THERAPEUTIC TREATMENT

The present invention relates to a combination comprising candesartan and rosuvastatin.

The present invention further relates to pharmaceutical compositions comprising the combination mentioned hereinbefore. The present invention further relates to the use of a combination mentioned hereinbefore in the prevention or treatment of atherosclerosis.

Atherosclerosis is a condition mediated by complex pathological processes which result in irregularly distributed lipid deposits in the arteries and is a major contributory factor to coronary heart disease. A reduction in atherosclerosis is therefore a major target for reducing the number of cardiovascular events for example, myocardial infarction, worsening of angina, cardiac arrest, stroke, congestive heart failure and cardiovascular death.

Dyslipidemia, particularly increased plasma level of low-density lipoprotein (LDL) is one of the major risk factors in atherosclerosis. Clinical studies have demostrated that reducing plasma LDL level with 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors, commonly known as statins, results in a lower risk of cardiovascular events.

Activation of the renin-angiotensin system (RAS) may be considered another important risk factor in atherosclerosis. Activation of RAS with the formation of angiotensin (II) (A (II)) and the activation of A (II) receptors have been implicated in atherogenesis, plaque rupture, myocardial ischemic dysfunction and congestive heart failure (Singh and Mehta, Arch Intern Med, 2003, vol 163, 1296-1304).

International Patent Application WO 95/26188 discloses treatment of atherosclerosis with A(II) receptor blockers, optionally in combination with HMGCoA reductase inhibitors. International Patent Application WO 01/76573 discloses the use of a combination of at least two of an A(II) antagonist, an ACE (angiotensin converting enzyme) inhibitor and an HMGCoA reductase inhibitor for the prevention or delay of progression in a list of conditions, amongst which is atherosclerosis.

We have surprisingly found that the combination of the A(II) antagonist candesartan and the HMG CoA reductase inhibitor rosuvastatin has a synergistic effect in the reduction of atherosclerosis. This synergistic effect appears to arise from synergistic inhibition of expresssion of a number of inflammatory mediators involved in the RAS (for example CD40, metalloproteinases (MMPs)) and/or inhibition of the expression of the receptor LOX-1 (which

is a receptor for oxidised LDL on endothelial cells). The synergistic effect provides strong evidence for cross-talk between the RAS and dyslipidemia in atherogenesis.

It will be appreciated that the activty of MMPs may be regulated in-vivo by their tissue inhibitors (TIMPs). We have also shown that the expression of TIMP-1 and TIMP-2 is up-regulated by high-cholesterol diet, and markedly attenuated by the combination of candesartan and rosuvastatin. These data lend credence to the concept that the balance between MMPs and TIMPs is altered by high-cholesterol diet, and that this imbalance can be "normalized" by the combination of an A(II) antagonist and a lipid-lowering agent.

In one aspect of the invention is provided a combination comprising candesartan, or a pharmaceutically acceptable salt thereof, and rosuvastatin, or a pharmaceutically acceptable salt thereof, for the prevention or treatment of atherosclerosis.

In one aspect of the invention is provided a combination comprising candesartan, or a pharmaceutically acceptable salt thereof, and rosuvastatin, or a pharmaceutically acceptable salt thereof, for the prevention of cardiovascular events.

Such a combination may also be useful in the treatment or prevention of other diseases associated with these mediators, for example in inflammatory diseases or conditions, such as ischemia-reperfusion injury (to the heart, brain, kidneys, lungs and liver), radiation-induced injury, burn injury and peripheral vascular disease,

Candesartan may suitably be in the form of candesartan, or in the pro-drug form candesartan cilexetil. These forms may be formulated with a further agent such as a diuretic such as hydrochlorothiazide (for example, as marketed as Atacand Plus™).

Where herein candesartan is referred to, this includes both candesartan and candesartan cilexetil.

Preferably the calcium salt of rosuvastatin, which may be referred to as rosuvastatin calcium, is used in the various aspects of the present invention.

