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(54) **Title**: A COMBINATION TREATMENT

(57) **Abstract**: A combination of a PDE III inhibitor and an angiotensin II receptor antagonist or an angiotensin converting enzyme (ACE) inhibitor shows synergistic effect in the prevention of stroke. Pharmaceutical compositions and medical kits comprising as a first active ingredient a PDE III inhibitor and as a second active ingredient an angiotensin II receptor antagonist or an angiotensin converting enzyme (ACE) inhibitor are provided.

A COMBINATION TREATMENT

Technical field

The present invention relates to a method of treatment of patients by administering a phosphodiesterase type III (PDE III) inhibitor in combination with an angiotensin II receptor antagonist or an angiotensin converting enzyme (ACE) inhibitor. The invention also relates to a pharmaceutical compositions and medical kits comprising as a first active ingredient a PDE III inhibitor and as a second active ingredient an angiotensin II receptor antagonist or an angiotensin converting enzyme (ACE) inhibitor.

Background of the invention

Stroke is the third leading cause of death and the main cause of permanent health damage in adults. High blood pressure is known to be one of the most important risk factors for acute stroke. Consequently, the risk of hypertensive patients suffering an acute stroke can be reduced through antihypertensive therapy.

Angiotensin II receptor antagonists are antihypertensive compounds that selectively block the AT_1 subtype of the angiotensin II receptor. Angiotensin II is a potent natural vasoconstrictor having blood pressure increasing effects as well as growth promoting effects contributing to left ventricular hypertrophy, vascular thickening, atherosclerosis and stroke. Angiotensin II receptor antagonists are mainly used in the treatment of high blood pressure, particularly in patients who are intolerant to ACE inhibitor therapy. Subsequently, clinical trials have indicated beneficial effects of angiotensin II receptor antagonists in the prevention of hypertensive complications such as stroke, whereby the stroke prevention effect at least partly appeared to be independent of blood pressure lowering effect.

Angiotensin II is formed from angiotensin I in the blood by an enzyme, angiotensin converting enzyme (ACE). ACE inhibitors are agents that inhibit the activity of the enzyme thereby decreasing the production of angiotensin II. ACE inhibitors are used primarily in the treatment of hypertension and congestive heart failure.

The cyclic nucleotide phosphodiesterases (PDE) are enzymes that degrade the phosphodiester bond in the second messenger molecules cAMP and cGMP. PDEs are therefore important regulators of signal transduction mediated by these second messenger molecules. PDE type III isoenzyme is specific for degrading cAMP and it predominates in myocardium, vascular smooth muscle and platelets.

PDE III inhibitors are compounds which preserve cAMP by blocking PDE III isoenzyme that is responsible for cAMP degradation. PDE III inhibitors increase contractility of the heart muscle and produce systemic vasodilation. Therefore, PDE III inhibitors have been suggested e.g. for the treatment of heart failure.

In spite of advances in the blood pressure control there is still need for improved therapies for angiotensin II related cardiovascular diseases such as prevention and treatment of stroke in high risk patients.

Summary of the invention

It has now been found that administration of a PDE III inhibitor together with an angiotensin II receptor antagonist or an angiotensin converting enzyme (ACE) inhibitor provides unexpectedly synergistic effect in reducing hypertensive complications, particularly the incidence and volume of brain lesions, morbidity and mortality associated with stroke in hypertensive salt sensitive rat model. Therefore, the combination is useful in the prevention and treatment of angiotensin II related cardiovascular diseases, such as hypertensive complications. In particular, the combination is useful in the prevention or inhibition of stroke or in reducing a risk of stroke, especially in the treatment of patients at high risk of stroke, such as hypertensive patients or patients who have suffered earlier stroke.

Thus, in one aspect present invention provides pharmaceutical composition comprising as a first active ingredient a PDE III inhibitor and as a second active ingredient an angiotensin II receptor antagonist or an angiotensin converting enzyme (ACE) inhibitor.

In another aspect the present invention provides a medical kit comprising in separate containers in a single package pharmaceutical compositions comprising in one container a pharmaceutical composition comprising a PDE III inhibitor and in a

second container a pharmaceutical composition comprising an angiotensin II receptor antagonist or an angiotensin converting enzyme (ACE) inhibitor.

In another aspect the present invention provides a method for prevention or inhibition of stroke or reducing a risk of stroke in a patient, which comprises the simultaneous, separate or sequential administration of an effective amount of a PDE III inhibitor and an angiotensin II receptor antagonist or an angiotensin converting enzyme (ACE) inhibitor to a patient in need thereof.

In another aspect, the present invention provides a method for prevention or inhibition of stroke or reducing a risk of stroke in a patient comprising administering to said patient an effective amount of a PDE III inhibitor in conjunction with an angiotensin II receptor antagonist or an angiotensin converting enzyme (ACE) inhibitor.

Brief description of the drawings

FIG. 1 shows the survival (%) of Dahl salt-sensitive rats on salt rich diet treated with levosimendan, valsartan or combination of levosimendan and valsartan in comparison to the control group.

FIG. 2 shows the increase of body weight of Dahl salt-sensitive rats on salt rich diet treated with levosimendan, valsartan or combination of levosimendan and valsartan in comparison to the control group, wherein the arrow denotes the start of the drug treatments.

FIG 3 shows the gross histology score of brain pathology in Dahl salt-sensitive rats on salt rich diet treated with levosimendan, valsartan or combination of levosimendan and valsartan in comparison to the control group. Percent of animals are given as pie presentation according to the severity of brain lesions in each treatment group.

FIG. 4 shows the survival (%) of Dahl salt-sensitive rats on salt rich diet treated with levosimendan, losartan or combination of levosimendan and losartan in comparison to the control group.

FIG. 5 shows the survival (%) of Dahl salt-sensitive rats on salt rich diet treated with ramipril or combination of levosimendan and ramipril in comparison to the control group.

FIG. 6 shows the survival (%) of Dahl salt-sensitive rats on salt rich diet treated with levosimendan or cilostazol alone or in combination with valsartan in comparison to the control group.

Detailed description of the invention

The method of the invention relates to a combination therapy for more effective treatment of angiotensin II related cardiovascular diseases. In particular, the present invention relates to a combination therapy for more effective treatment in the prevention or inhibition of stroke. According to one preferred embodiment of the invention, the combination treatment of the invention is able to synergistically reduce the incidence or the recurrence of stroke, reduce the severity of stroke or reduce the mortality and/or morbidity associated with stroke.

