Title: COMBINATION THERAPIES EMPLOYING PLATELET AGGREGATION DRUGS

Abstract: The present invention provides pharmaceutical compositions comprising a platelet aggregation inhibitor and a compound selected from pyridoxal-5'-phosphate, a pyridoxal-5'-phosphate related compound or a pharmaceutically acceptable salt thereof and methods for using a platelet aggregation inhibitor and a compound selected from pyridoxal-5'-phosphate, a pyridoxal-5'-phosphate related compound or a pharmaceutically acceptable salt thereof, for inhibiting platelet aggregation, for treating diseases that arise from prothrombotic and thrombotic states in which the coagulation cascade is activated and for reducing the risk of cardiovascular disease or cerebrovascular disease.
TITLE: Combination Therapies Employing Platelet Aggregation Drugs

FIELD OF INVENTION

[0001] The present invention relates to pharmaceutical compositions and uses thereof for treatment of cardiovascular disease, in particular the present invention relates to the use of combination therapies employing platelet aggregation drugs.

BACKGROUND

[0002] The role of platelets in the pathophysiology of atherosclerotic disease and thrombotic events is well known. Long term prophylactic use of antiplatelet drugs, which inhibit platelet aggregation, has been shown to be beneficial in the prevention of ischemic stroke, myocardial infarction, unstable angina, peripheral arterial disease, need for vascular bypass or angioplasty, and vascular death in patients at increase risk of such outcomes, including those with established atherosclerosis or a history of atherothrombosis.

[0003] Currently there are numerous antiplatelet drugs which are widely available and combination therapies have been and continued to be investigated. Most antiplatelet drugs have side effects, and increasing the dosage leads to increased side effects. Thus, combination therapies have been tried. However, many combination therapies are ineffective for various reasons. For example, many drugs are contraindicated. In other cases, drugs work through mechanisms of action (sometimes unknown) which result in a lack of synergy for attempted combinations.

[0004] The present inventors have found that P5P (pyridoxal-5-phosphate) and certain P5P related compounds, which also have antithrombic properties, are well tolerated drugs with no significant side effects. Furthermore, P5P and P5P related compounds positively modulate multiple cardiovascular risk factors including lipoprotein and homocysteine levels. Previous disclosures have taught the use of vitamin B6 (pyroxidine) with an antiplatelet agent wherein the inclusion of vitamin B6 was directed to decreasing homocysteine levels. For example, US Patent No. 6,323,188 discloses a method of reducing the incidence and severity of stroke,
primary heart attack and any subsequent stroke or heart attack comprising the daily administration of acetylsalicylic acid (ASA), a vitamin B12 compound, a folic acid compound, and vitamin B6. US Patent No. 6,121,249 discloses a method reducing the incidence and severity of atherosclerosis, atherosclerotic central nervous system disease, claudication, coronary artery disease, homocysteine related disorders, hypertension, peripheral vascular disease, presenile dementia, and/or restenosis comprising daily administration of ASA, a vitamin B12 compound, a folic acid compound, and vitamin B6. US Patent No. 6,274,170 discloses compounds for the treatment of atherosclerotic cardiovascular disease comprising ASA, ascorbic acid, folic acid, vitamin E, vitamin B6, and vitamin B12. However, there are currently no combination therapies which employ a pyridoxal-5'-phosphate or pyridoxal-5'-phosphate related compound with an antiplatelet agent.

SUMMARY OF INVENTION

[0005] In a first aspect, the present invention provides a novel pharmaceutical composition comprising: (a) a compound selected from pyridoxal-5'-phosphate, a pyridoxal-5'-phosphate related compound or a pharmaceutically acceptable salt thereof, (b) a platelet aggregation inhibitor, and (c) a pharmaceutically acceptable carrier.

[0006] In a second aspect, the present invention provides a method of inhibiting platelet aggregation in a mammal comprising administering a therapeutically effective dose of: (a) a compound selected from pyridoxal-5'-phosphate, a pyridoxal-5'-phosphate related compound or a pharmaceutically acceptable salt thereof, and (b) a platelet aggregation inhibitor.

[0007] In a third aspect, the present invention provides a method of treating a mammalian patient at risk for cardiovascular disease comprising administering a therapeutically effective dose of: (a) a compound selected from pyridoxal-5'-phosphate, a pyridoxal-5'-phosphate related compound or a pharmaceutically acceptable salt thereof, and (b) a platelet aggregation inhibitor.
[0008] In an embodiment of the invention, the cardiovascular disease is congestive heart failure, myocardial ischemia, arrhythmia, myocardial infarction, ischemic stroke, hemorrhagic stroke, coronary artery disease, peripheral arterial disease, hypertension (high blood pressure), atherosclerosis (clogging of the arteries), aneurysm, thrombophlebitis (vein inflammation), diseases of the heart lining, diseases of the heart muscle, carditis, congestive heart failure, endocarditis, ischemic heart disease, valvular heart disease (malfuction of a valve or valves in the blood vessels of the heart), Kawasaki disease, ischemic injury, arteriosclerosis (hardening of the arteries), deep vein thrombosis, or acute coronary syndrome.

[0009] In a fourth aspect, the present invention provides a method of treating a mammalian patient at risk for cerebrovascular disease comprising administering a therapeutically effective dose of: (a) a compound selected from pyridoxal-5'-phosphate, a pyridoxal-5'-phosphate related compound or a pharmaceutically acceptable salt thereof, and (b) a platelet aggregation inhibitor.

[0010] In an embodiment of the invention, the cerebrovascular disease is cerebral ischemia, cerebral hemorrhage, ischemic stroke, and hemorrhagic stroke.

[0011] In a fifth aspect, the present invention provides a method of treating a mammal having a disease which arises from prothrombotic and thrombotic states in which the coagulation cascade is activated, comprising administering a therapeutically effective dose of: (a) a compound selected from pyridoxal-5'-phosphate, a pyridoxal-5'-phosphate related compound or a pharmaceutically acceptable salt thereof, and (b) a platelet aggregation inhibitor.

[0012] In an embodiment of the invention, the disease arising from prothrombotic and thrombotic states in which the coagulation cascade is activated is deep vein thrombosis, disseminated intravascular coagulopathy, or pulmonary embolism.

[0013] In a sixth aspect, the present invention provides a method for treating a mammalian patient undergoing a cardiovascular surgical intervention comprising administering a therapeutically effective dose (a) a compound selected from
pyridoxal-5'-phosphate, a pyridoxal-5'-phosphate related compound or a pharmaceutically acceptable salt thereof, and (b) a platelet aggregation inhibitor, prior to the surgical intervention or following the surgical intervention.

[0014] In an embodiment of the invention, the surgical intervention is a coronary artery bypass graft, a percutaneous coronary intervention, or placement of a coronary stent.

[0015] In a seventh aspect, the present invention provides a use of: (a) a compound selected from pyridoxal-5'-phosphate, a pyridoxal-5'-phosphate related compound or a pharmaceutically acceptable salt thereof, and (b) a platelet aggregation inhibitor, for the preparation of a medicament.

[0016] In an eighth aspect, the present invention provides a use of: (a) a compound selected from pyridoxal-5'-phosphate, a pyridoxal-5'-phosphate related compound or a pharmaceutically acceptable salt thereof, and (b) a platelet aggregation inhibitor, for inhibiting platelet aggregation.

[0017] In a ninth aspect, the present invention provides a use of: (a) a compound selected from pyridoxal-5'-phosphate, a pyridoxal-5'-phosphate related compound or a pharmaceutically acceptable salt thereof, and (b) a platelet aggregation inhibitor, for reducing the risk of a condition selected from a group consisting of: cardiovascular disease, cerebrovascular disease, and a disease which arises from prothrombotic and thrombotic states in which the coagulation cascade is activated.

[0018] In a tenth aspect, the present invention provides a use of: (a) a compound selected from pyridoxal-5'-phosphate, a pyridoxal-5'-phosphate related compound or a pharmaceutically acceptable salt thereof, and (b) a platelet aggregation inhibitor, for treatment and prevention of thrombosis following a surgical intervention.

[0019] In a further embodiment of the invention, the pyridoxal-5'-phosphate related compound is pyridoxal, pyridoxal-5'-phosphate, pyridoxamine, a 3-acylated analogue
of pyridoxal, a 3-acylated analogue of pyridoxal-4,5-aminal, a pyridoxine phosphate analogue, or a mixture thereof.

[0020] In another embodiment of the invention, the platelet aggregation inhibitor is a thromboxane A₂ inhibitor, a glycoprotein IIb/IIIa inhibitor, an adenosine diphosphate antagonist, a fibrinogen-platelet binding inhibitor, or a cAMP phosphodiesterase inhibitor.

BRIEF DESCRIPTION OF THE DRAWINGS

[0021] Table 1 summarizes baseline clinical, electrocardiographic, and angiographic characteristics in patients treated with pyridoxal-5'-phosphate (P5P) or placebo.

[0022] Table 2 summarizes procedural and angiographic results for patients treated with P5P or placebo.

[0023] Table 3 summarizes periprocedural cardiac markers and ST monitoring results for patients treated with P5P or placebo.

