METHODS AND MATERIALS FOR TREATING PERIPHERAL ARTERY DISEASE

This document provides methods and materials involved in treating peripheral artery disease within a mammal. For example, methods and materials for using a solution containing L-lactic acid and D-gluconic acid to reduce calcification in peripheral arteries of a mammal having peripheral artery disease are provided.
METHODS AND MATERIALS FOR TREATING PERIPHERAL ARTERY DISEASE

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims priority to U.S. Application Serial No. 62/162,126, filed on May 15, 2015. The disclosure of the prior application is considered part of the disclosure of this application, and is incorporated in its entirety into this application.

BACKGROUND

1. Technical Field

This document relates to methods and materials involved in treating peripheral artery disease within a mammal. For example, this document provides methods and materials for using a solution containing L-lactic acid and D-gluconic acid to reduce calcification in peripheral arteries of a mammal having peripheral artery disease.

2. Background Information

Peripheral arterial disease is highly prevalent, particularly with advancing age, affecting 9 million Americans and 19% of those >70 years of age. The diagnosis of peripheral arterial disease confers a 25-30% 5-year risk of cardiovascular death and an additional 20% risk of nonfatal major adverse cardiovascular events. In addition to increasing age, the risk factors responsible for peripheral arterial disease are similar to those for coronary artery disease; diabetes, tobacco use, hypertension, and dyslipidemia have the strongest impact. Diabetes and tobacco use each confer a threefold to fourfold increase in the risk of developing peripheral arterial disease.

SUMMARY

This document provides methods and materials involved in treating peripheral artery disease within a mammal. For example, this document provides methods and materials for using a solution containing L-lactic acid and D-gluconic acid to reduce calcification in peripheral arteries of a mammal having peripheral artery disease. As described herein, a solution containing L-lactic acid and D-gluconic acid can be administered to a peripheral artery containing calcification under conditions wherein the level of calcification of the peripheral artery present within a mammal (e.g., a
human) is reduced following administration of the solution. In some cases, a mammal having peripheral artery disease requiring amputation of a limb can be treated with a solution containing L-lactic acid and D-gluconic acid as described herein such that blood flow to the limb is restored in a manner that allows the limb to be saved without the need for amputation.

As also described herein, a solution containing L-lactic acid and D-gluconic acid can be administered to a coronary artery containing calcification or to a cardiac valve containing calcification under conditions wherein the level of calcification of the coronary artery present within a mammal (e.g., a human) or the level of calcification of the cardiac valve present within a mammal (e.g., a human) is reduced following administration of the solution. In some cases, a mammal having one or more calcified coronary arteries can be treated by placing an embolic filter downstream of the region of calcification and administering a solution containing L-lactic acid and D-gluconic acid upstream of the region of calcification. In such cases, the embolic filter can reduce the number of emboli (e.g., calcification emboli) advancing past the filter into the general circulation of the mammal. In some cases, a mammal having one or more calcified cardiac valve can be treated by placing a catheter into the annulus of the calcified cardiac valve to inject a solution containing L-lactic acid and D-gluconic acid into the annulus of the calcified cardiac valve.