In general, pharmaceutically-acceptable salts include acid addition salts such as methanesulfonate, tosylate, α-glycerophosphate, fumarate, hydrochloride, citrate, maleate, tartrate and (less preferably) hydrobromide. Pharmaceutically-acceptable salts in general also include salts formed with phosphoric and sulfuric acid. Pharmaceutically-acceptable salts generally include base salts such as an alkali metal salt for example sodium, an alkaline earth metal salt for example calcium or magnesium, an organic amine salt for example triethylamine, morpholine, N-methylpiperidine, N-ethylpiperidine, procaine, dibenzylamine, N,N-dibenzylethylamine, tris-(2-hydroxyethyl)amine, tris(hydroxymethyl)methylammonium,

N-methyl d-glucamine and amino acids such as lysine. There may be more than one cation or anion depending on the number of charged functions and the valency of the cations or anions.

Herein, where the term "combination" is used it is to be understood that this refers to simultaneous, separate or sequential administration. In one aspect of the invention "combination" refers to simultaneous administration. In another aspect of the invention "combination" refers to separate administration. In a further aspect of the invention "combination" refers to sequential administration. Where the administration is sequential or separate, the delay in administering the second component should be such that both agents are present in the body so as to produce the synergistic effect of the combination.

In a further aspect of the invention is provided a pharmaceutical composition which comprises candesartan, or a pharmaceutically acceptable salt thereof, and rosuvastatin, or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable diluent or carrier for use in the prevention or treatment of atherosclerosis.

In a further aspect of the invention is provided a pharmaceutical composition which comprises candesartan, or a pharmaceutically acceptable salt thereof, and rosuvastatin, or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable diluent or carrier for use in the prevention or reduction of risk of cardiovascular events.

The compositions described herein may be in a form suitable for oral administration, for example as a tablet or capsule, for parenteral injection (including intravenous, subcutaneous, intramuscular, intravascular or infusion) for example as a sterile solution, suspension or emulsion, for topical administration for example as an ointment or cream, for rectal administration for example as a suppository or the route of administration may be by direct injection into the tumour or by regional delivery or by local delivery. In other embodiments of the present invention the compounds of the combination treatment may be delivered endoscopically, intratracheally, intralesionally, percutaneously, intravenously, subcutaneously, intraperitoneally or intratumourally. In general the compositions described herein may be prepared in a conventional manner using conventional excipients or carriers that are well known in the art.

Suitable pharmaceutically-acceptable excipients or carriers for a tablet formulation include, for example, inert excipients such as lactose, sodium carbonate, calcium phosphate or calcium carbonate, granulating and disintegrating agents such as corn starch or alginic acid; binding agents such as gelatin or starch; lubricating agents such as magnesium stearate, stearic acid or talc; preservative agents such as ethyl or propyl 4-hydroxybenzoate, and

anti-oxidants, such as ascorbic acid. Tablet formulations may be uncoated or coated either to modify their disintegration and the subsequent absorption of the active ingredient within the gastrointestinal tract, or to improve their stability and/or appearance, in either case using conventional coating agents and procedures well known in the art.

Compositions for oral use may be in the form of hard gelatin capsules in which the active ingredient is mixed with an inert solid excipient, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules in which the active ingredient is mixed with water or an oil such as peanut oil, liquid paraffin or olive oil.

Candesartan is commercially available as 'Atacand™' and 'Atacand Plus™'. Rosuvastatin calcium is commercially available as 'Crestor™'. Suitable formulations for the present invention include those which are commercially available.

Suitable dosages of each component of the combination are those of the marketed commercial products. Alternatively, the synergy between the components may allow a lower dosage of one or both components to be used. For example, a dose of 4mg, 8mg, 16mg, 32mg, or up to 160mg of candesartan in combination with a dose of 80mg, 40mg, 20mg, 10mg, 5mg or 2.5mg of rosuvastatin may be used. It will be understood that any one of the doses of candesartan may be combined with any suitable dose of rosuvastatin.

In one aspect, 80mg of rosuvastatin is used. In another aspect, 40mg of rosuvastatin is used. In a further aspect, 20mg of rosuvastatin is used. In a further aspect, 10mg of rosuvastatin is used. In a further aspect, 5mg of rosuvastatin is used. In a further aspect, 2.5mg of rosuvastatin is used.

In one aspect, between 32 and 160mg, such as about 64 to 128mg, for example 64 to 112mg, such as about 64-96mg of candesartan is used. Conveninelty, about 72mg of candesartan is used. In another aspect, 32mg of candesartan is used. In a further aspect, 16mg of candesartan is used. In a further aspect, 8mg of candesartan is used. In a further aspect, 4mg of candesartan is used.