As used herein the term "stroke" means a cerebrovascular accident (CVA), particularly the sudden death of some brain cells due to lack of oxygen when the blood flow to the brain is impaired by blockage or rupture of an artery to the brain. Examples of stroke include cerebral thrombosis, cerebral embolism, intracerebral hemorrhage (ICH), subarachnoid hemorrhage (SAH), transient ischemic attack (TIA) and vascular dementia.

The term "prevention of stroke" means reducing the incidence or the recurrence of stroke. The term "patient" means animals, preferably mammals, and humans.

The term "PDE III inhibitor" as used herein means compound that is capable of inhibiting phosphodiesterase (PDE) isoenzyme type III. PDE III inhibitors increase intracellular cAMP by inhibiting its degradation by PDE III.

According to one embodiment of the invention, a PDE III inhibitor is administered together with an angiotensin II receptor antagonist or an angiotensin converting enzyme (ACE) inhibitor for providing prevention or inhibition of stroke or reduction a risk of stroke.

The method of invention is particularly useful for the treatment of individuals having high risk of stroke. Conditions which are associated with high risk of stroke include, but are not limited to, earlier stroke; hypertension; diabetes; earlier heart

attack; heart disease; orthopaedic fractures or other injuries; prolonged bed rest; elevated blood lipid levels; atherosclerosis; and peri- and postoperative periods of surgical operations.

According one embodiment of the invention, a PDE III inhibitor is used in conjunction with an angiotensin II receptor antagonist or an angiotensin converting enzyme (ACE) inhibitor for the prevention or inhibition of stroke or in reducing a risk of stroke independent of lowering elevated blood pressure. Patients to be treated may or, according to another embodiment of the invention, may not suffer from hypertension.

The active ingredients may be administered simultaneously, separately or sequentially. In particular, the method comprises administering to a patient an amount of active ingredients or combination thereof which is effective for prevention or inhibition of stroke or reducing a risk of stroke in the patient. Preferably, the method comprises administering to a patient a synergistically effective amount of the combination. The administration routes of the active ingredients include, but are not limited to, enteral, e.g. oral or rectal, or parenteral, e.g. intravenous, intramuscular, intraperitoneal or transdermal. For the prevention of stroke, oral administration of the active ingredients is particularly preferred.

Any PDE III inhibitor known in the art may be used in the method of the invention. PDE type III selective inhibitors are preferred. Examples of suitable PDE III inhibitors include, but are not limited to, cilostazol, cilostamide, milrinone, amrinone, enoximone, piroximone, imazodan, indolidan, pimobendan, olprinone, toborinone, vesnarinone and levosimendan or pharmaceutically acceptable salts thereof.

Any angiotensin II receptor antagonist or an angiotensin converting enzyme (ACE) inhibitor known in the art may be used in the method of the invention in combination with a PDE III inhibitor. Examples of suitable angiotensin II receptor antagonists include sartans such as losartan, valsartan, telmisartan, candesartan, eprosartan, irbesartan, olmesartan, tasosartan and pharmaceutically acceptable salts thereof. Examples of suitable angiotensin converting enzyme (ACE) inhibitors include ramipril, captopril, enalapril, quinapril, perindopril, lisinopril, benazepril, moexipril, trandolapril and pharmaceutically acceptable salts thereof.

According to the invention, angiotensin II receptor antagonists may be administered in daily doses which are clinically accepted for such agents. For example, the angiotensin II receptor antagonist may suitably be administered orally to man in a daily dosage ranging from about 2 to about 600 mg, for example from 20 mg to 300 mg, depending upon the condition to be treated, the route of administration, age, weight and the condition of the patient, and the angiotensin II receptor antagonists used.

According to the invention, angiotensin converting enzyme (ACE) inhibitor may be administered in daily doses which are clinically accepted for such agents. For example, the angiotensin converting enzyme (ACE) inhibitor may suitably be administered orally to man in a daily dosage ranging from about 1 to about 150 mg, for example from 2 mg to 80 mg, depending upon the condition to be treated, the route of administration, age, weight and the condition of the patient, and the ACE inhibitor used.

According to the invention, a PDE III inhibitor may be administered in daily doses which are clinically accepted for such agents. For example, a PDE III inhibitor may suitably be administered orally to man in a daily dosage ranging from about 0.1 to about 400 mg, for example from 2 mg to 300 mg, depending upon the condition to be treated, age, weight and the condition of the patient, and the PDE III inhibitor used.

According to one embodiment of the invention, cilostazol or a pharmaceutically acceptable salt thereof is used as a PDE III inhibitor.

Cilostazol or a pharmaceutically acceptable salt thereof may suitably be administered orally to man in a daily dosage ranging from about 50 to 500 mg, preferably from about 150 to 300 mg, depending on the route of administration, age, weight and the condition of the patient given once a day or divided into several doses a day.

According to another embodiment of the invention, levosimendan compound or a pharmaceutically acceptable salt thereof is used as a PDE III inhibitor.

As used herein, the term "levosimendan compound" refers to any racemic mixture or enantiomer of levosimendan or a racemic mixture or enantiomer of the active metabolite of levosimendan. The term "levosimendan" specifically refers to

the (-)-enantiomer of [4-(1,4,5,6-tetrahydro-4-methyl-6-oxo-3-pyridazinyl)phenyl]-hydrazono]propanedinitrile. The term also is intended to encompass combinations of levosimendan and its active metabolite. The active metabolite of levosimendan is particularly (R)-N-[4-(1,4,5,6-tetrahydro-4-methyl-6-oxo-3-pyridazinyl)phenyl]-acetamide (II).

Levosimendan or its active metabolite may suitably be administered orally to man in a daily dosage ranging from about 0.1 to 10 mg, preferably from about 0.2 to 5 mg, depending on the age, weight and the condition of the patient given once a day or divided into several doses a day. For the long-term prevention of stroke in man, relatively low oral doses are generally preferred, e.g. an oral daily dose from about 0.1 to about 5 mg, preferably from about 0.2 to about 4 mg, more preferably from about 0.25 to about 3 mg.