[0024] Table 4 summarizes periprocedural cardiac markers results for patients treated with P5P in combination with acetylsalicylic acid, eptifibatide, or clopidogrel and patients treated with placebo in combination with acetylsalicylic acid, eptifibatide, or clopidogrel.

[0025] Figure 1 comprises line graphs illustrating the area under the curve CK-MB values fitted to a log-normal distribution for patients treated with P5P (A) and placebo (B).

DETAILED DESCRIPTION

[0026] Before describing the present invention in detail, it is to be understood that this invention is not limited to specific dosage forms, carriers, or the like, and as such
may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting.

[0027] Some of the compounds described herein contain one or more asymmetric centres and this may give rise to enantiomers, diastereomers, and other stereoisomeric forms which may be defined in terms of absolute stereochemistry as (R)- or (S)-. The present invention is meant to include all such possible diastereomers and enantiomers as well as their racemic and optically pure forms. Optically active (R)- and (S)- isomers may be prepared using chiral synths or chiral reagents, or resolved using conventional techniques. When the compounds described herein contain olefinic double bonds or other centres of geometric symmetry, and unless specified otherwise, it is intended that the compounds include both E and A geometric isomers. Likewise all tautomeric forms are intended to be included.

[0028] As used in this specification and the appended claims, the singular forms "a," "an", and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "an active agent" or "a pharmacologically active agent" includes a single active agent as well as two or more different active agents in combination, reference to "a carrier" includes mixtures of two or more carriers as well as a single carrier, and the like.

[0029] By "pharmaceutically acceptable," such as in the recitation of a "pharmaceutically acceptable carrier," or a "pharmaceutically acceptable salt," is meant herein a material that is not biologically or otherwise undesirable, i.e., the material may be incorporated into a pharmaceutical composition administered to a patient without causing any undesirable biological effects or interacting in a deleterious manner with any of the other components of the composition in which it is contained.

[0030] "Carriers" or "vehicles" as used herein refer to conventional pharmaceutically acceptable carrier materials suitable for drug administration, and include any such materials known in the art that are nontoxic and do not interact with
other components of a pharmaceutical composition or drug delivery system in a deleterious manner.

[0031] By an "effective" amount or a "therapeutically effective amount" of a drug or pharmacologically active agent is meant a nontoxic but sufficient amount of the drug or agent to provide the desired effect. In the combination therapy of the present invention, an "effective amount" of one component of the combination is the amount of that compound that is effective to provide the desired effect when used in combination with the other components of the combination. The amount that is "effective" will vary from subject to subject, depending on the age and general condition of the individual, the particular active agent or agents, and the like. Thus, it is not always possible to specify an exact "effective amount." However, an appropriate "effective" amount in any individual case may be determined by one of ordinary skill in the art using routine experimentation.

[0032] The terms "reduce the risk of cardiovascular disease" and "reducing the risk of cardiovascular disease" as used herein refer to the reduction or elimination of an underlying cause or biomarker associated with the increased incidence of a cardiovascular event.

[0033] As used herein, "cardiovascular disease" means any disease of the heart or blood vessels. Examples of cardiovascular disease include, but are not limited to: congestive heart failure, myocardial ischemia, arrhythmia, myocardial infarction (MI), ischemic stroke, hemorrhagic stroke, coronary artery disease, hypertension (high blood pressure), atherosclerosis (clogging of the arteries), aneurysm, peripheral artery disease (PAD), thrombophlebitis (vein inflammation), diseases of the heart lining, diseases of the heart muscle, carditis, congestive heart failure, endocarditis, ischemic heart disease, valvular heart disease (malfuction of a valve or valves in the blood vessels of the heart), arteriosclerosis (hardening of the arteries), acute coronary syndrome (ACS), high cholesterol, deep vein thrombosis (DVT), Kawasaki disease, peripheral vascular disease, ischemic injury, and heart transplant.
[0034] As used herein, “cerebrovascular disease” means any disease affecting blood supply to the brain. Examples of cerebrovascular disease include, but are not limited to: cerebral ischemia, cerebral hemorrhage, ischemic stroke, or hemorrhagic stroke.

[0035] As used herein, “a disease which arises from prothrombotic and thrombotic states in which the coagulation cascade activated” or a state of hypercoagulability, means any disease inherited or acquired or both, that meets the requirements of having one or more of Virchow’s triad: a) changes in the vessel wall, b) changes in the pattern of blood flow, and c) changes in the constituents of blood, and is associated with a predisposition to venous thrombosis and/or arterial thrombosis. For the inherited diseases, common risk factors include, but are not limited to; antithrombin deficiencies, Protein C deficiencies, Protein S deficiencies, Factor V Leiden deficiencies, Dysfibrinogenemia Factor XII deficiencies, prothrombin 20210 mutations, hyperhomocysteinemia, elevated factor XIII levels, and disorders of plasmin generation. For acquired hypercoagulable conditions, risk factors include, but are not limited to; pregnancy, immobility, trauma, postoperative state, use of oral contraceptives, use of estrogen and antiphospholipid syndrome. Examples of such diseases include, but are not limited to: deep vein thrombosis, disseminated intravascular coagulopathy, and pulmonary embolism.

[0036] As used herein, “pyridoxal-5’-phosphate compound” or “pyridoxal-5’-phosphate related compound”, means any vitamin B6 precursor, metabolite, derivative, or analogue but excludes vitamin B6 (pyridoxine).

[0037] As used herein, the terms “platelet aggregation inhibitor” and “antiplatelet agent”, mean any compound which inhibits activation, aggregation and adhesion of platelets.

[0038] The antithrombotic effect of vitamin B6 is known in the art. The present inventors have discovered that the platelet aggregation inhibition properties of pyridoxal-5’-phosphate and pyridoxal-5’-phosphate related compounds are significantly greater than those for vitamin B6 (pyridoxine). The present inventors
have now discovered that pyridoxal-5'-phosphate and pyridoxal-5'-phosphate related compounds in combination with presently available platelet aggregation inhibitors, reduce the formation of blood clots in a synergistic manner and are effective for reducing the risk of cardiovascular disease and lowering the incidence of a cardiovascular event.

[0039] In light of these discoveries, the present invention provides novel pharmaceutical compositions and uses thereof for inhibiting platelet aggregation, treating disease which arises from prothrombotic and thrombotic states in which the coagulation cascade is activated and reducing the risk of cardiovascular disease. The pharmaceutical compositions of the present invention are more effective than currently available combination antiplatelet therapies. Furthermore, the pharmaceutical compositions ameliorate multiple risk factors for cardiovascular disease including lipoproteins, homocysteine, vasoconstriction, and inflammation. The pharmaceutical compositions of the present invention are comprised of a platelet aggregation inhibitor, a pyridoxal-5'-phosphate or pyridoxal-5'-phosphate related compound or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

[0040] Examples of platelet aggregation inhibitors which may be used in accordance with the present invention include, but are not limited to: thromboxane A₂ inhibitors (e.g. acetylsalicylic acid (ASA)), glycoprotein IIb/IIIa inhibitors (e.g. abciximab, eptifibatide, tirofiban, lamifiban, xemilofiban, orbofiban, sibrafiban, fradafiban, roxifiban, lotrafiban), adenosine diphosphate (ADP) antagonist (e.g. clopidogrel (Plavix™), ticlopidine, sulfinpyrazone, AZD6140, AZD6933), cAMP phosphodiesterase inhibitors (e.g. dipyridamole, cilostazol (Pletal™), pentoxifylline (Trental™)) or fibrinogen-platelet binding inhibitors (e.g. ticlopidine).

[0041] The pharmaceutical compositions according to the invention can be prepared with a compound selected from: pyridoxal-5'-phosphate, a pharmaceutically acceptable salt of pyridoxal-5'-phosphate, a pyridoxal-5'-phosphate related compound or a pharmaceutically acceptable salt of a pyridoxal-5'-phosphate
related compound. Preferably, the pharmaceutical compositions according to the invention comprise pyridoxal-5'-phosphate.

[0042] Examples of pyridoxal-5'-phosphate related compounds which may be used in accordance with the present invention include, but are not limited to: pyridoxal-5-phosphate (P5P), pyridoxal, and pyridoxamine. Other pyridoxal-5'-phosphate related compounds which can also be used, include the 3-acylated analogues of pyridoxal, 3'acylated analogues of pyridoxal-4,5-aminal, and pyridoxine phosphonate analogues as disclosed in US Patent No. 6,585,414 and U.S. Patent Application No. 20030114424, both of which are incorporated herein by reference.

[0043] The 3-acylated analogue of pyridoxal includes:

![Chemical Structure Image]

wherein,

R₁ is alkyl, alkenyl, in which alkyl can interrupted by nitrogen, oxygen, or sulfur, and can be unsubstituted or substituted at the terminal carbon with hydroxy, alkoxy, alkanoyloxy, alkoxyalkanoyl, alkoxy carbonyl, or

R₁ is dialkylcarbamoyloxy; alkoxy; dialkylamino; alkanoyloxy; alkanoyloxyaryl; alkoxyalkanoyl; alkoxy carbonyl; dialkyl carbamoyloxy; or

R₁ is aryl, aryloxy, arylthio, or aralkyl, in which aryl can be substituted by alkyl, alkoxy, amino, hydroxy, halo, nitro, or alkanoyloxy.