It will be appreciated that the pharmaceutical composition according to the present invention includes a composition comprising candesartan or a pharmaceutically acceptable salt thereof and rosuvastatin or a pharmaceutically acceptable salt thereof and a pharmaceutically-acceptable excipient or carrier. Such a composition, for example in a single oral formulation conveniently provides the therapeutic combination product of the invention for simultaneous administration in the prevention or treatment of atherosclerosis.

Preferably the two components of the combination are both administered orally.

Preferably the two components of the combination are administered as a single oral formulation.

Preferably the combination is formulated for once-a-day dosing.

Conveniently, the combination is formulated as a single tablet or capsule.

The dosages and schedules described hereinbefore may be varied according to the particular disease state and the overall condition of the patient. For example, it may be necessary or desirable to reduce the above-mentioned doses of the components of the combination treatment in order to reduce toxicity. Dosages and schedules may also vary if, in addition to a combination treatment of the present invention, one or more additional chemotherapeutic agents are used. Scheduling can be determined by the practitioner who is treating any particular patient using his professional skill and knowledge.

A pharmaceutical composition according to the present invention also includes separate compositions comprising a first composition comprising candesartan or a pharmaceutically acceptable salt thereof and a pharmaceutically-acceptable excipient or carrier, and a second composition comprising rosuvastatin or a pharmaceutically acceptable salt thereof and a pharmaceutically-acceptable excipient or carrier. Such a composition conveniently provides the therapeutic combination of the invention for sequential or separate administration in the synergistic prevention or treatment of atherosclerosis but the separate compositions may also be administered simultaneously.

In another aspect of the invention there is provided a combination comprising candesartan, or a pharmaceutically acceptable salt thereof, and rosuvastatin, or a pharmaceutically acceptable salt thereof, for use as a medicament for the prevention or treatment of atherosclerosis.

In another aspect of the invention there is provided a combination comprising candesartan, or a pharmaceutically acceptable salt thereof, and rosuvastatin, or a pharmaceutically acceptable salt thereof, for use as a medicament for the prevention of cardiovascular events.

In another aspect of the invention there is provided a combination comprising candesartan, or a pharmaceutically acceptable salt thereof, and rosuvastatin, or a pharmaceutically acceptable salt thereof, for use in the manufacture of a medicament.

In another aspect of the invention there is provided a combination comprising candesartan, or a pharmaceutically acceptable salt thereof, and rosuvastatin, or a

pharmaceutically acceptable salt thereof, for use in the manufacture of a medicament for the prevention or treatment of atherosclerosis.

In another aspect of the invention there is provided a combination comprising candesartan, or a pharmaceutically acceptable salt thereof, and rosuvastatin, or a pharmaceutically acceptable salt thereof, for use in the manufacture of a medicament for the prevention of cardiovascular events.

In a further aspect of the invention there is provided a method of preventing or treating atherosclerosis in a warm-blooded animal, such as man, which comprises administering a combination of candesartan, or a pharmaceutically acceptable salt thereof, and rosuvastatin, or a pharmaceutically acceptable salt thereof.

In a further aspect of the invention there is provided a method of preventing cardiovascular events in a warm-blooded animal, such as man, which comprises administering a combination of candesartan, or a pharmaceutically acceptable salt thereof, and rosuvastatin, or a pharmaceutically acceptable salt thereof.

According to a further aspect of the present invention there is provided a kit comprising a combination of candesartan or a pharmaceutically acceptable salt thereof, and rosuvastatin; or a pharmaceutically acceptable salt thereof ,optionally with instructions for use in the prevention or treatment of atherosclerosis.

According to a further aspect of the present invention there is provided a kit comprising:

a) candesartan in a first unit dosage form;

b) rosuvastatin in a second unit dosage form; and

c) container means for containing said first and second dosage forms; and optionally

d) with instructions for use in the prevention or treatment of atherosclerosis.

According to another aspect of the present invention there is provided a method of inhibiting expression of CD40 and/or metalloproteinases (MMPs) by administering a combination of candesartan, or a pharmaceutically acceptable salt thereof and rosuvastatin, or a pharmaceutically acceptable salt thereof.

Particular metalloproteinases are MMP-1, MMP-2 and MMP-9.