In general, one aspect of this document features a method for reducing calcification in a peripheral artery of a mammal. The method comprises, or consists essentially of, (a) identifying a mammal as having a calcific peripheral artery, and (b) administering a solution comprising L-lactic acid and D-gluconic acid into the calcific peripheral artery of the mammal, wherein the level of calcification of the calcific peripheral artery is reduced. The mammal can be a human. The peripheral artery can be a carotid, iliac, femoral, popliteal, anterior tibial, posterior tibial, or peroneal artery. The solution can comprise between about 10 percent and about 20 percent of L-lactic acid. The solution can comprise between about 7.5 percent and about 2.5 percent of D-gluconic acid. The solution can comprise between about 10 percent and about 20 percent of L-lactic acid and between about 7.5 percent and about 2.5 percent of D-gluconic acid. The solution can comprise about 15 percent of L-lactic acid. The solution can comprise about 5 percent of D-gluconic acid.
In another aspect, this document features a method for restoring at least 50 percent of patency to an occluded blood vessel in a limb identified as needing amputation from a mammal, thereby obviating the need for the amputation. The method comprises, or consists essentially of, administering a solution comprising L-lactic acid and D-gluconic acid into the occluded blood vessel of the mammal, wherein at least 50 percent of patency is restored to the occluded blood vessel, thereby obviating the need for the amputation. The mammal can be a human. The occluded blood vessel can be an occluded carotid, iliac, femoral, popliteal, anterior tibial, posterior tibial, or peroneal artery. The solution can comprise between about 10 percent and about 20 percent of L-lactic acid. The solution can comprise between about 7.5 percent and about 2.5 percent of D-gluconic acid. The solution can comprise between about 10 percent and about 20 percent of L-lactic acid and between about 7.5 percent and about 2.5 percent of D-gluconic acid. The solution can comprise about 15 percent of L-lactic acid. The solution can comprise about 15 percent of L-lactic acid and about 5 percent of D-gluconic acid.

In another aspect, this document features a method for reducing calcification in a coronary artery of a mammal. The method comprises, or consists essentially of, (a) identifying a mammal as having a calcific coronary artery, (b) inserting an embolic filter into the calcific coronary artery downstream of a region of calcification, and (c) administering a solution comprising L-lactic acid and D-gluconic acid into the calcific coronary artery of the mammal, wherein the level of calcification of the calcific coronary artery is reduced. The mammal can be a human. The coronary artery can be a left main, left anterior descending, diagonal, circumflex, ramus, obtuse marginal, right coronary, or posterior descending artery. The solution can comprise between about 10 percent and about 20 percent of L-lactic acid. The solution can comprise between about 7.5 percent and about 2.5 percent of D-gluconic acid. The solution can comprise between about 10 percent and about 20 percent of L-lactic acid and between about 7.5 percent and about 2.5 percent of D-gluconic acid. The method of claim 19, wherein the solution can comprise about 15 percent of L-lactic acid. The solution can comprise about 5 percent of D-gluconic acid. The method of claim 19, wherein the solution can comprise about 15 percent of L-lactic acid and about 5 percent of D-gluconic acid.
In another aspect, this document features a method for reducing calcification in a calcific cardiac valve of a mammal. The method comprises, or consists essentially of, (a) identifying a mammal as having a calcific cardiac valve, and (b) injecting a solution comprising L-lactic acid and D-gluconic acid into an annulus of the calcific cardiac valve of the mammal, wherein the level of calcification of the calcific cardiac valve is reduced. The mammal can be a human. The cardiac valve can be an aortic, mitral, tricuspid, or pulmonic valve. The solution can comprise between about 10 percent and about 20 percent of L-lactic acid. The solution can comprise between about 7.5 percent and about 2.5 percent of D-gluconic acid. The solution can comprise between about 10 percent and about 20 percent of L-lactic acid and between about 7.5 percent and about 2.5 percent of D-gluconic acid. The solution can comprise about 15 percent of L-lactic acid. The solution can comprise about 5 percent of D-gluconic acid. The solution can comprise about 15 percent of L-lactic acid and about 5 percent of D-gluconic acid.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention pertains. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, suitable methods and materials are described below. All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety. In case of conflict, the present specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting.

Other features and advantages of the invention will be apparent from the following detailed description, and from the claims.

**DESCRIPTION OF DRAWINGS**

Figure 1 is an angiograph of a patient's amputated leg prior to administering a solution containing L-lactic acid and D-gluconic acid. A complete occlusion of the popliteal artery was observed.