[0044] The 3-acylated analogue of pyridoxal-4,5-aminal includes:
wherein,

$R_1$ is alkyl, alkenyl, in which alkyl can interrupted by nitrogen, oxygen, or sulfur, and can be unsubstituted or substituted at the terminal carbon with hydroxy, alkoxy, alkanoyloxy, alkoxyalkanoyl, alkoxy carbonyl, or

$R_1$ is dialkyl carbamoyloxy; alkoxy; dialkylamino; alkanoyloxy; alkanoyloxyaryl; alkoxy alkyl; alkoxy alkyl; dialkylcarbamoyloxy; or

$R_1$ is aryl, aryloxy, arylthio, or aralkyl, in which aryl can be substituted by alkyl, alkoxy, amino, hydroxy, halo, nitro, or alkanoyloxy;

$R_2$ is a secondary amino group.

[0045] The pyridoxine phosphate analogue includes:

(a)

wherein,

$R_1$ is hydrogen or alkyl;

$R_2$ is $-\text{CHO}$, $-\text{CH}_2\text{OH}$, $-\text{CH}_3$, $-\text{CO}_2\text{R}_6$ in which $\text{R}_6$ is hydrogen, alkyl, aryl; or

$R_2$ is $-\text{CH}_2\text{-O}$ alkyl in which alkyl is covalently bonded to the oxygen at the 3-position instead of $R_1$;
R₃ is hydrogen and R₄ is hydroxy, halo, alkoxy, alkanoyloxy, alkylamino, or arylamino; or

R₃ and R₄ are halo; and

R₅ is hydrogen, alkyl, aryl, aralkyl, or -CO₂R₇ in which R₇ is hydrogen, alkyl, aryl, or aralkyl;

(b)

wherein,

R₁ is hydrogen or alkyl;

R₂ is -CHO, -CH₂OH, -CH₃, -CO₂R₅ in which R₅ is hydrogen, alkyl, aryl; or

R₂ is -CH₂-O alkyl in which alkyl is covalently bonded to the oxygen at the 3-position instead of R₁;

R₃ is hydrogen, alkyl, aryl, aralkyl,

R₄ is hydrogen, alkyl, aryl, aralkyl, or -CO₂R₆ in which R₆ is hydrogen, alkyl, aryl or aralkyl;

n is 1 to 6; and

(c)

wherein,
$R_1$ is hydrogen or alkyl;

$R_2$ is $-\text{CHO}$, $\text{CH}_2\text{OH}$, $-\text{CH}_3$, $-\text{CO}_2R_8$ in which $R_8$ is hydrogen, alkyl, aryl; or

$R_2$ is $-\text{CH}_2\text{O}$ alkyl- in which alkyl is covalently bonded to the oxygen at the 3-position instead of $R_1$;

$R_3$ is hydrogen and $R_4$ is hydroxy, halo, alkoxy, or alkanoyloxy; or

$R_3$ and $R_4$ can be taken together to form $=\text{O}$;

$R_5$ and $R_6$ are hydrogen; or

$R_5$ and $R_6$ are halo;

$R_7$ is hydrogen, alkyl, aryl, aralkyl, or $-\text{CO}_2R_8$ in which $R_8$ is hydrogen, alkyl, aryl, or aralkyl.

[0046] The pharmaceutical composition according to the invention may be prepared using pyridoxal 5'-phosphate, a pharmaceutically acceptable salt of pyridoxal 5'-phosphate, a pyridoxal 5'-phosphate related compound or a pharmaceutically acceptable salt of a pyridoxal 5'-phosphate related compound. Preferably, pharmaceutical compositions are prepared using pyridoxal 5'-phosphate. Both the monohydrate and the anhydrous forms of pyridoxal 5'-phosphate are suitable for preparation of the pharmaceutical compositions of the invention. Pyridoxal 5'-phosphate or the pyridoxal 5'-phosphate related compound may be provided as salt forms with pharmaceutically compatible counterions such as but not limited, to citrate, tartate, bisulfate, etc. The pharmaceutically compatible salts may be formed with many acids, including but, not limited to, hydrochloric, sulfuric, acetic, lactic, tartaric, malic, succinic, etc. The salt forms tend to be more soluble in aqueous or other protonic solvents than the corresponding free base forms.
[0047] In a preferred embodiment of the invention, the pharmaceutical composition comprises ASA and pyridoxal-5'-phosphate. In another preferred embodiment of the invention, the pharmaceutical composition comprises clopidogrel (Plavix™) and pyridoxal-5'-phosphate. In a further preferred embodiment of the invention, the pharmaceutical composition comprises eptifibatide (Integrillin™) and pyridoxal-5'-phosphate.

[0048] Pharmaceutical compositions for use in accordance with the present invention may be formulated in a conventional manner using one or more physiologically acceptable carriers comprising excipients and auxiliaries which facilitate processing of the active compounds into preparations which can be used pharmaceutically. Proper formulation is dependent upon the route of administration chosen.

[0049] For injection, the agents of the invention may be formulated in aqueous solutions, preferably in physiologically compatible buffers such as Hanks' solution, Ringer's solution, or physiological saline buffer.

[0050] For oral administration, the compounds can be formulated readily by combining the active compounds with pharmaceutically acceptable carriers well known in the art. Such carriers enable the compounds of the invention to be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions and the like, for oral ingestion by a patient to be treated. Pharmaceutical preparations for oral use can be obtained by solid excipient, optionally grinding a resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients are, in particular, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol, or cellulose preparations such as, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethyl-cellulose, sodium carboxymethylcellulose, and/or polyvinylpyrrolidone. If desired, disintegrating agents may be added, such as the cross-linked polyvinylpyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate.
[0051] Preferably, the pharmaceutical compositions of the present invention are administered orally. Preferred oral dosage forms contain a therapeutically effective unit dose of each active agent, wherein the unit dose is suitable for a once-daily oral administration. The therapeutic effective unit dose of any of the active agents will depend on number of factors which will be apparent to those skilled in the art and in light of the disclosure herein. In particular these factors include: the identity of the compounds to be administered, the formulation, the route of administration employed, the patient's gender, age, and weight, and the severity of the condition being treated. Where the dose provided does not reduce platelet aggregation levels, as measured by the closure time (CL) using, for example the Platelet Function Analyzer PFA-100®, or by measuring the bleeding time (BL), to appropriate levels, following at least 10 days of treatment, the dose can be increased.

[0052] The therapeutic effective unit dosage for the platelet aggregation inhibitor will vary on depending on the particular inhibitor used and the condition to be treated. The pharmaceutical compositions according to the invention can be used in cases where it is desirable to inhibit platelet aggregation. The pharmaceutical compositions according to the invention can also be used to treat patients at risk of a cardiovascular disease. The pharmaceutical compositions according to the invention can further be used to treat a patient undergoing a surgical intervention and preferably a cardiovascular surgical intervention such as but not limited to: a coronary artery bypass graft, a percutaneous coronary intervention or placement of a coronary stent. The pharmaceutical compositions can be used to treat or prevent the occurrence of thrombosis following the surgical intervention.

[0053] Where the platelet aggregation inhibitor used is ASA and it is used for the prevention of myocardial infarction (MI), transient ischemic attack (TIA), or ischemic stroke, the therapeutic effective unit dosage can be between 5 to 500 mg per day, and preferably between 30 mg and 81 mg per day. More preferably, the unit dosage will be between 75 mg and 81 mg per day and even more preferably, the unit dosage will be 81 mg per day. When ASA is used postoperatively in the case of a coronary artery bypass graft (CABG) or a percutaneous coronary intervention (PCI), the
effective dose is preferably 325 mg three times daily, continued until further notice from a physician.

[0054] Where the platelet aggregation inhibitor used is eptifibatide and it is used for prophylaxis of percutaneous coronary intervention (PCI) related thrombosis, the therapeutic effective unit dosage is between 30 to 500 μg/kg. A bolus IV injection of 135 μg/kg can be administered immediately before surgery and a continuous IV infusion of between 0.1 to 5 μg/kg/min and more preferably a continuous IV infusion of 0.5 μg/kg/min, can be administered 20 to 24 hours after surgery.

[0055] Where the platelet aggregation inhibitor used is eptifibatide and it is used for the treatment of acute coronary syndrome, the therapeutic effective unit dosage of eptifibatide is preferably between 30 to 500 μg/kg. A bolus injection of 180 μg/kg can be administered as soon as possible after diagnosis, immediately followed by continuous IV infusion of between 0.1 to 5 μg/kg/min, and more preferably a continuous IV infusion of 2 μg/kg/min until hospital discharge (up to 72 hours).

[0056] Where the platelet aggregation inhibitor used is eptifibatide and it is used for prophylaxis for coronary stenting, the therapeutic effective unit dosage of eptifibatide is preferably between 30 to 500 μg/kg. Preferably, the eptifibatide can be administered as a first bolus injection of 180 μg/kg followed by a continuous infusion of between 0.1 to 5 μg/kg/min, and more preferably, a continuous IV infusion of 2 μg/kg/min for 10 minutes, which is then followed by a second bolus injection of 180 μg/kg. A continuous infusion can then be resumed for 18 to 24 hours.