According to another embodiment of the invention, a PDE III inhibitor other than levosimendan compound or a pharmaceutically acceptable salt thereof is used as a PDE III inhibitor.

A specific method of prevention according to the present invention comprises administering orally 50 - 500 mg of cilostazol or a pharmaceutically acceptable salt thereof and 2 - 600 mg of an angiotensin II receptor antagonist daily to a patient, for example 100 - 300 mg of cilostazol and 40-320 mg of valsartan, or 100 - 300 mg of cilostazol and 25 - 100 mg of losartan, in oral daily dosage.

A further specific method of prevention according to the present invention comprises administering orally 50 - 500 mg of cilostazol or a pharmaceutically acceptable salt thereof and 1 - 150 mg of an angiotensin converting enzyme (ACE) inhibitor daily to a patient, for example 100 - 300 mg of cilostazol and 1 - 10 mg of ramipril in oral daily dosage.

A further specific method of prevention according to the present invention comprises administering orally 0.05 - 5 mg of a levosimendan compound or a pharmaceutically acceptable salt thereof and 2 - 600 mg of an angiotensin II receptor antagonist daily to a patient, for example 0.2 – 3 mg of levosimendan and 40-320 mg of valsartan, or 0.2 – 3 mg of levosimendan and 25 - 100 mg of losartan, in oral daily dosage.

A further specific method of prevention according to the present invention comprises administering orally 0.05 - 5 mg of a levosimendan compound or a pharmaceutically acceptable salt thereof and 1 - 150 mg of an angiotensin converting enzyme (ACE) inhibitor daily to a patient, for example 0.2 – 3 mg of levosimendan and 1 - 10 mg of ramipril in oral daily dosage.

The combination may be supplemented with one or more other active ingredients.

The active ingredients can be formulated into pharmaceutical dosage forms suitable for the treatment according to the present invention using the principles known in the art. They are given to a patient as such or preferably in combination with suitable pharmaceutical excipients in the form of tablets, granules, capsules, suppositories, emulsions, suspensions or solutions whereby the contents of the active compound in the formulation is from about 0.5 to 100 % per weight. Choosing suitable ingredients for the composition is a routine for those of ordinary skill in the art. It is evident that suitable carriers, solvents, gel forming ingredients, dispersion forming ingredients, antioxidants, colours, sweeteners, wetting compounds, release controlling components and other ingredients normally used in this field of technology may be also used.

The active ingredients may be formulated in the same pharmaceutical formulation. Alternatively, the active ingredients are formulated as separate pharmaceutical dosage forms. The combination of the pharmaceutical dosage forms may be packaged as a single medical product or kit for use in the method of the invention, optionally together with a package insert instructing to the correct use of the medical product.

For example, according to one embodiment of the invention, the invention provides a medical product in the form of a kit comprising a first pharmaceutical dosage form comprising a PDE III inhibitor, a second pharmaceutical dosage form comprising an angiotensin II receptor antagonist or an angiotensin converting enzyme (ACE) inhibitor, a package for containing said first and second dosage forms, and optionally instructions for simultaneous, separate or sequential administration of said first and second dosage forms to a patient.

For oral administration of the active ingredients in tablet form, suitable carriers and excipients include e.g. lactose, corn starch, magnesium stearate, calcium

phosphate and talc. For oral administration in capsule form, useful carriers and excipients include e.g. lactose, corn starch, magnesium stearate and talc. For controlled release oral compositions release controlling components can be used. Typical release controlling components include hydrophilic gel forming polymers such as hydroxypropylmethyl cellulose, hydroxypropyl cellulose, carboxymethyl celluloses, alginic acid or a mixture thereof; vegetable fats and oils including vegetable solid oils such as hydrogenated soybean oil, hardened castor oil or castor seed oil (sold under trade name Cutina HR), cotton seed oil (sold under the trade names Sterotex or Lubritab) or a mixture thereof; fatty acid esters such as triglycerides of saturated fatty acids or their mixtures e.g. glyceryl tristearates, glyceryl tripalmitates, glyceryl trimyristates, glyceryl tribehenates (sold under the trade name Compritol) and glyceryl palmitostearic acid ester.

Tablets can be prepared by mixing the active ingredient or active ingredients with the carriers and excipients and compressing the powdery mixture into tablets. Capsules can be prepared by mixing the active ingredient with the carriers and excipients and placing the powdery mixture in capsules, e.g. hard gelatin capsules.

Typically a tablet or a capsule comprises, for example, from about 10 to 200 mg, more typically 50 to 100 mg, of cilostazol or/and from about 40 to 320 mg of valsartan, from about 25 to 100 mg of losartan, from about 20 to 80 mg of telmisartan, from about 2 to 32 mg of candesartan or from about 300 to 600 mg of eprosartan, or from about 10 to 40 mg of olmesartan.

Alternatively, a tablet or a capsule comprises, for example, from about 10 to 200 mg, more typically 50 to 100 mg, of cilostazol or/and from about 25 to 100 mg of ramipril, from about 20 to 80 mg of benazepril, from about 2 to 20 mg of enalapril maleate, from about 12 to 100 mg of captopril, from about 10 to 25 mg of quinalapril hydrochloride, from about 5 to 80 mg of lisinopril, or from about 4 to 8 mg of perindopril.

The angiotensin II receptor antagonist or the angiotensin converting enzyme (ACE) inhibitor may be included in the formulation of a PDE III inhibitor or may be formulated separately as described above using principles well known in the art. For example, a composition according the present invention, e.g. a tablet or capsule, may comprise from 50 to 100 mg of cilostazol and from 40 to 320 mg of valsartan, or from 50 to 100 mg of cilostazol and from 1 to 10 mg of ramipril.

Examples

Pharmaceutical examples.

Example 1.

Hard gelatin capsule size 3	
Valsartan	40.0 mg
Levosimendan	1.0 mg
Lactose	159 mg

The pharmaceutical preparation in the form of a capsule is prepared by mixing levosimendan with lactose and placing the powdery mixture in hard gelatin capsule.

Example 2.

Hard gelatin capsule size 3	
Ramipril	10.0 mg
Levosimendan	1.0 mg
Lactose	189 mg

Example 3.

Hard gelatin capsule size 3	
Valsartan	40.0 mg
Cilostazol	100 mg
Lactose	160 mg

Example 4.