Figure 2 contains angiographs of the patient's amputated leg from Figure 1 after administering a solution containing L-lactic acid and D-gluconic acid. Patency of the popliteal artery was 100% restored, and significant improvement in the peroneal and posterior tibial arteries was observed.
Figure 3 is a photograph of a calcific left anterior descending coronary artery not exposed to a solution containing L-lactic acid (15%) and D-gluconic acid (5%).

Figure 4 is a photograph of a calcific left anterior descending coronary artery following exposure to a solution containing L-lactic acid (15%) and D-gluconic acid (5%).

Figure 5 is a photograph of a calcific aortic valve not exposed to a solution containing L-lactic acid (15%) and D-gluconic acid (5%).

Figure 6 is a photograph of a calcific aortic valve following exposure to a solution containing L-lactic acid (15%) and D-gluconic acid (5%).

Detailed Description

This document provides methods and materials involved in treating peripheral artery disease within a mammal. In some cases, a solution containing L-lactic acid and D-gluconic acid can be administered into a blood vessel (e.g., a peripheral artery) to reduce calcification in one or more peripheral arteries of a mammal having peripheral artery disease. For example, a mammal having peripheral artery disease requiring amputation of a limb can be treated with a solution containing L-lactic acid and D-gluconic acid as described herein such that blood flow to the limb is restored in a manner that allows the limb to be saved without the need for amputation.

In some cases, a solution containing L-lactic acid and D-gluconic acid can be administered to a coronary artery containing calcification under conditions wherein the level of calcification of the coronary artery present within a mammal (e.g., a human) is reduced following administration of the solution. For example, a mammal having one or more calcified coronary arteries can be treated by placing an embolic filter downstream of the region of calcification and administering a solution containing L-lactic acid and D-gluconic acid upstream of the region of calcification. In such cases, the embolic filter can reduce the number of emboli (e.g., calcification emboli) advancing past the filter into the general circulation of the mammal.

Examples of embolic filters that can be inserted downstream of the region of calcification as described herein include, without limitation, SpiderFX (Covidien), NeuroShield (MedNova), Rubicon (Boston Scientific), AngioGuard™ (Cordis), Triactive system ShieldWire and FlushCath (Kensey-Nash), Proxis (St. Jude), GORE® Embolic Filter (Gore), and Emboshield NAV® (Abbott Vascular’s) filters. In some cases, an embolic filter described elsewhere (Mauri et al., Circulation,
In some cases, a solution containing L-lactic acid and D-gluconic acid can be administered to a cardiac valve containing calcification under conditions wherein the level of calcification of the cardiac valve present within a mammal (e.g., a human) is reduced following administration of the solution. For example, a mammal having one or more calcified cardiac valve can be treated by placing a catheter into the annulus of the calcified cardiac valve. Once placed, a solution containing L-lactic acid and D-gluconic acid can be injected into the annulus of the calcified cardiac valve to reduce the level of calcification of the cardiac valve. Any appropriate catheter can be used to inject a solution containing L-lactic acid and D-gluconic acid into the annulus of the calcified cardiac valve.

In some cases, a solution containing L-lactic acid and D-gluconic acid as described herein can be used to demineralize vessels in a patient having peripheral artery disease, to achieve successful endovascularization of otherwise completely occluded vessels, to improve blood flow, to enhance wound healing, and/or to prevent the need to amputate a limb (e.g., an arm or a leg).

Any type of mammal having peripheral artery disease, one or more calcific peripheral arteries (e.g., calcific iliac, femoral, popliteal, anterior tibial, posterior tibial, peroneal, or carotid arteries), one or more calcific coronary arteries (e.g., calcific left main, left anterior descending, diagonal, ramus, circumflex, obtuse marginal, right coronary, or posterior descending arteries), one or more calcific cardiac valves (e.g., calcific aortic, mitral, tricuspid, or pulmonic valves), and/or one or more occluded blood vessels (e.g., occluded radial, brachial, axillary, brachiocephalic, or subclavian blood vessels) can be treated with a solution containing L-lactic acid and D-gluconic acid as described herein. For example, humans and other primates such as monkeys can be treated with a solution containing L-lactic acid and D-gluconic acid as described herein. In some cases, dogs, cats, horses, cows, pigs, sheep, mice, and rats can be treated with a solution containing L-lactic acid and D-gluconic acid as described herein.