[0057] Where the platelet aggregation inhibitor used is clopidogrel and it is used as a prophylaxis for MI, stroke, or thrombotic or vascular injury, the therapeutic effective unit dosage is between 10 and 1000 mg per day and preferably between 75 mg and 150 mg per day. More preferably the unit dosage per day would be 75 mg. When used immediately before surgery, the therapeutic effective dosage unit would be between 300 mg and 500 mg. More preferably, the unit dosage would be 300 to 350 mg and even more preferably the unit dosage would be 300 mg.
The preferable therapeutic effective unit dosage for the pyridoxal-5'-phosphate or pyridoxal-5'-phosphate related compound is between 0.1 to 50 mg/kg body weight daily. More preferably, the unit dosage will be 1 to 5 mg/kg body weight daily.

For reducing the risk of cerebrovascular disease, a similar dose range of 0.1-100 mg/kg or more preferably 0.5 to 50 mg orally, can be used. For pyridoxal-5'-phosphate, the dosage used would be similar, e.g. 1 mg/kg to 15 mg/kg per day given intravenously to the patient immediately after they have a stroke the dosage, until otherwise directed by physician. More preferably, the dosage will be 10 to 15 mg/kg per day given intravenously. For reducing the risk of cardiovascular disease, the daily dosage may be the same as for stroke.

Although the present invention has been described with reference to illustrative embodiments, it is to be understood that the invention is not limited to these precise embodiments, and that various changes and modifications may be effected therein by one skilled in the art. All such changes and modifications are intended to be encompassed in the appended claims.

Example 1 - Effectiveness of pyridoxal-5'-phosphate for the reduction of myocardial ischemic injury following coronary intervention

AMI (≤7 days), diminished epicardial blood flow, angiographic thrombus, ejection fraction ≤30%, or vein graft lesion. In addition to any general contraindication to the PCI procedure or standard concomitant therapies, major exclusion criteria were creatine kinase (CK-MB) elevation above the upper limit of normal immediately before PCI, electrocardiographic evidence of atrial fibrillation or left bundle branch block, or evidence of any clinically significant abnormal laboratory finding (transaminases, bilirubin, or alkaline phosphatase >1.5 times the upper limit of normal or serum creatinine >1.8 mg/dl). Patients with elevated troponin measurements were permitted in the study provided that the peak troponin value was reported >24 hours before scheduled PCI, with documentation of a decreasing value before revascularization. After providing informed consent, patients randomized to treatment with P5P were administered enteric-coated P5P as a 10 mg/kg oral dose ≥4 hours before PCI followed by 2 daily doses of 5 mg/kg orally for 14 days. Compliance and reasons for discontinued treatments were recorded for all patients.

[0063] Study end points and definitions: The primary objective of the study was to evaluate the feasibility of treatment with P5P as a cardioprotective agent in high-risk elective PCI. The primary end point of infarct size was evaluated by the trapezoidal rule (Press WH, Teukolsky SA, Vetterling WT, Flannery BP. Numerical Recipes. Cambridge, UK: Cambridge University Press, 1994:127–133.) using serial CK-MB enzyme measures performed at baseline and every 6 hours for 24 hours beginning immediately before initiation of PCI. The occurrence of myocardial ischemia within 24 hours after PCI was assessed as a secondary end point using continuous 12-lead electrocardiographic monitoring (Northeast Monitoring, Boston, Massachusetts). Evidence of periprocedural ischemia was defined as ST-segment depression of ≥100 μV within a 60-minute period of PCI, lasting ≥1 minute and separated from other episodes by ≥1 minute. Area under the curve ST-segment deviation was measured from the onset of the first to the last contrast injection. All cardiac markers and ST-segment monitoring data were analyzed by core laboratories blinded to treatment assignment (University of Maryland School of Medicine, Baltimore, Maryland; Duke Ischemia Monitoring Laboratory, Durham,
North Carolina). Additional prespecified secondary end points included the 30-day composite and individual event rates of death; nonfatal infarction; new or worsening heart failure, or recurrent ischemia in addition to net clinical safety, which was defined as the absence of major adverse ischemic events; thrombolysis in myocardial infarction (TIMI) major bleeding; and liver function or coagulation test abnormalities. Acute myocardial infarction (AMI) was defined as CK-MB elevation ≥3 times the upper limit of normal (upper limit of normal 7 ng/ml) and/or troponin T levels ≥1.5 times the upper limit of normal (upper limit of normal 0.1 ng/ml). If previous troponin (or CKMB) values were above the upper limit of normal, values were required to be >50% of the baseline measurement in addition to ≥2 times (≥3 times for CK-MB) the upper limit of normal to meet the definition of AMI. Routine chemistries, complete blood count, and coagulation assays were performed at baseline, 7 days, and 30 days after randomization. Peak periprocedural CK-MB and the maximum difference in troponin levels from baseline to within 24 hours after PCI were also examined.

[0064] **Data collection and statistical analyses:** Patients who received ≥1 dose of the study drug and underwent PCI were analyzed for all primary and secondary efficacy and safety end points. Patients who received ≥1 dose of study drug but who did not undergo PCI were excluded from the primary efficacy and ST segment monitoring analyses but were included in the safety analyses. Statistical tests were 2-sided with an α level of 0.05 and employed the intent-to-treat principle. The Wilcoxon rank-sum test was used to analyze all continuous variables. Due to small sample sizes, categorical variables were compared using the Fisher’s exact test with the exception of the ST-segment monitoring data, which utilized the Pearson’s chi-square test. Statistical analyses were performed using SAS version 8.2 (SAS Institute, Cary, North Carolina).

[0065] **Results** - Of the 60 patients enrolled in the study of P5P in high-risk PCI, all patients received treatment with P5P or placebo; however, 4 patients (3 P5P, 1 placebo) did not undergo planned revascularization. An additional 3 patients were excluded from the area under the curve analyses due to incomplete collection of
cardiac enzyme data. As a result, 53 and 60 patients were included in the primary efficacy and 30-day clinical and/or safety analyses, respectively.

[0066] The presence of established cardiovascular disease, prior revascularization, and cardiovascular risk factors were similar between patients randomized to P5P or placebo and representative of patient populations in larger contemporary trials that studied patients with acute coronary syndromes (Table 1). Overall, the mean age of the population was 58 years, 81.7% of patients were men, and 21.7% had undergone previous PCI and/or bypass surgery. Although recent AMI as an indication for revascularization occurred more commonly among patients treated with P5P, a similar number of patients in each group presented with an acute coronary syndrome, and approximately half of all patients had elevated troponin levels before PCI.

[0067] Except for a higher incidence of reduced epicardial flow among control patients, baseline angiographic and procedural characteristics also appeared similar between treatment groups (Table 1). Administration of P5P or placebo occurred an average of 6.1 and 8.4 hours before PCI, respectively. Stent implantation was performed in 100% and 97.3% of the placebo and P5P treatment groups, respectively. Only 1 vein graft intervention was performed using distal embolic protection. Although the right coronary artery was most commonly treated in both groups, fewer patients treated with placebo underwent revascularization of a saphenous vein graft (Table 2). Procedural angiographic complications (e.g., major dissection, abrupt vessel closure) were infrequent (Table 2).
<table>
<thead>
<tr>
<th>TABLE 1 Baseline Clinical Electrocardiographic, and Angiographic Characteristics</th>
<th>P5P (n = 40)</th>
<th>Placebo (n = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical Characteristics</strong>&lt;sup&gt;*&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (yrs) (range)</td>
<td>54 (48-66)</td>
<td>59 (55-69)</td>
</tr>
<tr>
<td>Men</td>
<td>32 (80)</td>
<td>17 (85)</td>
</tr>
<tr>
<td>Baseline troponin positive</td>
<td>14/30 (47)</td>
<td>6/14 (43)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>9 (23)</td>
<td>4 (20)</td>
</tr>
<tr>
<td>Systemic hypertension</td>
<td>17 (43)</td>
<td>9 (45)</td>
</tr>
<tr>
<td>Hyperlipidemia (requiring medical treatment or LDL &gt; 130 mg/dl)</td>
<td>31 (78)</td>
<td>17 (85)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>12 (30)</td>
<td>5 (25)</td>
</tr>
<tr>
<td>Prior myocardial infarction</td>
<td>14 (35)</td>
<td>9 (45)</td>
</tr>
<tr>
<td>Prior PCI</td>
<td>6 (15)</td>
<td>2 (10)</td>
</tr>
<tr>
<td>Prior coronary bypass graft surgery</td>
<td>5 (13)</td>
<td>2 (10)</td>
</tr>
<tr>
<td>Prior stroke or transient ischemic attack</td>
<td>1 (3)</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>3 (8)</td>
<td>7 (35)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>3 (8)</td>
<td>2 (10)</td>
</tr>
<tr>
<td>Qualifying electrocardiogram</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ST-segment depression</td>
<td>2 (5)</td>
<td>2 (10)</td>
</tr>
<tr>
<td>ST-segment elevation</td>
<td>7 (18)</td>
<td>2 (10)</td>
</tr>
<tr>
<td>T-wave inversion</td>
<td>6 (15)</td>
<td>4 (20)</td>
</tr>
<tr>
<td><strong>Angiographic characteristics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCI performed</td>
<td>37 (93)</td>
<td>19 (95)</td>
</tr>
<tr>
<td>Reason for PCI</td>
<td>(n = 37)</td>
<td>(n = 19)</td>
</tr>
<tr>
<td>Acute coronary syndrome</td>
<td>9 (24)</td>
<td>5 (25)</td>
</tr>
<tr>
<td>Recent AMI</td>
<td>16 (42)</td>
<td>3 (15)</td>
</tr>
<tr>
<td>Reduced epicardial flow</td>
<td>6 (16)</td>
<td>8 (40)</td>
</tr>
<tr>
<td>Thrombus</td>
<td>1 (3)</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>2 (5)</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Saphenous vein graft lesion</td>
<td>4 (11)</td>
<td>2 (10)</td>
</tr>
<tr>
<td>No. of coronary arteries narrowed ≥50%</td>
<td>(n = 37)</td>
<td>(n = 19)</td>
</tr>
<tr>
<td>In diameter</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>1 (3)</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>19 (48)</td>
<td>14 (70)</td>
</tr>
<tr>
<td>2</td>
<td>13 (33)</td>
<td>2 (10)</td>
</tr>
<tr>
<td>3</td>
<td>5 (13)</td>
<td>3 (15)</td>
</tr>
<tr>
<td>Left main</td>
<td>2 (5)</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Left ventricular ejection fraction</td>
<td>0.50 (0.40-0.68)</td>
<td>0.56 (0.37-0.64)</td>
</tr>
<tr>
<td>No. of coronary narrowings treated</td>
<td>(n = 37)</td>
<td>(n = 19)</td>
</tr>
<tr>
<td>1</td>
<td>25 (70)</td>
<td>15 (79)</td>
</tr>
<tr>
<td>2</td>
<td>8 (22)</td>
<td>3 (16)</td>
</tr>
<tr>
<td>3</td>
<td>3 (8)</td>
<td>1 (5)</td>
</tr>
</tbody>
</table>