Hard gelatin capsule size 3	
Ramipril	10.0 mg
Cilostazol	100 mg
Lactose	190 mg

Experiments

Experiment 1.

Effects of levosimendan and an angiotensin II receptor antagonist alone and in combination in salt sensitive rat model

Effect of levosimendan and valsartan on survival, weight gain and stroke incidence in Dahl salt-sensitive rats (Dahl SS) was studied. Dahl salt-sensitive rats on high salt diet develop hypertension and increased mortality. In the early stages of hypertension the incidence of death is almost entirely due to stroke and sudden death. See Qu, P. et al., Hypertens. Res., 2000; 23:613-623.

Four groups of 5-6-week-old male SS/JrHsd Dahl salt-sensitive rats (180 total + 6 sentinel rats) received salt rich diet until 13 % mortality was observed in the studied population of rats (approximately four weeks). Thereafter the rats received the following drug regimens up to 36 days while continuing on salt rich diet:
1) normal drinking water (n=20),
2) valsartan 10 mg/kg/day in drinking water (n=46),
3) levosimendan 1 mg/kg/day in drinking water (n=45), and
4) valsartan 10 mg/kg/day and levosimendan 1 mg/kg/day in drinking water (n=46).

a) Survival

The survival results are shown in Figure 1 as Kaplan-Meier Plot. Levosimendan and valsartan as a combination lengthened the survival highly significantly when compared to all other groups. Levosimendan and valsartan appeared to have a beneficial synergistic effect on stroke-related mortality.

b) Weight gain

The mean body weight of the rats in each group during the study is shown in Figure 2. The arrow denotes the start of the drug treatments. The increase in body weight that is normal in laboratory rats was evident during the salt diet period prior to drug treatments. However, the weight gain was strongly reduced at the time when mortality began to occur (about one week prior to the start of drug treatments). Only those rats that received the combined levosimendan and valsartan continued to gain

further weight approaching to the weight of the sentinel Dahl SS rats in the study room that were not receiving salt rich diet.

c) Brain pathology

Histopathological analyses of the brain were performed for all rats that survived at least three weeks from the beginning of the drug treatments. Brains were sectioned and stained using standard methods and were subjected to microscopic analyses. The observed changes were scored (normal, minor lesions, mild to moderate lesions, severe lesions or very severe lesions). The results for each treatment group are presented in Fig. 3. It can be seen that the combination of levosimendan and valsartan reduced the incidence and volume of brain lesions associated with cerebral strokes in much higher extent than the levosimendan or valsartan alone.

Experiment 2.

Effects of levosimendan and losartan alone and in combination in salt sensitive rat model

Four groups of 5-6-week-old male SS/JrHsd Dahl salt-sensitive rats received salt rich diet until 13 % mortality was observed in the studied population of rats (approximately four weeks). Thereafter the rats received the following drug regimens up to 77 days while continuing on salt rich diet:

1) normal drinking water,
2) losartan 30 mg/kg/day in drinking water,
3) levosimendan 1 mg/kg/day in drinking water, and
4) losartan 30 mg/kg/day and levosimendan 1 mg/kg/day in drinking water.

The survival results are shown in Figure 4 as Kaplan-Meier Plot. Levosimendan and losartan appeared to have a beneficial synergistic effect on stroke-related mortality.

Experiment 3.

Effects of levosimendan and ramipril alone and in combination in salt sensitive rat model

Three groups of 5-6-week-old male SS/JrHsd Dahl salt-sensitive rats received salt rich diet until 13 % mortality was observed in the studied population of rats (approximately four weeks). Thereafter the rats received the following drug regimens up to 70 days while continuing on salt rich diet:

1) normal drinking water (n=10),

2) ramipril 1 mg/kg/day in drinking water (n=23),

3) ramipril 1 mg/kg/day and levosimendan 1 mg/kg/day in drinking water (n=22).

The survival results are shown in Figure 5 as Kaplan-Meier Plot. Levosimendan and ramipril appeared to have a beneficial synergistic effect on stroke-related mortality.

Experiment 4.

Effects of cilostazol or levosimendan in combination with valsartan in salt sensitive rat model

Five groups (n = 25/group) of 6-week-old male SS/JrHsd Dahl salt-sensitive rats received salt rich diet for five weeks (to reach approximately 13% mortality). Thereafter the rats received the following drug regimens up to 77 days while continuing on salt rich diet:

1) vehicle (water),

2) levosimendan 0.5 mg/kg/day,

3) cilostazol 50 mg/kg/day,

4) levosimendan 0.5 mg/kg/day + valsartan 10 mg/kg/day and,

5) cilostazol 50 mg/kg/day + valsartan 10 mg/kg/day.

Drug administrations were performed once daily per oral with dosing gavage. The survival results are shown in Figure 6 as Kaplan-Meier Plot. Both levosimendan and cilostazol appeared to have a beneficial synergistic effect on stroke-related mortality when combined with valsartan.

Claims

1. A pharmaceutical composition comprising as a first active ingredient a PDE III inhibitor and as a second active ingredient an angiotensin II receptor antagonist or an angiotensin converting enzyme (ACE) inhibitor.

2. A composition according to claim 1 wherein the second active ingredient is an angiotensin II receptor antagonist.

3. A composition according to claim 1 wherein the second active ingredient is an an angiotensin converting enzyme (ACE) inhibitor.

4. A composition according to claim 2 wherein the angiotensin II receptor antagonist is losartan, valsartan, telmisartan, candesartan, eprosartan, irbesartan, olmesartan, tasosartan or a pharmaceutically acceptable salt thereof.

5. A composition according to claim 3 wherein the angiotensin converting enzyme (ACE) inhibitor is ramipril, captopril, enalapril, quinapril, perindopril, lisinopril, benazepril, moexipril, trandolapril or a pharmaceutically acceptable salt thereof.