Any appropriate method can be used to identify a mammal having peripheral artery disease, one or more calcific peripheral arteries, one or more calcific coronary
arteries, one or more calcific cardiac valves, and/or one or more occluded blood vessels. For example, echocardiography, computed tomography scanning, or magnetic resonance imaging can be used to identify a human having calcific cardiac valves. In some cases, ultrasound, computed tomography angiography, or magnetic resonance can be used to identify a human having peripheral artery disease.

Once identified as peripheral artery disease, one or more calcific peripheral arteries, one or more calcific coronary arteries, one or more calcific cardiac valves, and/or one or more occluded blood vessels, the mammal can be administered a solution containing L-lactic acid and D-gluconic acid. Any appropriate method can be used to deliver a solution containing L-lactic acid and D-gluconic acid described herein to a mammal. For example, the methods and materials described herein can be used to deliver a solution containing L-lactic acid and D-gluconic acid to a mammal. In some cases, percutaneous delivery methods can be used to deliver a solution containing L-lactic acid and D-gluconic acid to a mammal. For example, local therapeutic infusion catheters such as ClearWay™ RX Local Therapeutic Infusion Catheter (a low-profile, rapid-exchange therapeutic infusion catheter available from Atrium Medical, Hudson, NH) can be used to deliver a solution containing L-lactic acid and D-gluconic acid to a mammal.

A solution containing L-lactic acid and D-gluconic acid can include from about 10 percent to about 20 percent (e.g., from about 10 percent to about 18 percent, from about 10 percent to about 16 percent, from about 12 percent to about 20 percent, from about 14 percent to about 20 percent, from about 12 percent to about 18 percent, or about 15 percent) of L-lactic acid and from about 2.5 percent to about 7.5 percent (e.g., from about 3.5 percent to about 6.5 percent or about 5 percent) of D-gluconic acid. In some cases, a solution containing L-lactic acid and D-gluconic acid can be formulated as a pharmaceutical composition in liquid form such as in the form of a sterile solution.

A solution containing L-lactic acid and D-gluconic acid can be administered to a mammal in any amount, at any frequency, and for any duration effective to achieve a desired outcome (e.g., to reduce calcification of blood vessels or heart valves).

Effective doses can vary, as recognized by those skilled in the art, depending on the severity of the condition (e.g., blood vessel occlusion or cardiac valve calcification), the route of administration, the sex, age and general health condition of
the subject, excipient usage, the possibility of co-usage with other therapeutic
treatments such as use of other agents and the judgment of the treating physician.

An effective amount of a solution containing L-lactic acid and D-gluconic acid
can be any amount that reduces the severity of a symptom of a condition being treated
(e.g., blood vessel occlusion or cardiac valve calcification) without producing
significant toxicity to the mammal. For example, an effective amount of a solution
containing L-lactic acid and D-gluconic acid can be such that from about 20 mg/kg to
about 50 mg/kg (e.g., from about 25 mg/kg to about 50 mg/kg, from about 30 mg/kg
to about 50 mg/kg, from about 20 mg/kg to about 45 mg/kg, from about 20 mg/kg to
about 40 mg/kg, or from about 30 mg/kg to about 40 mg/kg) of L-lactic acid and from
about 10 mg/kg to about 20 mg/kg (e.g., from about 12 mg/kg to about 20 mg/kg,
from about 14 mg/kg to about 20 mg/kg, from about 10 mg/kg to about 18 mg/kg,
from about 10 mg/kg to about 16 mg/kg, or from about 13 mg/kg to about 17 mg/kg)
of D-gluconic acid are delivered to a mammal (e.g., a human). If a particular
mammal fails to respond to a particular amount, then the amount of the solution
containing L-lactic acid and D-gluconic acid can be increased by, for example, two
fold. After receiving this higher amount, the mammal can be monitored for both
responsiveness to the treatment and toxicity symptoms, and adjustments made
accordingly. The effective amount can remain constant or can be adjusted as a sliding
scale or variable dose depending on the mammal’s response to treatment. Various
factors can influence the actual effective amount used for a particular application. For
example, the frequency of administration, duration of treatment, use of multiple
treatment agents, route of administration, and severity of the condition (e.g., blood
vessel occlusion or cardiac valve calcification) may require an increase or decrease in
the actual effective amount administered.