Values are expressed as median (Interquartile range) or number (percent).
*Patients may be double counted
IDL = low-density lipoprotein

[0068] The primary end point of periprocedural infarct size measured according to median periprocedural CK-MB area under the curve was reduced from 32.9 to 18.6 ng/ml (p= 0.038), reflecting a shift in the distribution of CK-MB (Table 3 and Figure 1). Similarly, the maximum periprocedural CK-MB level was significantly lower
TABLE 2 Procedural and Angiographic* results

<table>
<thead>
<tr>
<th></th>
<th>P5P (n = 37)</th>
<th>Placebo (n = 19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥1 stent implanted</td>
<td>36 (97)</td>
<td>19 (100)</td>
</tr>
<tr>
<td>Patients received GP IIb/IIIa inhibitor</td>
<td>29/35 (83)</td>
<td>15/19 (79)</td>
</tr>
<tr>
<td>Target vessel</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left anterior descending</td>
<td>11 (30)</td>
<td>4 (21)</td>
</tr>
<tr>
<td>Right</td>
<td>14 (38)</td>
<td>11 (58)</td>
</tr>
<tr>
<td>Left circumflex</td>
<td>8 (22)</td>
<td>3 (16)</td>
</tr>
<tr>
<td>Saphenous vein graft</td>
<td>4 (11)</td>
<td>1 (5)</td>
</tr>
<tr>
<td>TIMI flow preprocedure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0/1</td>
<td>3 (8)</td>
<td>4 (22)</td>
</tr>
<tr>
<td>2</td>
<td>7 (19)</td>
<td>4 (22)</td>
</tr>
<tr>
<td>3</td>
<td>27 (73)</td>
<td>10 (56)</td>
</tr>
<tr>
<td>TIMI flow final</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0/1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>1 (5)</td>
</tr>
<tr>
<td>3</td>
<td>37 (100)</td>
<td>18 (95)</td>
</tr>
<tr>
<td>Diameter stenosis preprocedure (%)</td>
<td>90.0 (80.0-95.0)</td>
<td>95.0 (90.0-99.0)</td>
</tr>
<tr>
<td>Diameter stenosis final (%)</td>
<td>0 (0-0)</td>
<td>0 (0-0)</td>
</tr>
<tr>
<td>Procedural complications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>35 (95)</td>
<td>18 (95)</td>
</tr>
<tr>
<td>Major dissection</td>
<td>1 (3)</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Abrupt closure</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>No reflow</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Thrombus formation</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Side branch closure</td>
<td>1 (3)</td>
<td>0</td>
</tr>
<tr>
<td>Distal embolization</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Values are expressed as median (Interquartile range) or number (percent)
* Investigator-reported angiographic values
GP = glycoprotein

[0069] among patients receiving P5P. By categorical classification, the occurrence of 30-day nonfatal AMI did not differ between groups (12.8% with P5P vs 10.0% with placebo, p = 1.0). There were no deaths, and 30-day composite adverse event rates (death, nonfatal AMI, new and/or worsening heart failure, or recurrent ischemia) were similar (17.9% with P5P vs 15.0% with placebo, p = 1.0).

[0070] Electrocardiographic ST monitoring data were available for 94.6% of the patients who underwent PCI and who received treatment (Table 3). Post-PCI ischemia occurred in approximately 15% of patients in both groups. Although lower
rates of post-PCI ischemia were observed with P5P treatment (14.7% vs 17.6%, p = 0.78), there were no significant differences in ischemia parameters per continuous electrocardiographic monitoring (Table 3).

<table>
<thead>
<tr>
<th>TABLE 3 Periprocedural Cardiac Markers and ST Monitoring Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Periprocedural cardiac markers</td>
</tr>
<tr>
<td>Area under the curve CK-MB (ng/ml)</td>
</tr>
<tr>
<td>Peak CK-MB (ng/ml)</td>
</tr>
<tr>
<td>Change in troponin T (ng/ml)</td>
</tr>
<tr>
<td>Time to peak CK-MB (h)</td>
</tr>
<tr>
<td>24-h continuous electrocardiographic ST monitoring</td>
</tr>
<tr>
<td>Duration of monitoring (h)</td>
</tr>
<tr>
<td>Area under the curve ST deviation (µV-min)</td>
</tr>
<tr>
<td>Any post PCI ischemia (%)</td>
</tr>
<tr>
<td>P5P</td>
</tr>
<tr>
<td>18.6 (10.2-34.5), 35</td>
</tr>
<tr>
<td>1.1 (0.5-2.4), 39</td>
</tr>
<tr>
<td>0 (0-0.07), 35</td>
</tr>
<tr>
<td>11.0 (0-18.0), 36</td>
</tr>
<tr>
<td>22.6 (20.4-23.9), 36</td>
</tr>
<tr>
<td>1349 (951-2.283), 35</td>
</tr>
<tr>
<td>14.7-34</td>
</tr>
</tbody>
</table>

Values are expressed in median (interquartile range) or percent followed by n (number of observations)

[0071] No safety issues related to treatment with P5P were identified. The occurrence of major bleeding (2.8% P5P vs 10.5% placebo, p = 0.27) and need for blood product transfusion (2.5% P5P vs 10.0% placebo, p = 0.26) was infrequent and did not significantly differ between groups. There were no apparent differences in abnormalities of routine chemistries or coagulation studies at 7 and 30 days. In both groups, however, approximately 1/4 of patients discontinued drug therapy before completion of the prescribed 2 weeks (30.8% P5P vs 25.0% placebo, p = 0.77). For patients taking P5P, but who did not undergo PCI (3 patients, 7.5%), the most common causes for early discontinuation were gastrointestinal intolerance followed by non-specific musculoskeletal pain.

[0072] Conclusion: In high-risk patients for periprocedural ischemic complications, treatment with P5P was associated with a decrease in myocardial injury, reflected by a reduction in the total amount of CK-MB released after PCI. P5P therapy was associated with a significant decrease in peak periprocedural CK-MB elevation, a shift in the distribution of CK-MB to lower levels (Figure 1), and reduced periprocedural infarct size.
[0073] **Example 2 - Effectiveness of pyridoxal-5'-phosphate in combination with aspirin for the reduction of myocardial ischemic injury following coronary intervention**

[0074] **Method:** The study data of Example 1 was examined. Of the 60 patients described in Example 1, 35 patients received adjunctive treatment with acetylsalicylic acid [82 mg (6 patients) and 325 mg (29 patients)] in addition to P5P treatment.

[0075] **Results:** In patients treated with P5P and ASA, the secondary end point of maximum periprocedural CK-MB levels was reduced from 3.41 ng/ml (placebo and ASA) to 2.09 ng/ml (P5P and ASA; Table 4).