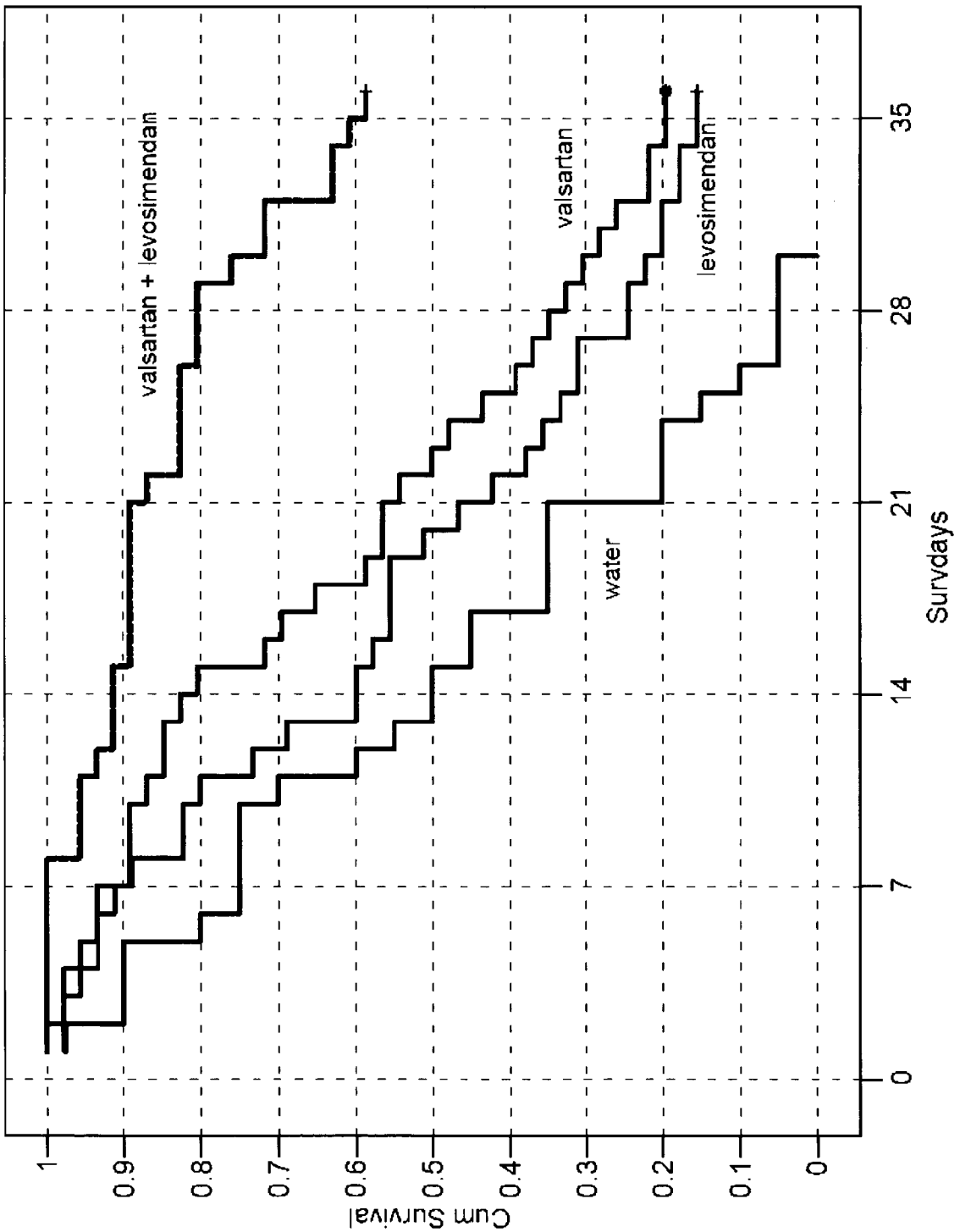
6. A medical kit comprising in separate containers in a single package pharmaceutical compositions comprising in one container a pharmaceutical composition comprising a PDE III inhibitor and in a second container a pharmaceutical composition comprising an angiotensin II receptor antagonist or an angiotensin converting enzyme (ACE) inhibitor.

7. A method for the prevention or inhibition of stroke or reducing a risk of stroke in a patient comprising administering to said patient a PDE III inhibitor in conjunction with angiotensin II receptor antagonist or an angiotensin converting enzyme (ACE) inhibitor.

8. A combination comprising as a first active ingredient a PDE III inhibitor and as a second active ingredient an angiotensin II receptor antagonist or an angiotensin converting enzyme (ACE) inhibitor for use in the prevention or inhibition of stroke or reducing a risk of stroke.

9. Use of a PDE III inhibitor in conjunction with an angiotensin II receptor antagonist or an angiotensin converting enzyme (ACE) inhibitor in the manufacture of a medicament for the prevention or inhibition of stroke or reducing a risk of stroke.

10. Use of a PDE III inhibitor in the manufacture of a medicament for prevention or inhibition of stroke or reducing a risk of stroke when used in conjunction with an angiotensin II receptor antagonist or an angiotensin converting enzyme (ACE) inhibitor.


Cum Survival
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0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
7
14
21
28
35
Survdays
valsartan + levosimendan
valsartan
levosimendan
water