The frequency of administration can be any frequency that reduces the
severity of a symptom of a condition to be treated (e.g., blood vessel occlusion or
cardiac valve calcification) without producing significant toxicity to the mammal. For
example, the frequency of administration can be a one-time administration or can be
from about one time a year to about three times a year. As with the effective amount,
various factors can influence the actual frequency of administration used for a
particular application. For example, the effective amount, duration of treatment, use
of multiple treatment agents, route of administration, and severity of the condition
(e.g., blood vessel occlusion or cardiac valve calcification) may require an increase or
decrease in administration frequency.

An effective duration for administering a solution containing L-lactic acid and D-gluconic acid can be any duration that reduces the severity of a symptom of the condition to be treated (e.g., blood vessel occlusion or cardiac valve calcification) without producing significant toxicity to the mammal. Thus, the effective duration can vary from about 30 minutes to about 90 minutes (e.g., from about 40 minutes to about 90 minutes, from about 50 minutes to about 90 minutes, from about 30 minutes to about 70 minutes). Multiple factors can influence the actual effective duration used for a particular treatment. For example, an effective duration can vary with the frequency of administration, effective amount, use of multiple treatment agents, route of administration, and severity of the condition being treated.

In certain instances, a course of treatment and the severity of one or more symptoms related to the condition being treated can be monitored. Any appropriate method can be used to determine whether or not the severity of a symptom is reduced. For example, the severity of a symptom of blood vessel occlusion or cardiac valve calcification can be assessed using imaging techniques at different time points.

The invention will be further described in the following examples, which do not limit the scope of the invention described in the claims.

## EXAMPLES

Example 1 - Using a solution containing L-lactic acid and D-gluconic acid to restore patency to an occluded peripheral artery

A patient with severe calcific peripheral underwent amputation of the leg. Baseline angiography revealed complete occlusion of the popliteal artery (Figure 1). 20 mL of a solution containing L-lactic acid (15%) and D-gluconic acid (5%) were administered to the popliteal artery of the amputated leg at a rate of 20 mL/minute over one minute. Forty five minutes following the administration of the solution, patency of the popliteal artery was 100% restored and significant improvement also was noted in the peroneal and posterior tibial arteries (Figure 2).

These results demonstrate that a solution containing L-lactic acid and D-gluconic acid can be used in vivo to restore patency to occluded arteries (e.g., occluded peripheral arteries).
Example 2 - Demineralizing vessels in patients suffering from peripheral arterial disease

Five human patients with severe calcific peripheral arterial disease who were deemed not to be a candidate for revascularization and were scheduled for amputation of the leg (below knee or above knee) are selected. Inclusion criteria are (1) patients with severe calcific peripheral arterial disease who have been deemed to have unreconstructable arterial disease and who have already been scheduled to undergo limb amputation (below knee or above knee amputation), (2) age 20-85 years, (3) patients who are able to consent, and (4) patients who have no contraindications to undergo surgery. Exclusion criteria are (1) patients who are undergoing amputation of the limb because of infection, osteomyelitis, or cancer, (2) patients with chronic kidney disease stage IV and stage V, (3) patients with liver cirrhosis, (4) patients with history of deep vein thrombosis or pulmonary embolization in the last three months, (5) patients with history of stroke in the last three months, (6) patients with unstable angina or history of myocardial infarction in the last three months, and (7) patients with sepsis, respiratory failure, hypovolemic shock, or cardiogenic shock.