<table>
<thead>
<tr>
<th>Combination Therapy</th>
<th>CK-MB max (mean) ng/ml</th>
<th>Sample size</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASA + placebo</td>
<td>3.41</td>
<td>18</td>
</tr>
<tr>
<td>ASA + P5P</td>
<td>2.09</td>
<td>35</td>
</tr>
<tr>
<td>Eptifibatide + placebo</td>
<td>3.40</td>
<td>9</td>
</tr>
<tr>
<td>Eptifibatide + P5P</td>
<td>1.36</td>
<td>19</td>
</tr>
<tr>
<td>Clopidogrel + placebo</td>
<td>3.41</td>
<td>14</td>
</tr>
<tr>
<td>Clopidogrel + P5P</td>
<td>2.14</td>
<td>25</td>
</tr>
</tbody>
</table>

[0076] **Conclusions:** P5P and ASA combination therapy was associated with a significant decrease in peak periprocedural CK-MB elevation, and reduced periprocedural infarct size.

[0077] **Example 3 - Effectiveness of pyridoxal-5'-phosphate in combination with eptifibatide (Integrilin) for the reduction of myocardial ischemic injury following coronary intervention**

[0078] **Methods:** The study data of Example 1 was examined. Of the 60 patients described in Example 1, 19 patients received adjunctive treatment with eptifibatide in addition to P5P treatment.
[0079] **Results:** In patients treated with P5P and eptifibatide, the secondary end point of maximum periprocedural CK-MB levels was reduced from 3.40 ng/ml (placebo and eptifibatide) to 1.36 ng/ml (P5P and eptifibatide).

[0080] **Conclusions:** P5P and eptifibatide combination therapy was associated with a significant decrease in peak periprocedural CK-MB elevation (Table 4), and reduced periprocedural infarct size.

[0081] **Example 4 - Effectiveness of pyridoxal-5'-phosphate in combination with clopidogrel (Plavix) for the reduction of myocardial ischemic injury following coronary intervention**

[0082] **Methods:** The study data of Example 1 was examined. Of the 60 patients described in Example 1, 25 patients received adjunctive treatment with clopidogrel (75 mg, 16 patients and 300 mg, 9 patients) in addition to P5P treatment.

[0083] **Results:** In patients treated with P5P and clopidogrel, the secondary end point of maximum periprocedural CK-MB levels was reduced from 3.41 ng/ml (placebo and clopidogrel) and to 2.14 ng/ml (P5P and clopidogrel).

[0084] **Conclusions:** P5P and clopidogrel combination therapy was associated with a significant decrease in peak periprocedural CK-MB elevation (Table 4), and reduced periprocedural infarct size.
What is claimed is:

1. A pharmaceutical composition comprising: (a) a compound selected from pyridoxal-5'-phosphate, a pyridoxal-5'-phosphate related compound or a pharmaceutically acceptable salt thereof, (b) a platelet aggregation inhibitor and (c) a pharmaceutically acceptable carrier.

2. The pharmaceutical composition according to claim 1, wherein the pyridoxal-5'-phosphate related compound is selected from a group comprising: pyridoxal, pyridoxal-5'-phosphate, pyridoxamine, a 3-acylated analogue of pyridoxal, a 3-acylated analogue of pyridoxal-4,5-aminal, a pyridoxine phosphate analogue, and a mixture thereof.

3. The pharmaceutical composition according to claim 1, wherein the compound is pyridoxal-5'-phosphate.

4. The pharmaceutical composition according to claim 2, wherein the 3-acylated analogue of pyridoxal is:

\[
\begin{align*}
\text{R}_1 & \quad \text{O} \\
\text{H} & \quad \text{C} \\
\text{H}_2 & \quad \text{C} \\
\text{C} & \quad \text{O} \\
\text{C}_{\text{H}_2} & \quad \text{H}
\end{align*}
\]

wherein,

\(\text{R}_1\) is alkyl, alkenyl, in which alkyl can interrupted by nitrogen, oxygen, or sulfur, and can be unsubstituted or substituted at the terminal carbon with hydroxy, alkoxy, alkanoyloxy, alkoxyalkanoyl, alkoxy carbonyl, or

\(\text{R}_1\) is dialkylcarbamoyloxy; alkoxy; dialkylamino; alkanoyloxy; alkanoyloxyaryl; alkoxyalkanoyl; alkoxy carbonyl; dialkyl carbamoyloxy; or
R₁ is aryl, aryloxy, arythio, or aralkyl, in which aryl can be substituted by alkyl, alkoxy, amino, hydroxy, halo, nitro, or alkanoyloxy;

5. The pharmaceutical composition according to claim 2, wherein the 3-acylated analogue of pyridoxal-4,5-aminal is

![Chemical Structure](image)

wherein,

R₁ is alkyl, alkenyl, in which alkyl can interrupted by nitrogen, oxygen, or sulfur, and can be unsubstituted or substituted at the terminal carbon with hydroxy, alkoxy, alkanoyloxy, alkoxyalkanoyl, alkoxy carbonyl, or

R₁ is dialkylcarbamoyloxy; alkoxy; dialkylamino; alkanoyloxy; alkanoyloxyaryl; alkoxyalkanoyl; alkoxy carbonyl; dialkylcarbamoyloxy; or

R₁ is aryl, aryloxy, arythio, or aralkyl, in which aryl can be substituted by alkyl, alkoxy, amino, hydroxy, halo, nitro, or alkanoyloxy;

R₂ is a secondary amino group.

6. The pharmaceutical composition according to claim 2, wherein the pyridoxine phosphate analogue is selected from a group comprising:

![Chemical Structure](image)

(a)

wherein,
$R_1$ is hydrogen or alkyl;

$R_2$ is $\text{CHO}$, $\text{CH}_2\text{OH}$, $\text{CH}_3$, $\text{CO}_2R_6$ in which $R_6$ is hydrogen, alkyl, aryl; or

$R_2$ is $\text{CH}_2\text{O}$ alkyl in which alkyl is covalently bonded to the oxygen at the 3-position instead of $R_1$;

$R_3$ is hydrogen and $R_4$ is hydroxy, halo, alkoxy, alkanoyloxy, alkylamino, or arylamino; or

$R_3$ and $R_4$ are halo; and

$R_5$ is hydrogen, alkyl, aryl, aralkyl, or $\text{CO}_2R_7$ in which $R_7$ is hydrogen, alkyl, aryl, or aralkyl;

![Diagram](attachment:image.png)

(b)

wherein,

$R_1$ is hydrogen or alkyl;

$R_2$ is $\text{CHO}$, $\text{CH}_2\text{OH}$, $\text{CH}_3$, $\text{CO}_2R_5$ in which $R_5$ is hydrogen, alkyl, aryl; or

$R_2$ is $\text{CH}_2\text{O}$ alkyl in which alkyl is covalently bonded to the oxygen at the 3-position instead of $R_1$;

$R_3$ is hydrogen, alkyl, aryl, aralkyl,

$R_4$ is hydrogen, alkyl, aryl, aralkyl, or $\text{CO}_2R_6$ in which $R_6$ is hydrogen, alkyl, aryl or aralkyl;
n is 1 to 6; and

wherein,

- $R_1$ is hydrogen or alkyl;

- $R_2$ is $-\text{CHO}$, $\text{CH}_2\text{OH}$, $-\text{CH}_3$, $-\text{CO}_2\text{R}_8$ in which $R_8$ is hydrogen, alkyl, aryl; or

- $R_2$ is $-\text{CH}_2\text{-O}$ alkyl- in which alkyl is covalently bonded to the oxygen at the 3-position instead of $R_1$;

- $R_3$ is hydrogen and $R_4$ is hydroxy, halo, alkoxy, or alkanoyloxy; or

- $R_3$ and $R_4$ can be taken together to form $=\text{O}$;

- $R_5$ and $R_6$ are hydrogen; or

- $R_5$ and $R_6$ are halo;

- $R_7$ is hydrogen, alkyl, aryl, aralkyl, or $-\text{CO}_2\text{R}_8$ in which $R_8$ is hydrogen, alkyl, aryl, or aralkyl.

7. The pharmaceutical composition according to any one of claims 1 to 6, wherein the platelet aggregation inhibitor is a thromboxane A$_2$ inhibitor.

8. The pharmaceutical composition according to claim 7, wherein the thromboxane A$_2$ inhibitor is acetylsalicylic acid (ASA).
9. The pharmaceutical composition according to any one of claims 1 to 6 wherein the platelet aggregation inhibitor is a glycoprotein IIb/IIIa inhibitor.

10. The pharmaceutical composition according to claim 9, wherein the platelet glycoprotein IIb/IIIa inhibitor is selected from the group consisting of eptifibatide, tirofiban, lamifiban, xemilofiban, orbofibran, sibrafiban, fradafiban, roxifiban, lotrafiban, and abciximab.

11. The pharmaceutical composition according to any one of claims 1 to 6, wherein the platelet aggregation inhibitor is an adenosine diphosphate antagonist.

12. The pharmaceutical composition according to claim 11, wherein the adenosine diphosphate antagonist is selected from the group consisting of clopidogrel, ticlopidine, sulfinpyrazone, AZD6140, and AZD6933.

13. The pharmaceutical composition according to any one of claims 1 to 6, wherein the platelet aggregation inhibitor is a cAMP phosphodiesterase inhibitor.

14. The pharmaceutical composition according to claim 13, wherein the cAMP phosphodiesterase inhibitor is selected from the group consisting of: dipyridamole, cilostazol, and pentoxifylline.