According to another aspect of the present invention there is provided a method of treating atherosclerotic patients by inhibition of expression of CD40 and/or metalloproteinases (MMPs) by administering an amount of a combination of candesartan, or a

pharmaceutically acceptable salt thereof and rosuvastatin, or a pharmaceutically acceptable salt thereof suitable for inhibition of expression of CD40 and/or metalloproteinases (MMPs).

According to a further aspect of the invention, there is provided a method for normalizing the balance between MMPs and TIMPS by administration of an amount of a combination of candesartan, or a pharmaceutically acceptable salt thereof and rosuvastatin, or a pharmaceutically acceptable salt thereof.

According to another aspect of the present invention there is provided a method of inhibiting expression of LOX-1 by administering a combination of candesartan, or a pharmaceutically acceptable salt thereof and rosuvastatin, or a pharmaceutically acceptable salt thereof.

According to another aspect of the present invention there is provided a method of treating atherosclerotic patients by inhibition of expression of LOX-1 by administering an amount of a combination of candesartan, or a pharmaceutically acceptable salt thereof and rosuvastatin, or a pharmaceutically acceptable salt thereof suitable for inhibition of expression of LOX-1.

Materials and Methods

Animal Model

Five pairs of C57BL/6J mice and three pairs of homozygous apo-E knockout mice (on C57BL/6J background) were obtained from Jackson Laboratories (Bar Harbor, ME). They were bred by brother-sister mating and housed in a room lit from 6:00 AM to 6:00 PM and kept at 21°C. The C57BL/6J mice (n=10) were continued on regular diet for the entire study period. The apo-E knockout mice were divided into four groups. Group 1 (n=10) animals were given high-cholesterol diet (1% cholesterol) alone for 12 weeks since the age of 6 weeks; Group 2 (n=10) animals were given high-cholesterol diet with candesartan (1mg/kg/d) for 12 weeks since the age of 6 weeks; Group 3 (n=10) animals were given high-cholesterol diet with the rosuvastatin (1mg/kg/d) for 12 weeks since the age of 6 weeks; Group 4 (n=10) animals were given high-cholesterol diet with candesartan (1mg/kg/d) and rosuvastatin (1mg/kg/d) for 12 weeks since the age of 6 weeks.

At the end of 12-week-treatment, the mice were sacrificed and subject to studies described below. All experimental procedures were performed in accordance with protocols approved

by the Institutional Animal Care and Usage Committee of University of Arkansas for Medical Sciences.

Quantitative Analysis of Atherosclerotic Plaques

At the end of 12-week-treatment, 5 mice from each group were euthanized and the aortas were separated from surrounding tissues. After removal of the adventitial fat tissue, the aortas were opened longitudinally from the aorta arch to the iliac bifurcation, and fixed in 10% formalin for 24 hours. Then the aortas were rinsed in 70% alcohol briefly, stained with Sudan IV solution for 15 minutes, differentiated in 80% alcohol for 20 minutes and washed in running water for 1 hour (Russell L. Techniques for studying atherosclerotic lesion, Lab Invest. 1958; 7:42-47). The aortas were mounted and their pictures were taken with a camera connected to a dissection microscope. The images were analyzed by soft ware (Image Pro Plus, Media Cybernetics).

RNA Preparation and Analysis by RT-PCR

At the end of 12-week-treatment, 5 mice from each group were euthanized and the aortas (from aorta arch to iliac bifurcation) were separated from surrounding tissues and stored on dry ice. Each aorta was cut into four segments, two of which were used to extract total RNA with the single-step acid-guanidinium thiocyanate-phenol-chloroform method as described earlier (27). One microgram of total RNA was reverse transcripted into cDNA with oligo-dT (Promega, Madison, WI, U.S.A.) and Maloney murine leukemia virus (M-MLV) reverse transcription (Promega) at 42°C for 1 hour. Two microliters of reverse transcription (RT) material was amplified with Taq DNA polymerase (Promega) and a primer pair specific to mouse LOX-1, CD40 or MMPs (MMP-1, -2, -9). For mouse LOX-1, forward primer: 5′-TTACTCTCCATGGTGGTGCC-3′, reverse primer: 5′-AGCTTCTTCTGCTTGTTGCC-3′ were used. 30 cycles of polymerase chain reaction (PCR) were performed at 94°C for 40 seconds (denaturation), 55°C for 1 minute (annealing), and 72°C for 1 minute (extension). The size of polymerase chain reaction (PCR) product was 193 base pairs. For mouse CD40, forward primer 5′-GTTTAAAGTCCCGGATGCGA-3′ and reverse primer 5′-CTCAAGGCTATGCTGTCTGT-3′ were used. 35 cycles of polymerase chain reaction (PCR) were performed at 94°C for 1 minute (denaturation), 55°C for 1 minute (annealing), and 72°C for 1 minute (extension). The size of PCR product was 408 base pairs. For mouse MMP-1, forward primer 5′-GGACTCTCCCATTCTTAATGA T-3′ and reverse primer 5′-

