspartame, colesevelam, colestipol, cholesterol absorption inhibitors, ezetimibe, ezetimibe-simvastatin, fibric acid derivatives, fenofibrates, gemfibrozil, HMG-CoA reductase inhibitors, amlodipine-atorvastatin, atorvastatin, fluvastatin, lovastatin, niacin-lovastatin, pravastatin, rosuvastatin, simvastatin, aspirin, salsalate, diflunisal, ibuprofen, ketoprofen, nabumetone, piroxicam, naproxen, diclofenac, indomethacin, sulindac, tolmetin, etodolac, ketorolac, oxaprozin or celecoxib.

29. The use of a composition according to any of claims 25-28 for the manufacture of a medicament for the reduction of serum cholesterol levels; triglyceride

levels; serum glucose levels, blood sugar levels, serum homocysteine levels, inflammatory proteins, inflammation, blood pressure/hypertension, retarding vascular disease or reversing vascular disease in a subject.

30. The use of a composition according to any of claims 25-28 for the treatment of high serum cholesterol levels; high triglyceride levels; high serum glucose levels; high blood sugar levels; high serum homocysteine levels; high inflammatory protein levels; inflammation; high blood pressure or hypertension; or vascular disease in a subject.

31. The use according to claim 29 or claim 30, wherein the subject is consuming a low fat diet.

32. The use according to any of claims 29-31, wherein racemic β-hydroxybutyrate or D-β-hydroxybutyrate, optionally in the acid form, physiologically compatible salts of racemic β-hydroxybutyrate or D-β-hydroxybutyrate, esters of D-β-hydroxybutyrate, oligomers of D-β-hydroxybutyrate containing from 2 to 20 or more monomeric units in either linear or cyclic form, racemic 1,3 butandiol, R-1,3 butandiol or combinations thereof are administered in amounts that a) provide for blood levels of D-β-hydroxybutyrate plus acetoacetate ranging from 0.1 to 25 mM, between 0.4 to 10 mM or between 0.6 and 3 mM in an individual; or b) range from 2-100% of the total caloric intake of an individual, 5-70% of the total caloric intake of an individual, or 5-30% of the total caloric intake of the individual.

33. The method according to any one of claims 1-24, wherein racemic β-hydroxybutyrate or D-β-hydroxybutyrate, optionally in the acid form, physiologically compatible salts of racemic β-hydroxybutyrate or D-β-hydroxybutyrate, esters of D-β-hydroxybutyrate, oligomers of D-β-hydroxybutyrate containing from 2 to 20 or more monomeric units in either linear or cyclic form, racemic 1,3 butandiol, R-1,3 butandiol or combinations thereof are administered in amounts that a) provide for blood levels of D-β-hydroxybutyrate plus acetoacetate ranging from between 0.1 to 25 mM, between 0.4 to 10 mM or between 0.6 and 3 mM in an individual; or b) range from 2-100% of the total caloric intake of an individual, 5-70% of the total caloric intake of an individual, or 5-30% of the total caloric intake of the individual.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 09/30095

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A01N 37/00; A61K 31/19 (2009.01)
USPC - 514/557
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
USPC: 514/557

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC: 424/468, 489; 435/135; 514/25, 221, 310, 473; 800/278 (see search terms below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Electronic Databases Searched: USPTO WEST (PGPUB, EPAB, JPAB, USPT), Google Patent. search terms: racemic hydroxybutyrate, acetoacetate, vascular disease, fosinopril or captopril, oligomer, lipd or sugar, biological parameter

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2004/0266872 A1 (Veech et al.) 30 December 2004 (30.12.2004) abstract; para [0043], [0046]-[0048], [0050]-[0051], [0065], [0071], [0076], [0085]-[0086], [0093]	1-5, 14-23 and 25-30
X	US 2003/0022937 A1 (Veech et al.) 30 January 2003 (30.01.2003) entire document	1-5, 14-23 and 25-30

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
10 February 2009 (10.02.2009)	23 FEB 2009
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (April 2007)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 09/30095

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 6-13, 24, 31-33
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.