15. A method of inhibiting platelet aggregation in a mammal comprising administering a therapeutically effective dose of: (a) a compound selected from pyridoxal-5'-phosphate, a pyridoxal-5'-phosphate related compound or a pharmaceutically acceptable salt thereof and (b) a platelet aggregation inhibitor.

16. The method according to claim 15, wherein the pyridoxal-5'-phosphate related compound is selected from a group consisting of: pyridoxal, pyridoxal-5'-phosphate, pyridoxamine, a 3-acylated analogue of pyridoxal, a 3-acylated analogue of pyridoxal-4,5-aminal, a pyridoxine phosphate analogue, and a mixture thereof.
17. The method according to claim 16, wherein the compound is pyridoxal-5-phosphate.

18. The method according to claim 16, wherein the 3-acylated analogue of pyridoxal is:

![Chemical Structure](image)

wherein,

$R_1$ is alkyl, alkenyl, in which alkyl can interrupted by nitrogen, oxygen, or sulfur, and can be unsubstituted or substituted at the terminal carbon with hydroxy, alkoxy, alkanoyloxy, alkoxyalkanoyl, alkoxy carbonyl, or

$R_1$ is dialkylcarbamoyloxy; alkoxy; dialkylamino; alkanoyloxy; alkanoyloxyaryl; alkoxyalkanoyl; alkoxy carbonyl; dialkylcarbamoyloxy; or

$R_1$ is aryl, aryloxy, arylthio, or aralkyl, in which aryl can be substituted by alkyl, alkoxy, amino, hydroxy, halo, nitro, or alkanoyloxy;

19. The method according to claim 16, wherein the 3-acylated analogue of pyridoxal-4,5-aminal is

![Chemical Structure](image)

wherein,
R₁ is alkyl, alkenyl, in which alkyl can interrupted by nitrogen, oxygen, or sulfur, and can be unsubstituted or substituted at the terminal carbon with hydroxy, alkoxy, alkanoyloxy, alkoxyalkanoyl, alkoxy carbonyl, or

R₁ is dialkylcarbamoyloxy; alkoxy; dialkylamino; alkanoyloxy; alkanoyloxyaryl; alkoxyalkanoyl; alkoxy carbonyl; dialkylcarbamoyloxy; or

R₁ is aryl, aryloxy, arylthio, or aralkyl, in which aryl can be substituted by alkyl, alkoxy, amino, hydroxy, halo, nitro, or alkanoyloxy;

R₂ is a secondary amino group.

20. The method according to claim 16, wherein the pyridoxine phosphate analogue is selected from a group comprising:

(a)

wherein,

R₁ is hydrogen or alkyl;

R₂ is –CHO-, -CH₂OH, -CH₃, -CO₂R₆ in which R₆ is hydrogen, alkyl, aryl; or

R₂ is –CH₂-O alkyl in which alkyl is covalently bonded to the oxygen at the 3-position instead of R₁;

R₃ is hydrogen and R₄ is hydroxy, halo, alkoxy, alkanoyloxy, alkylamino, or arylamino; or

R₃ and R₄ are halo; and
R₅ is hydrogen, alkyl, aryl, aralkyl, or \(-\text{CO}_2\)R₇ in which R₇ is hydrogen, alkyl, aryl, or aralkyl;

\[
\begin{array}{c}
\text{R}_2 \\
\text{R}_3
\end{array}
\]

(b) wherein,

R₁ is hydrogen or alkyl;

R₂ is \(-\text{CHO}, \text{-CH}_2\text{OH}, \text{-CH}_3, \text{-CO}_2\text{R}_5\) in which R₅ is hydrogen, alkyl, aryl; or

R₂ is \(-\text{CH}_2\text{-O} \text{ alkyl in which alkyl is covalently bonded to the oxygen at the 3-position instead of R}_1;\)

R₃ is hydrogen, alkyl, aryl, aralkyl,

R₄ is hydrogen, alkyl, aryl, aralkyl, or \(-\text{CO}_2\text{R}_6\) in which R₆ is hydrogen, alkyl, aryl or aralkyl;

n is 1 to 6; and

\[
\begin{array}{c}
\text{R}_3 \\
\text{R}_4 \\
\text{R}_5
\end{array}
\]

(c) wherein,

R₁ is hydrogen or alkyl;

R₂ is \(-\text{CHO}, \text{-CH}_2\text{OH}, \text{-CH}_3, \text{-CO}_2\text{R}_8\) in which R₈ is hydrogen, alkyl, aryl; or
R₂ is \( -\text{CH}_2\text{-O alkyl} \) in which alkyl is covalently bonded to the oxygen at the 3-position instead of R₁;

R₃ is hydrogen and R₄ is hydroxy, halo, alkoxy, or alkanoyloxy; or

R₃ and R₄ can be taken together to form =O;

R₅ and R₆ are hydrogen; or

R₅ and R₆ are halo;

R₇ is hydrogen, alkyl, aryl, aralkyl, or \(-\text{CO}_2\text{R₆}\) in which R₆ is hydrogen, alkyl, aryl, or aralkyl.

21. The method according to any one of claims 15 to 20, wherein the platelet aggregation inhibitor is a thromboxane A₂ inhibitor.

22. The method according to claim 21, wherein the thromboxane A₂ inhibitor is acetylsalicylic acid (ASA).

23. The method according to any one of claims 15 to 20, wherein the platelet aggregation inhibitor is a glycoprotein IIb/IIIa inhibitor.

24. The method according to claim 23, wherein the platelet glycoprotein IIb/IIIa inhibitor is eptifibatide.

25. The method according to any one of claims 15 to 20, wherein the platelet aggregation inhibitor is an adenosine diphosphate antagonist.

26. The method according to claim 25, wherein the adenosine diphosphate antagonist is selected from the group consisting of: clopidogrel, ticlopidine, AZD6140, and AZD6933.
27. The method according to any one of claims 15 to 20, wherein the platelet aggregation inhibitor is a cAMP phosphodiesterase inhibitor.

28. The method according to claim 27, wherein the cAMP phosphodiesterase inhibitor is selected from a group consisting of dipyridamole, cilostazol, and pentoxifylline.

29. A method of treating a mammalian patient at risk of a cardiovascular disease comprising administering a therapeutically effective dose of the pharmaceutical composition according to any one of claims 1 to 14.

30. The method according to claim 29, wherein the cardiovascular disease is selected from a group comprising: congestive heart failure, myocardial ischemia, arrhythmia, myocardial infarction, ischemic stroke, hemorrhagic stroke, coronary artery disease, hypertension (high blood pressure), atherosclerosis (clogging of the arteries), aneurysm, peripheral artery disease, thrombophlebitis (vein inflammation), diseases of the heart lining, diseases of the heart muscle, carditis, congestive heart failure, endocarditis, ischemic heart disease, valvular heart disease (malfuction of a valve or valves in the blood vessels of the heart), peripheral vascular disease, ischemic injury, Kawazaki disease, arteriosclerosis (hardening of the arteries), deep vein thrombosis, and acute coronary syndrome.

31. A method of treating a mammal having a disease which arises from thrombotic and prothrombotic states in which the coagulation cascade is activated, comprising administering a therapeutically effective dose of the pharmaceutical composition according to any one of claims 1 to 14.

32. The method according to claim 31, wherein the disease is selected from a group consisting of: deep vein thrombosis, disseminated intravascular coagulopathy, and pulmonary embolism.
33. A method of treating a mammalian patient at risk of cerebrovascular disease comprising administering a therapeutically effective dose of the pharmaceutical composition according to any one of claims 1 to 14.

34. The method according to claim 33, wherein the cerebrovascular disease is selected from a group consisting of: cerebral ischemia, cerebral hemorrhage, ischemic stroke, and hemorrhagic stroke.

35. The method according to any one of claims 15 to 34, wherein the dose of the pyridoxal-5'-phosphate or pyridoxal-5'-phosphate related compound is between 0.1 to 50 mg/kg per day.

36. The method according to any one of claims 15 to 34, wherein the dose of the pyridoxal-5'-phosphate or pyridoxal-5'-phosphate related compound is between 1 to 5 mg/kg per day.

37. A method for of treating a mammalian patient at risk of a cardiovascular disease comprising administering a therapeutically effective dose of: (a) a compound selected from pyridoxal-5'-phosphate, a pyridoxal-5'-phosphate related compound or a pharmaceutically acceptable salt thereof and (b) a platelet aggregation inhibitor

38. The method according to claim 37, wherein the cardiovascular disease is selected from a group comprising: congestive heart failure, myocardial ischemia, arrhythmia, myocardial infarction, ischemic stroke, hemorrhagic stroke, coronary artery disease, hypertension (high blood pressure), atherosclerosis (clogging of the arteries), aneurysm, peripheral artery disease, thrombophlebitis (vein inflammation), diseases of the heart lining, diseases of the heart muscle, carditis, congestive heart failure, endocarditis, ischemic heart disease, valvular heart disease (malfucntion of a valve or valves in the blood vessels of the heart), peripheral vascular disease, ischemic injury, Kawasaki disease, arteriosclerosis (hardening of the arteries), deep vein thrombosis, and acute coronary syndrome.
39. The method according to claim 38, wherein the cardiovascular disease is myocardial infarction, transient ischemic attack or ischemic stroke and wherein the platelet aggregation inhibitor is acetylsalicylic acid (ASA) and the compound is pyridoxal-5'-phosphate.