CCTCTTTCTGGATAACATCATCA AC-3′ were used. For mouse MMP-2, forward primer 5′-ATCAAGGGGATCCAGGAGC-3′ and reverse primer 5′-GCAGCGATGAAG ATGATAG-3′ were used. For mouse MMP-9, forward primer 5′-AGTTTGGTGTCGCGGAGCAC-3′ and reverse primer 5′-TACATGAGCGCTTCCGGCAC-3′ were used. For all MMPs, 35 cycles of PCR were performed at 94°C for 1 minute (denaturation), 58°C for 1 minute (annealing), and 75°C for 1 minute (extension). The sizes of PCR product were 627, 718 and 753 base pairs, respectively. A primer pair specific to mouse β-actin was used as housekeeping gene (forward primer: 5′-TTCTACAATGAGCTGCGTTG-3′, reverse primer: 5′-CACTGTGTTGGCATAGAGGTC-3′). 30 cycles were used at 94°C for 30 seconds (denaturation), 55°C for 1 minute (annealing), and 72°C for 1 minute (extension). PCR product was 560 base pairs. The reverse transcription PCR (RT-PCR)-amplified sample was visualized on 1.5% agarose gel using ethidium bromide.

Protein Preparation and Analysis by Western Blot

Each mouse aorta was cut into four segments. Two of them were used to extract RNA, and the remaining two were used to extract protein as described previously (14). In brief, the aortic tissues were homogenized and lysed in lysis buffer, then centrifuged at 4000 rpm for 10 minutes at 4°C. The lysate proteins from aortas (20 μg/lane) were separated by 10% SDS-PAGE, and transferred to nitrocellulose membranes. After incubation in blocking solution (5% non-fat milk, Sigma), membranes were incubated with 1:750 dilution monoclonal antibody to mouse LOX-1, 1:500 dilution polyclonal antibody to mouse CD40 (Santa Cruz), 1μg/ml dilution monoclonal antibody to mouse MMP-1 (Oncogene), 1μg/ml dilution monoclonal antibody to mouse MMP-2 (Oncogene), 1μg/ml dilution monoclonal antibody to mouse MMP-9 (Oncogene), 1:500 dilution polyclonal antibody to mouse TIMP-1 (Santa Cruz), 1:500 dilution polyclonal antibody to mouse TIMP-2 (Santa Cruz), or 1:5000 dilution monoclonal antibody to mouse β-actin (Sigma) for overnight at 4°C. Membranes were washed and then incubated with 1:5000 dilution specific secondary antibody (Amersham Life Science) for 2 hours at room temperature, and the membranes were washed and detected with the ECL system (Amersham Life Science). The relative intensities of protein bands were analyzed by Scan-gel-it software (Li DY, Zhang YC, Sawamura T, Mehta JL. Circ Res. 1999; 84:1043-1049).

Data Analysis

All data represent mean of duplicate samples. Data are presented as mean ± SD. Statistical significance was determined in multiple comparisons among independent groups of data in which ANOVA and the F test indicated the presence of significant differences. A P value <0.05 was considered significant.

Results

The synergistic anti-atherosclerotic effect of candesartan and rosuvastatin

Compared with the control mice (C57BL/6J mice fed regular diet), the apo-E knockout mice fed high-cholesterol diet developed extensive atherosclerosis (P<0.01 vs control mice). Although both candesartan and rosuvastatin alone decreased the extent of atherosclerosis (p<0.05 vs high-cholesterol diet alone), the combination reduced atherosclerosis to a much greater extent (P<0.05 vs candesartan or rosuvastatin alone plus high-cholesterol diet). Figure 1 shows results of representative experiments and the extent of atherosclerosis (mean ± SD) in different groups of animals.