The efficacy of a solution containing L-lactic acid (15%) and D-gluconic acid (5%) (LA/GA solution) to restore patency to occluded arteries is examined at the time of surgery, just before the leg amputation is carried out. The conversions (mg/mMol) of L-lactic acid is as follows (listed for comparison purposes): 15% of L-Lactic acid = 15,000 mg/dL = 1665 mM/L. Thus, 20 mL of 15% L-lactic acid = 3000 mg of L-lactic acid = 33.3 mM L-lactic acid. In an average subject of 75 kg weight, 20 mL of 15% L-lactic acid = 40 mg/kg = 0.444 mM/kg. The LD50 of acute toxicity of L-lactic acid in rats is 4936 mg/kg, which is more than 123 time the 40 mg/kg dose. The 20 mL solution, which contains 3 gm of L-lactic acid, is equivalent to the same amount of L-lactic acid that is present in 1.2 L of lactate ringer solution (28 mmol/L equal to 2522 mg/L of lactate). 5% of D-gluconic acid = 5,000 mg/dL. 20 mL of the 5% D-gluconic acid = 1000 mg of D-gluconic acid. In an average subject of 75 kg weight; 20 mL of 5% D-gluconic acid = 13.3 mg/kg. The LD50 of acute toxicity of D-gluconic acid in rats is 7850 mg/kg, which is more than 590 x the 13.3 mg/kg.

Briefly, the procedure is carried as follows. During pre-op, the patients consent to the amputation and solution administration. In addition, a standard of care angiography is completed as a baseline prior to surgery. This is used to confirm the status of unreconstructable arterial disease. A limb ischemia infusion protocol is used...
to deliver the solution containing L-lactic acid and D-gluconic acid and to minimize potential systematic side effects. Briefly, a sheath/cannula is inserted in the femoral vein, and the blood coming back from the lower extremity arterial circulation is directed to the venous side. In addition, the blood from the femoral vein is collected and is sent back to the arterial side via a pump, creating a closed circuit. In particular, the common femoral artery and femoral vein are accessed percutaneously under ultrasound and fluoroscopy guidance. The main sheaths are advanced over the aortic bifurcation and inferior vena cava confluence and parked in the common femoral artery and femoral vein, respectively, under fluoroscopy guidance. The patient is then fully anticoagulated using intravenous heparin. ACT (activated clotting time) levels are measured every 15 minutes and are maintained above 250.

Following standard angiogram, the target artery or arteries are selectively cannulated. The arterial and venous sheaths/cannulations are connected to a pump. An occluding balloon located at the tip of the venous sheath is inflated to occlude the limb’s venous return. The arteriovenous pump is then initiated. 20 mL of the LA/GA solution is directly infused into the diseased (calcific) arterial distribution with a wait period of 45 minutes to allow the demineralization process take place. The artery or arteries are then flushed with saline, and a completion angiography is performed in the operating room to determine if calcification is dissolved and revascularization is restored. In some cases, an additional 20 mL of the LA/GA solution is administered if the first dose is not effective due to the size of the artery (especially in those cases involving an above the knee amputation where a higher dose is used to cover the whole artery segment). The LA/GA solution is aseptic and is delivered in an aseptic manner.

If revascularization is restored successfully with a patency of the vessel lumen being more than 50%, then the surgeon makes a decision whether the amputation procedure should be aborted or not. If revascularization is not restored, then the surgeon proceeds with amputation that was already planned.

The extent of vascular calcification and patency of the calcific arterial segment following installation of the LA/GA solution is compared to that observed in the baseline angiography.

The methods and materials provided herein can be used to alleviate the burden of peripheral arterial disease, which is associated with high morbidity and mortality. They also represent a major breakthrough discovery and will help to save patients
from the process of amputation, which is associated not only with an economic
burden on society but also with social issues especially elderly patients who may
require special care because of their physical disability.