FIG. 1

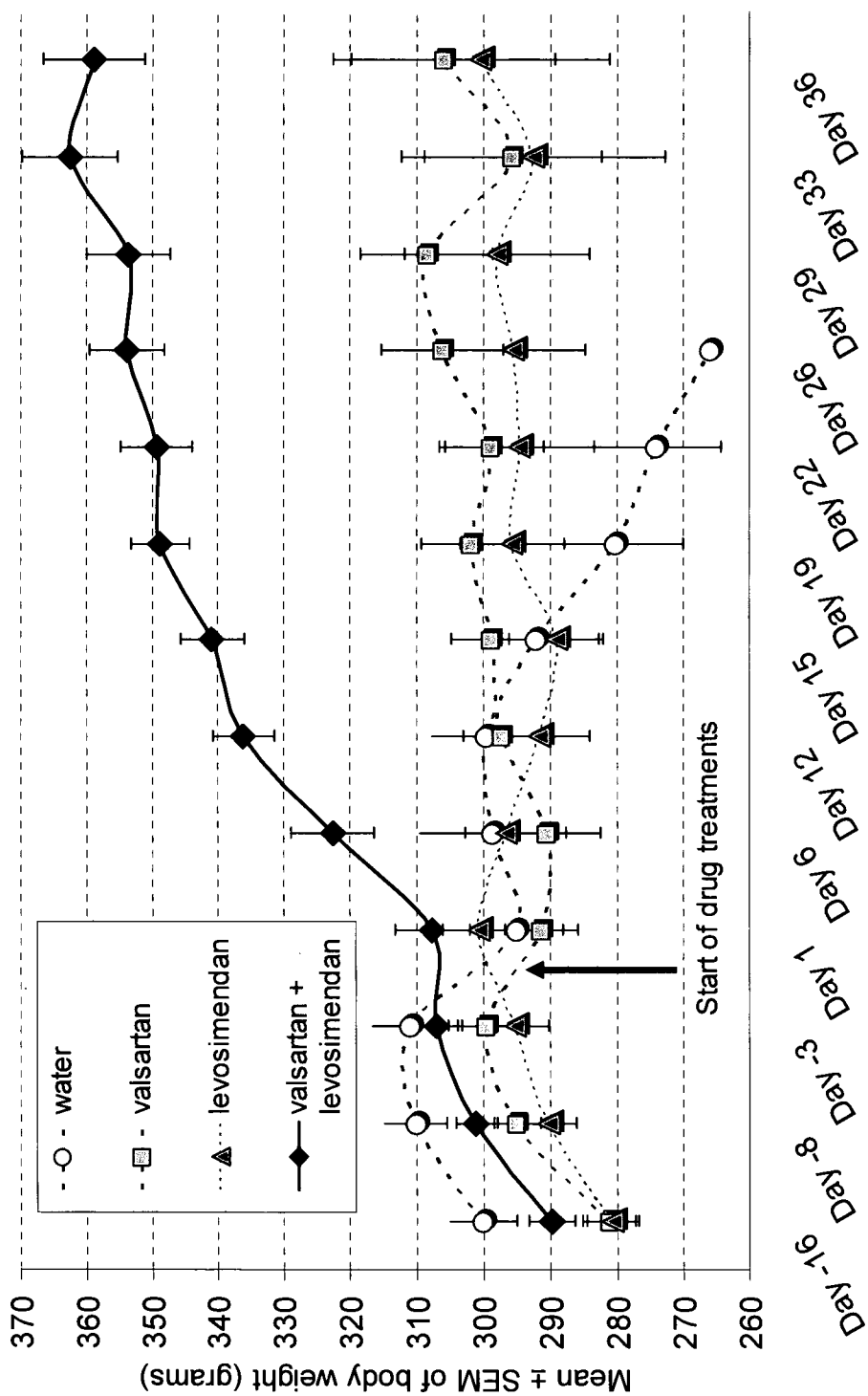
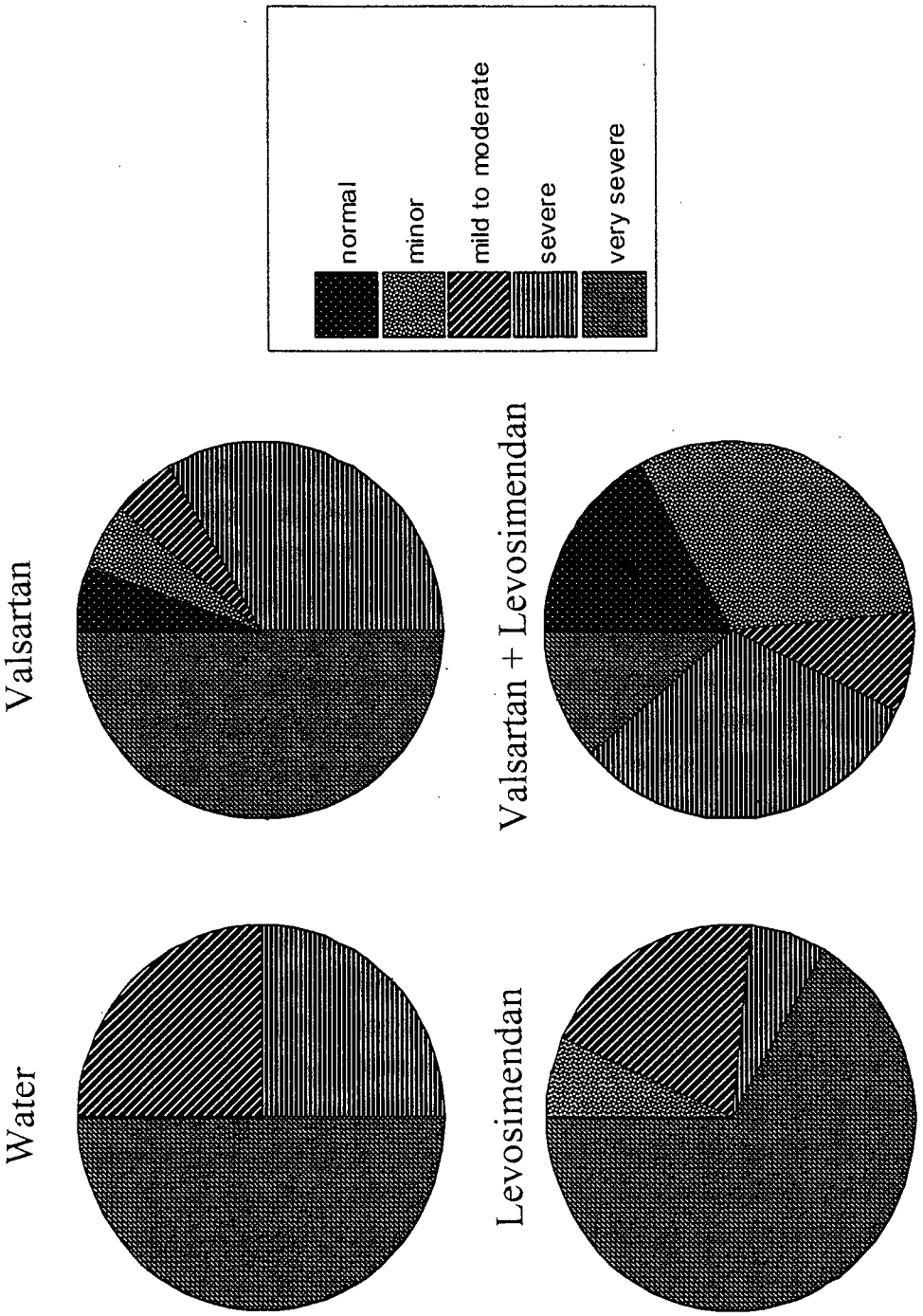