Candersartan and rosuvastatin alone decreased atherosclerosis by about 35% and 25% respectively. The combination reduced atherosclerosis by 70%, demonstrating a synergistic effect. This effect is illustrated graphically in Figure 2.

The synergistic effect of candesartan and rosuvastatin on LOX-1 expression

In the control C57BL/6J mice, the expression of LOX-1 (mRNA and protein) was low. In contrast, LOX-1 expression (mRNA and protein) was markedly increased by high-cholesterol diet in apo-E knockout mice (P<0.01 vs control mice). Both candesartan and rosuvastatin alone decreased the LOX-1 expression (mRNA and protein), albeit modestly (P<0.05 vs high-cholesterol diet alone). The combination of candesartan and rosuvastatin had a dramatic inhibitory effect on the up-regulation of LOX-1 (mRNA and protein) in apo-E knockout mice (P<0.01 vs high-cholesterol diet alone).

The synergistic effect of candesartan and rosuvastatin on CD40 expression

Compared with the expression in control C57BL/6J mice, CD40 expression (mRNA and protein) was markedly increased in apo-E knockout mice fed a high-cholesterol diet in (P<0.01 vs control mice). Although candesartan and rosuvastatin treatment alone slightly

decreased CD40 expression (P<0.05 vs high-cholesterol diet alone), the combination of candesartan and rosuvastatin had a dramatic inhibitory effect on the up-regulation of CD40 (mRNA and protein) in the apo-E knockout mice (P<0.01 vs high-cholesterol diet alone).

The synergistic effect of candesartan and rosuvastatin on MMPs expression

Compared with the expression in control C57BL/6J mice, MMP-1, -2 and -9 expression (mRNA and protein) was markedly increased in high-cholesterol diet-fed apo-E knockout mice (P<0.01 vs control mice). Both candesartan and rosuvastatin alone decreased MMP-1, -2 and -9 expression (mRNA and protein), albeit modestly (P<0.05 vs high-cholesterol diet alone). The combination of candesartan and rosuvastatin had a dramatic inhibitory effect on their expression (P<0.01 vs high-cholesterol diet alone).

The effect of candesartan and rosuvastatin on TIMPs expression

TIMP-1 and TIMP-2 protein expression was also increased in apo-E knockout mice by high-cholesterol diet (P<0.01 vs. control mice), but the increase was less than that of MMPs. Both candesartan and rosuvastatin alone reduced TIMP-1 and TIMP-2 expression by a small degree (P<0.05 vs. high-cholesterol diet alone), but the combination of candesartan and rosuvastatin had a greater inhibitory effect on their expression (P<0.01 vs. high-cholesterol diet alone, P<0.05 vs. high-cholesterol diet with candesartan or rosuvastatin).

Claims

1. A combination comprising candesartan or a pharmaceutically acceptable salt thereof and rosuvastatin or a pharmaceutically acceptable salt thereof for prevention or treatment of atherosclerosis.

2. A pharmaceutical composition which comprises a combination as claimed in Claim 1 in association with a pharmaceutically acceptable diluent or carrier for use in the prevention or treatment of atherosclerosis.

3. A pharmaceutical composition which comprises a combination as claimed in Claim 1, in association with a pharmaceutically acceptable diluent or carrier for use in the prevention of cardiovascular events.

4. A combination as claimed in Claim 1 for use in the manufacture of a medicament for the prevention or treatment of atherosclerosis.

5. A combination as claimed in Claim 1 for use in the manufacture of a medicament for the prevention of cardiovascular events.

6. A combination as claimed in Claim 1 for use as a medicament for the prevention or treatment of atherosclerosis.

7. A combination as claimed in Claim 1 for use as a medicament for prevention of cardiovascular events.

8. A method of preventing or treating atherosclerosis in a warm-blooded animal, such as man, which comprises administering a combination as claimed in Claim 1.

9. A method of preventing cardiovascular events in a warm-blooded animal, such as man, which comprises administering a combination as claimed in Claim 1.

10. A kit comprising a combination as claimed in Claim 1; optionally with instructions for use in the prevention or treatment of atherosclerosis.

11. A combination as claimed in Claim 1 wherein candesartan is in the form of candesartan cilexetil.