40. The method according to claim 39, wherein the therapeutically effective dose of the acetylsalicylic acid is between 5 and 500 mg/day.

41. The method according to claim 39, wherein the therapeutically effective dose of the acetylsalicylic acid is between 30 and 81 mg/day.

42. The method according to claim 39, wherein the therapeutically effective dose of the acetylsalicylic acid is between 75 and 81 mg/day.

43. The method according to claim 38, wherein the cardiovascular disease is acute coronary syndrome and wherein the platelet aggregation inhibitor is eptifibatide and the compound is pyridoxal-5'-phosphate.

44. The method according to claim 43, wherein therapeutically effective dose of eptifibatide is between 30 and 500 µg/kg.

45. The method according to claim 43, wherein the eptifibatide is administered intravenously.

46. The method according to claim 43, wherein the eptifibatide is administered as a bolus injection of 180 µg/kg following diagnosis of acute coronary syndrome and is then administered as a continuous IV infusion of between 0.1 to 5 µg/kg/min for up to 72 hours.

47. The method according to claim 46, wherein the eptifibatide is administered as a continuous IV infusion of 2µg/kg/min.
48. The method according to claim 38, wherein the platelet aggregation inhibitor is clopidogrel and the compound is pyridoxal-5'-phosphate.

49. The method according to claim 48, wherein the therapeutically effective dose of clopidogrel is between 10 and 1000 mg per day.

50. The method according to claim 48, wherein the therapeutically effective dose of clopidogrel is between 75 and 150 mg per day.

51. The method according to claim 48, wherein the therapeutically effective dose of clopidogrel is 75 mg per day.

52. A method for of treating a mammalian patient undergoing a cardiovascular surgical intervention comprising administering a therapeutically effective dose of (a) a compound selected from pyridoxal-5'-phosphate, a pyridoxal-5'-phosphate related compound or a pharmaceutically acceptable salt thereof and (b) a platelet aggregation inhibitor, prior to the surgical intervention or following the surgical intervention.

53. The method according to claim 52, wherein the surgical intervention is percutaneous coronary intervention and the platelet aggregation inhibitor is eptifibatide.

54. The method according to claim 53, wherein the therapeutically effective dose of eptifibatide is between 30 to 500 µg/kg.

55. The method according to claim 52, wherein the eptifibatide is administered as a bolus IV injection of 135 µg/kg immediately prior to the percutaneous coronary intervention and as a continuous IV infusion of between 0.1 and 5 µg/kg/min following for between 20 to 24 hours following the percutaneous coronary intervention.
56. The method according to claim 52, wherein the surgical intervention is the placement of a coronary stent and the platelet aggregation inhibitor is eptifibatide.

57. The method according to claim 56, wherein the eptifibatide is administered as a first bolus IV injection of 180 µg/kg immediately prior to the placement of the coronary stent intervention, as a continuous IV infusion of between 0.1 and 5 µg/kg/min following for 10 minutes following placement of the coronary stent, and then as a second bolus IV injection of 180 µg/kg.

58. The method according to claim 57, wherein the eptifibatide is administered as a continuous IV infusion of 2 µg/kg/min.

59. The method according to claims 56 or 57, wherein following the second bolus IV injection of the eptifibatide, a continuous IV infusion of between 0.1 and 5 µg/kg/min of the eptifibatide is administered for between 18 and 24 hours.

60. The method according to claim 52, wherein platelet aggregation inhibitor is clopidogrel.

61. The method according to claim 60, wherein the therapeutically effective dosage is between 300 and 500 mg and wherein the clopidogrel is administered prior to the surgical intervention.

62. The method according to claim 60, wherein the therapeutically effective dosage is between 300 and 350 mg and wherein the clopidogrel is administered prior to the surgical intervention.

63. The method according to claim 60, wherein the therapeutically effective dosage is 300 mg and wherein the clopidogrel is administered prior to the surgical intervention.
64. The method according to claim 52, wherein the surgical intervention is a coronary artery bypass graft or a percutaneous coronary intervention and the platelet aggregation inhibitor is acetylsalicylic acid.

65. The method according to claim 64, wherein the therapeutically effective dosage is 325 mg and wherein the acetylsalicylic acid is administered following the surgical intervention.

66. The method according to claim 64, wherein the therapeutically effective dosage is 325 mg and wherein the acetylsalicylic acid is administered daily for 3 days following the surgical intervention.

67. Use of a platelet aggregation inhibitor and a compound selected from pyridoxal-5'-phosphate, a pyridoxal-5'-phosphate related compound or a pharmaceutically acceptable salt thereof, for the preparation of a medicament.

68. Use of a platelet aggregation inhibitor and a compound selected from pyridoxal-5'-phosphate, a pyridoxal-5'-phosphate related compound or a pharmaceutically acceptable salt thereof, for inhibiting platelet aggregation.

69. Use of a platelet aggregation inhibitor and a compound selected from pyridoxal-5'-phosphate, a pyridoxal-5'-phosphate related compound or a pharmaceutically acceptable salt thereof, for reducing the risk of a condition selected from a group consisting of: cardiovascular disease, cerebrovascular disease, and a disease which arises from prothrombotic and thrombotic states in which the coagulation cascade is activated.

70. Use of a platelet aggregation inhibitor and a compound selected from pyridoxal-5'-phosphate, a pyridoxal-5'-phosphate related compound or a pharmaceutically acceptable salt thereof, for treatment and prevention of thrombosis following a surgical intervention.
71. The use according to claim 70, wherein the surgical intervention is a cardiovascular surgical intervention selected from a group consisting of: coronary artery bypass graft, percutaneous coronary intervention and placement of a coronary stent.

72. The use according to any one of claims 67 to 71, wherein the pyridoxal-5'-phosphate related compound is selected from a group consisting of: pyridoxal, pyridoxal-5'-phosphate, pyridoxamine, a 3-acylated analogue of pyridoxal, a 3-acylated analogue of pyridoxal-4,5-aminal, a pyridoxine phosphate analogue, and a mixture thereof.

73. The use according to any one of claims 67 to 71, wherein the compound is pyridoxal-5'-phosphate.

74. The use according to any one of claims 67 to 73, wherein the platelet aggregation inhibitor is selected from a group consisting of: a thromboxane A₂ inhibitor, a glycoprotein IIb/IIIa inhibitor, an adenosine diphosphate antagonist, and a cAMP phosphodiesterase inhibitor.
### INTERNATIONAL SEARCH REPORT

**A. CLASSIFICATION OF SUBJECT MATTER**

IPC(7): A61K 38/08, A61P 7/02, A61K 31/675, A61K 31/616, A61K 31/4365

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)

IPC(7): A61K 38/08, A61P 7/02, A61K 31/675, A61K 31/616, A61K 31/4365

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic database(s) consulted during the international search (name of database(s) and, where practicable, search terms used)

Canadian Patent Database, USP TO, Delphion, PUBMED

Key words: pyridoxal-5-phosphate, platelet aggregation inhibitor, glycoprotein IIb/IIIa inhibitor, ADP antagonist, cAMP phosphodiesterase inhibitor, clopidogrel, cilostazol, epifibatide, ticlopidine

### C. DOCUMENTS CONSIDERED TO BE RELEVANT

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<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
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( X ) Further documents are listed in the continuation of Box C.  

[X]  See patent family annex.

**Date of the actual completion of the international search**

8 November, 2005 (08-11-2005)

**Date of mailing of the international search report**

10 November 2005 (10-11-2005)

**Name and mailing address of the ISA/CA**

Canadian Intellectual Property Office

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50 Victoria Street

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Facsimile No.: 001(819)953-2476

**Authorized officer**

Steven Koledziejczyk (819) 997-3239

Form PCT/ISA/210 (second sheet) (April 2005)  

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<td>all claims</td>
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<td>A</td>
<td>BERTRAND, M. E. et al. Double-Blind Study of the Safety of Clopidogrel With and Without a Loading Dose in Combination With Aspirin Compared With Ticlopidine in Combination With Aspirin After Coronary Stenting: The Clopidogrel Aspirin Stent International Cooperative Study (CLASSICS). Circulation, 8 August 2000, Vol. 102, No. 6, pages 624-629. ISSN 1524-4539.</td>
<td>11, 12, 25, 26, 48-51 and 60-63</td>
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**INTERNATIONAL SEARCH REPORT**

**Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of the 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. [X] Claim Nos.: 15-66
   - because they relate to subject matter not required to be searched by this Authority, namely:
     
     Claims 15-66 are directed to methods of medical treatment of the human/animal body which the Authority is not required to search under Rule 39.1 (v) of the PCT.

2. [X] Claim Nos.: 1-6 and 15-20
   - 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:
     
     the aforementioned claims relate to an extremely large number of possible products. A meaningful search over the whole of the claimed scope is impossible. A search has been carried out for those parts of the claims which appear to be clear and supported, namely those parts relating to the products and methods disclosed in the examples of the present application.

3. [ ] Claim Nos.:
   - because they are dependant 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 claim 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 claim 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.
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