Example 3 - Using a solution containing L-lactic acid and D-gluconic acid to dissolve
calcification within a human left anterior descending coronary artery

A specimen of a calcific left anterior descending coronary artery was obtained
from a human patient. A portion of the specimen was stained with von Kossa staining
without being exposed to a solution containing L-lactic acid and D-gluconic acid
(Figure 3). Another portion of the same specimen was stained with von Kossa
staining after being exposed to a solution containing L-lactic acid (15%) and D-
gluconic acid (5%) for 30 minutes (Figure 4). Complete dissolution of calcification
(dark brown color) was noted following the use of the solution containing L-lactic
acid (15%) and D-gluconic acid (5%).

Example 4 - Using a solution containing L-lactic acid and D-gluconic acid to dissolve
calcification within a human aortic valve

A specimen of a calcific aortic valve was obtained from a human patient. A
portion of the specimen was stained with von Kossa staining without being exposed to
a solution containing L-lactic acid (15%) and D-gluconic acid (5%) (Figure 5).

Another portion of the same specimen was stained with von Kossa staining after
being exposed to a solution containing L-lactic acid (15%) and D-gluconic acid (5%)
for 30 minutes (Figure 6). Complete dissolution of calcification (dark brown color)
was noted following the use of the solution containing L-lactic acid (15%) and D-
gluconic acid (5%).

OTHER EMBODIMENTS

It is to be understood that while the invention has been described in
conjunction with the detailed description thereof, the foregoing description is intended
to illustrate and not limit the scope of the invention, which is defined by the scope of
the appended claims. Other aspects, advantages, and modifications are within the
scope of the following claims.
WHAT IS CLAIMED IS:

1. A method for reducing calcification in a peripheral artery of a mammal, wherein said method comprises:
   (a) identifying a mammal as having a calcific peripheral artery, and
   (b) administering a solution comprising L-lactic acid and D-gluconic acid into said calcific peripheral artery of said mammal, wherein the level of calcification of said calcific peripheral artery is reduced.

2. The method of claim 1, wherein said mammal is a human.

3. The method of claim 1, wherein said peripheral artery is a carotid, iliac, femoral, popliteal, anterior tibial, posterior tibial, or peroneal artery.

4. The method of claim 1, wherein said solution comprises between about 10 percent and about 20 percent of L-lactic acid.

5. The method of claim 1, wherein said solution comprises between about 7.5 percent and about 2.5 percent of D-gluconic acid.

6. The method of claim 1, wherein said solution comprises between about 10 percent and about 20 percent of L-lactic acid and between about 7.5 percent and about 2.5 percent of D-gluconic acid.

7. The method of claim 1, wherein said solution comprises about 15 percent of L-lactic acid.

8. The method of claim 1, wherein said solution comprises about 5 percent of D-gluconic acid.

9. The method of claim 1, wherein said solution comprises about 15 percent of L-lactic acid and about 5 percent of D-gluconic acid.
10. A method for restoring at least 50 percent of patency to an occluded blood vessel in a limb identified as needing amputation from a mammal, thereby obviating the need for said amputation, wherein said method comprises administering a solution comprising L-lactic acid and D-gluconic acid into said occluded blood vessel of said mammal, wherein at least 50 percent of patency is restored to said occluded blood vessel, thereby obviating the need for said amputation.

11. The method of claim 10, wherein said mammal is a human.

12. The method of claim 10, wherein said occluded blood vessel is an occluded carotid, iliac, femoral, popliteal, anterior tibial, posterior tibial, or peroneal artery.

13. The method of claim 10, wherein said solution comprises between about 10 percent and about 20 percent of L-lactic acid.

14. The method of claim 10, wherein said solution comprises between about 7.5 percent and about 2.5 percent of D-gluconic acid.

15. The method of claim 10, wherein said solution comprises between about 10 percent and about 20 percent of L-lactic acid and between about 7.5 percent and about 2.5 percent of D-gluconic acid.