Mean ± SEM of body weight (grams)
370
360
350
340
330
320
310
300
290
280
270
260
- water
- valsartan
levosimendan
valsartan + levosimendan
Start of drug treatments
Day -16
Day -8
Day -3
Day 1
Day 6
Day 12
Day 15
Day 19
Day 22
Day 26
Day 29
Day 33
Day 36

FIG. 2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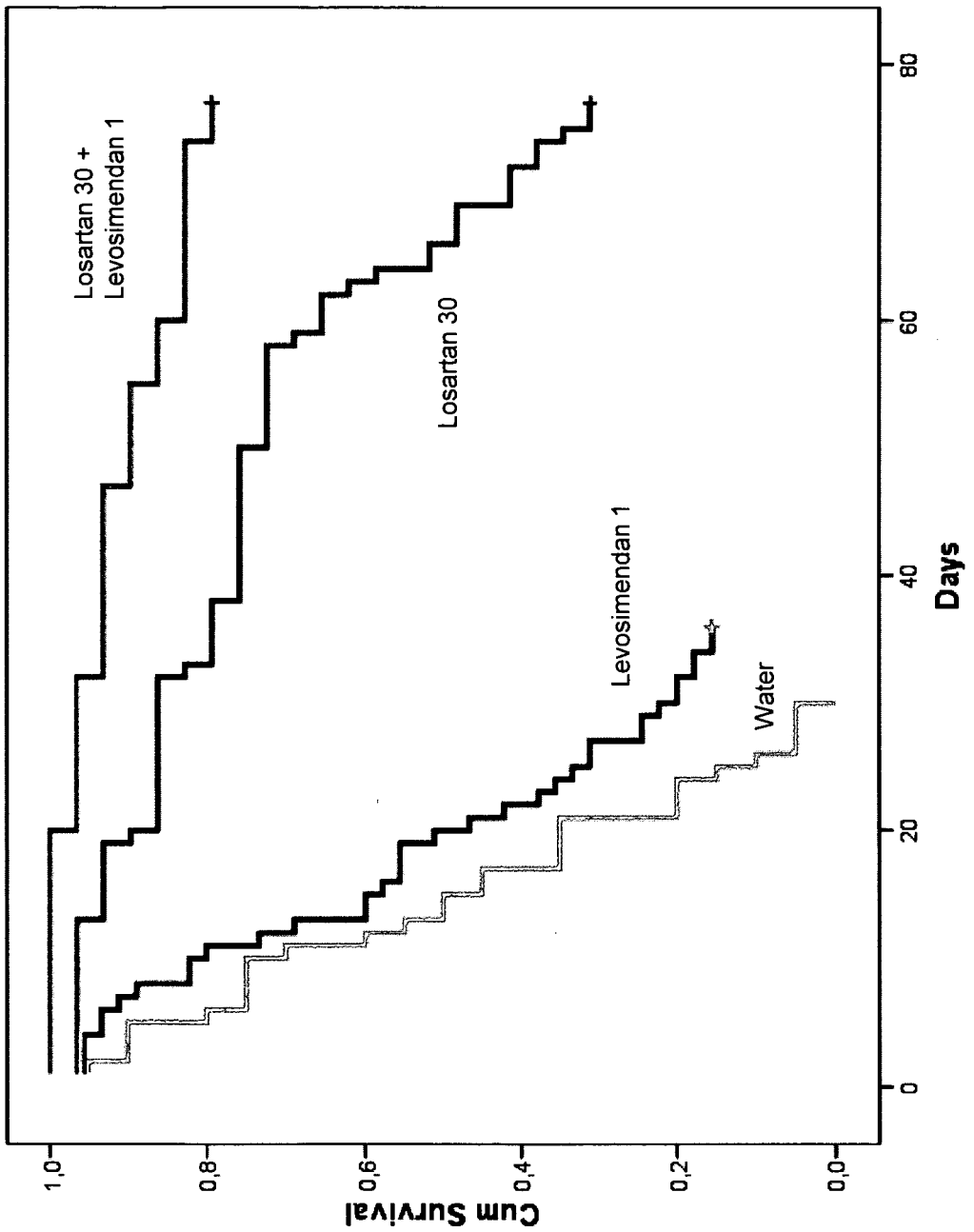
minor
mild to moderate
severe
very severe
Valsartan
Valsartan + Levosimendan
Water
Levosimendan

FIG. 3


Losartan 30 +
Levosimendan 1
Losartan 30
Levosimendan 1
Water
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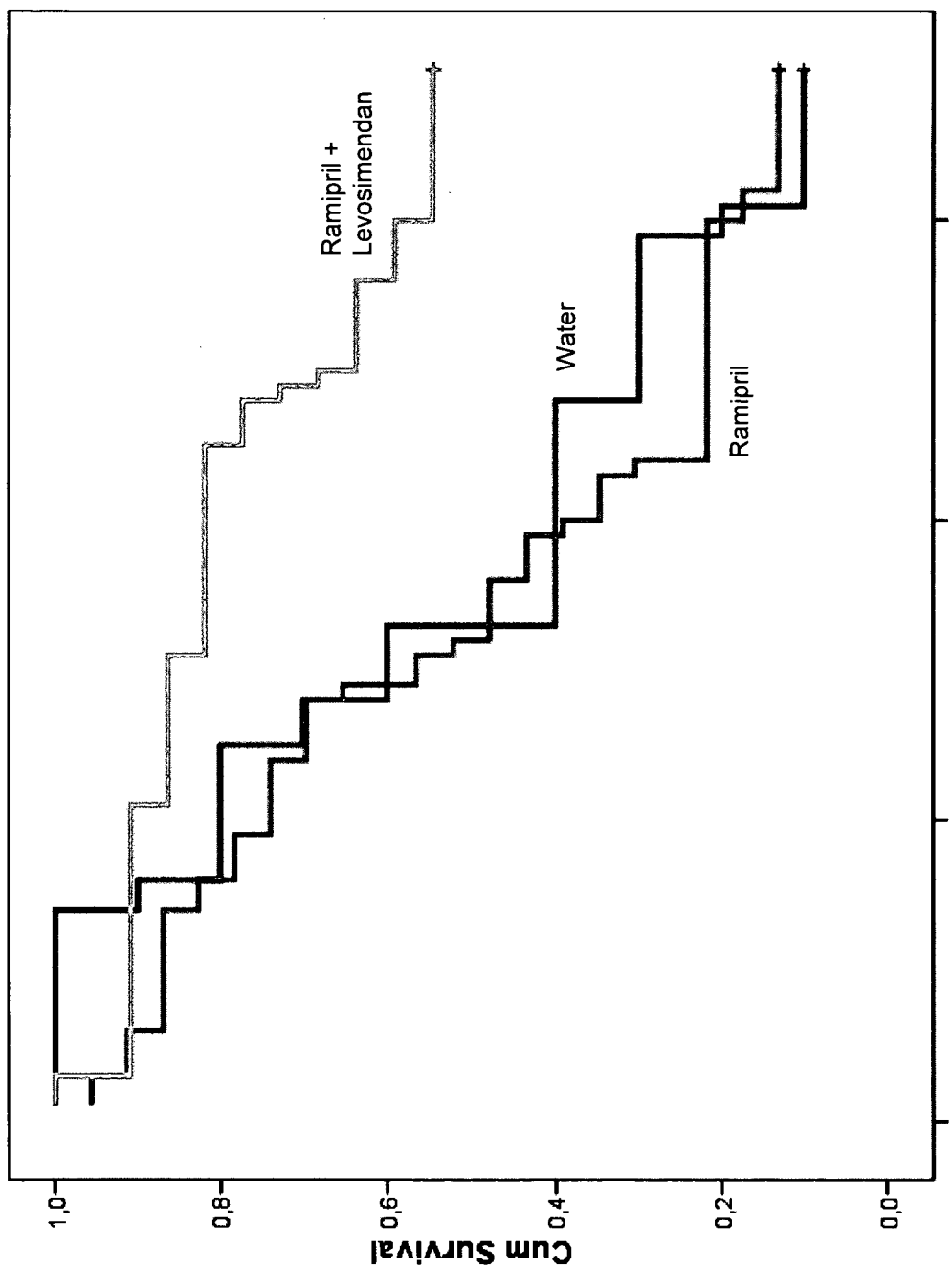
0,8
0,6
0,4
0,2
0,0
0
20
40
60
80
Days

FIG. 4


Ramipril +
Levosimendan
Water
Ramipril
Cum Survival
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0,8
0,6
0,4
0,2
0,0
0
20
40
60
Days from start of the treatment

FIG. 5

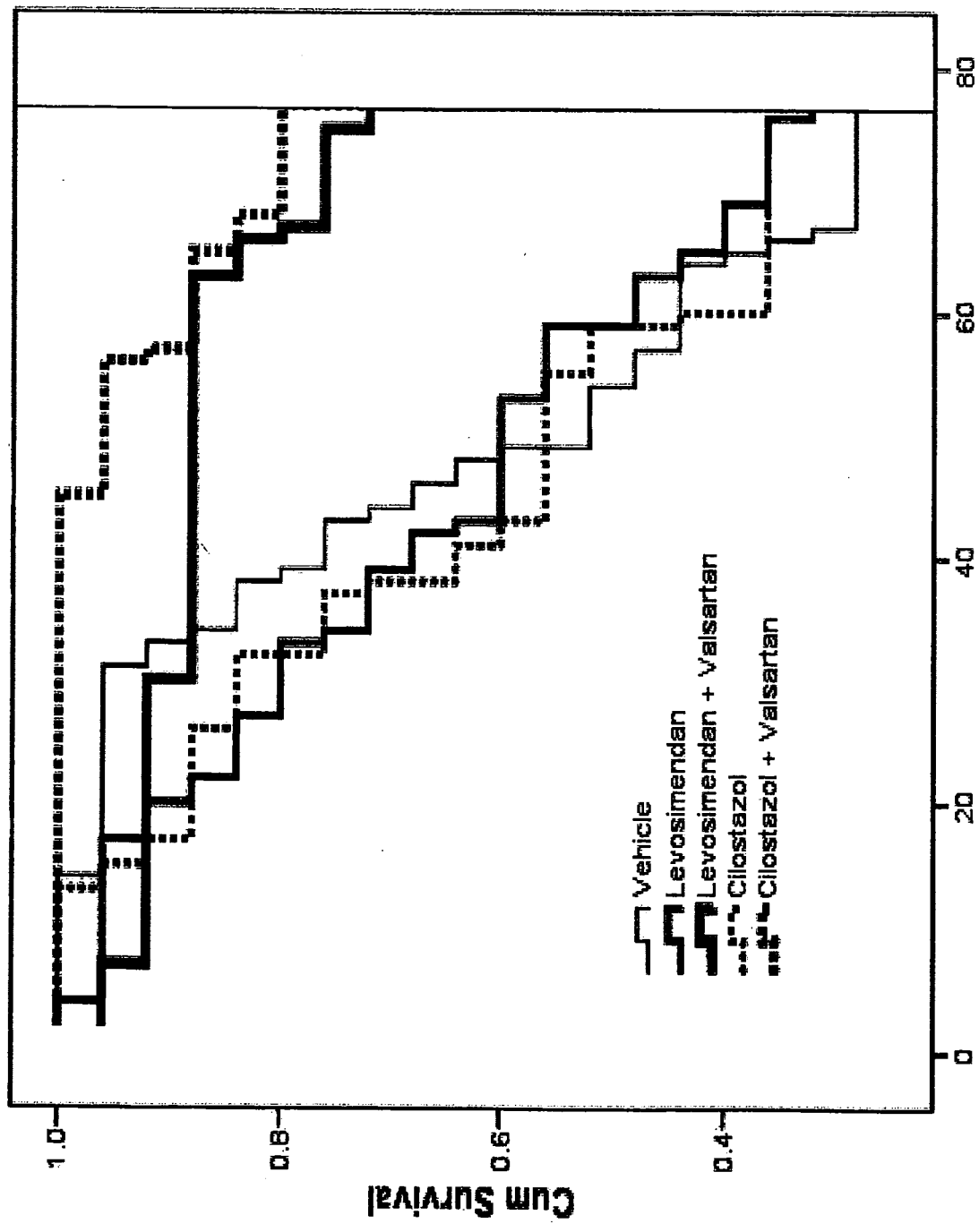
Cum Survival
1.0
0.8
0.6
0.4
0
20
40
60
80
Days of dosing
Vehicle
Levosimendan
Levosimendan + Valsartan
Cilostazol
Cilostazol + Valsartan

FIG. 6