16. The method of claim 10, wherein said solution comprises about 15 percent of L-lactic acid.

17. The method of claim 10, wherein said solution comprises about 5 percent of D-gluconic acid.

18. The method of claim 10, wherein said solution comprises about 15 percent of L-lactic acid and about 5 percent of D-gluconic acid.

19. A method for reducing calcification in a coronary artery of a mammal, wherein said method comprises:

   (a) identifying a mammal as having a calcific coronary artery,
(b) inserting an embolic filter into said calcific coronary artery downstream of a region of calcification, and
(c) administering a solution comprising L-lactic acid and D-gluconic acid into said calcific coronary artery of said mammal, wherein the level of calcification of said calcific coronary artery is reduced.

20. The method of claim 19, wherein said mammal is a human.

21. The method of claim 19, wherein said coronary artery is a left main, left anterior descending, diagonal, circumflex, ramus, obtuse marginal, right coronary, or posterior descending artery.

22. The method of claim 19, wherein said solution comprises between about 10 percent and about 20 percent of L-lactic acid.

23. The method of claim 19, wherein said solution comprises between about 7.5 percent and about 2.5 percent of D-gluconic acid.

24. The method of claim 19, wherein said solution comprises between about 10 percent and about 20 percent of L-lactic acid and between about 7.5 percent and about 2.5 percent of D-gluconic acid.

25. The method of claim 19, wherein said solution comprises about 15 percent of L-lactic acid.

26. The method of claim 19, wherein said solution comprises about 5 percent of D-gluconic acid.

27. The method of claim 19, wherein said solution comprises about 15 percent of L-lactic acid and about 5 percent of D-gluconic acid.

28. A method for reducing calcification in a calcific cardiac valve of a mammal, wherein said method comprises:
   (a) identifying a mammal as having a calcific cardiac valve, and
(b) injecting a solution comprising L-lactic acid and D-gluconic acid into an
annulus of said calcific cardiac valve of said mammal, wherein the level of
calcification of said calcific cardiac valve is reduced.

29. The method of claim 28, wherein said mammal is a human.

30. The method of claim 28, wherein said cardiac valve is an aortic, mitral,
tricuspid, or pulmonic valve.

31. The method of claim 28, wherein said solution comprises between about 10
percent and about 20 percent of L-lactic acid.

32. The method of claim 28, wherein said solution comprises between about 7.5
percent and about 2.5 percent of D-gluconic acid.

33. The method of claim 28, wherein said solution comprises between about 10
percent and about 20 percent of L-lactic acid and between about 7.5 percent and about
2.5 percent of D-gluconic acid.

34. The method of claim 28, wherein said solution comprises about 15 percent of
L-lactic acid.

35. The method of claim 28, wherein said solution comprises about 5 percent of
D-gluconic acid.

36. The method of claim 28, wherein said solution comprises about 15 percent of
L-lactic acid and about 5 percent of D-gluconic acid.
FIG. 1
FIG. 3
FIG. 4
FIG. 6
A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 31/19; A61K 31/191 (2016.01)
CPC - A61K 31/19; A61K 31/191 (2016.05)

D. FIELDS SEARCHED
Minimum documentation searched (classification system followed by classification symbols)
IPC(8) - A61K 31/19, A61K 31/191 (2016.01)
CPC - A61K 31/19, A61K 31/191 (2016.05)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Y</td>
<td>US 201 1/0196383 A (AZIZ et al) 11 August 201 1 (11.08.201 1) entire document</td>
<td>1-36</td>
</tr>
<tr>
<td>Y</td>
<td>US 201 1/01 18595 A1 (AULBACH et al) 19 May 201 1 (19.05.201 1) entire document</td>
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Further documents are listed in the continuation of Box C.

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Date of the actual completion of the international search: 24 June 2016
Date of mailing of the international search report: 05 AUG 2016

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