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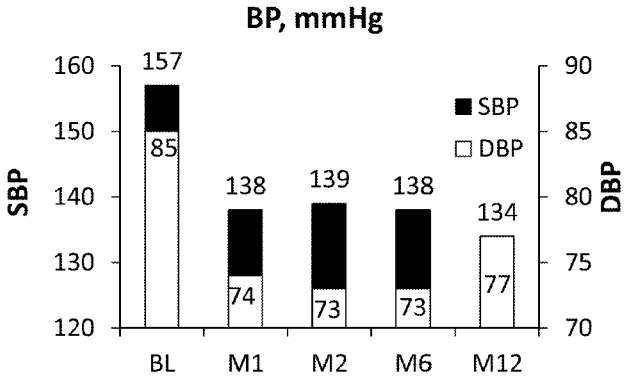
FIG. 9



(57) Abstract: The present invention generally relates to methods of treating hypertension (HTN) in patients in need thereof wherein the patient optionally further suffers from chronic kidney disease (CKD) or Type II diabetes mellitus (T2DM). The invention also relates to methods of treating hyperkalemia in a patient in need thereof, wherein the patient suffers from CKD, T2DM or HTN and are optionally being treated with an effective amount of a renin-angiotensin-aldosterone system (RAAS) agent. The invention also relates to methods of treating kidney disease in a patient in need thereof, wherein the patient is optionally being treated with an effective amount of a renin-angiotensin-aldosterone system (RAAS) agent. The methods can comprise administering an effective amount of a potassium-binding agent to the patient to lower the patient's blood pressure and/or increase or stabilize the patient's kidney function.

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POTASSIUM-BINDING AGENTS FOR TREATING HYPERTENSION AND HYPERKALEMIA

FIELD OF THE INVENTION

[0001] The present invention generally relates to methods of treating hypertension (HTN) in patients in need thereof wherein the patient optionally further suffers from chronic kidney disease (CKD) or Type II diabetes mellitus (T2DM). The invention also relates to methods of treating kidney disease in a patient in need thereof, wherein the patient is optionally being treated with an effective amount of a renin-angiotensin-aldosterone system (RAAS) agent. The invention also relates to methods of treating hyperkalemia in a patient in need thereof, wherein the patient suffers from CKD, T2DM or HTN and are optionally being treated with an effective amount of a renin-angiotensin-aldosterone system (RAAS) agent. The methods can comprise administering an effective amount of a potassium-binding agent to the patient to lower the patient's blood pressure and/or increase or stabilize the patient's kidney function.

BACKGROUND OF THE INVENTION

[0002] Normal kidney function is critical for the maintenance of potassium homeostasis. The ability of the kidney to maintain potassium homeostasis depends on several factors, including the normal production of aldosterone, sodium delivery to the distal nephron, and adequate sodium-potassium exchange in the cortical collecting duct (Palmer, B.F., N. Engl. J. Med. 2004, 351:585-92). Of these factors, aldosterone production and action is closely regulated by the renin-angiotensin-aldosterone system (RAAS), a cornerstone of the regulatory components controlling blood pressure, blood volume and cardiovascular function. RAAS inhibition, designed to limit aldosterone production and function, is therefore an important treatment strategy for hypertension, diabetes, chronic kidney disease and heart failure. Several studies have demonstrated the renal protective effects of angiotensin receptor blockers (ARBs) such as losartan or irbesartan (Brenner, B.M. et al., N. Engl. J. Med. 2001, 345:861-869; de Zeeuw, D. et al. Kidney Intl. 2004, 65:2309-2320; Miao, Y. et al., Diabetologia 2010; Lewis, E.J. et al., N. Engl. J. Med. 2001, 345:851-860; Atkins, R.C. et al., Am. J. Kidney Dis. 2005, 45:281-287), while studies using dual blockade of the RAAS with an aldosterone antagonist (spironolactone or eplerenone), added to either angiotensin converting enzyme inhibitor (ACEI) or ARB therapy, were shown to substantially reduce cardiovascular endpoints in heart failure or post-myocardial infarction patients (Pitt, B. et al., N. Engl. J. Med. 1999, 341:709-717; Pitt, B.,

Molecular & Cellular Endocrinol. 2004, 217:53-58; Zannad, F. et al., European J. Heart Failure 2010).

[0003] Despite the demonstrated clinical benefits of RAAS inhibitors, the fundamental mode of action of the drugs disturbs the exchange of sodium for potassium in the kidney tubule. As a result, potassium retention can precipitate hyperkalemia, defined as a serum potassium value > 5.0 mEq/L. This is particularly problematic in patients with reduced renal function resulting from chronic kidney disease and common co-morbidities such as hypertension, diabetes and heart failure. In this situation, the combination of RAAS inhibition and reduced renal function can aggravate the nascent positive potassium balance and trigger a hyperkalemic event. The discontinuation or reduction in the dose of RAAS inhibitors is a common intervention for patients taking RAAS inhibitors who show abnormally elevated serum potassium levels, which deprives patients of the benefits of RAAS inhibitors. Thus, there is a need to control blood pressure in patients and treat hyperkalemia.

SUMMARY OF THE INVENTION

[0004] One aspect of the invention is a method of treating hypertension in a patient in need thereof. The method comprises administering an effective amount of a medication that controls the serum potassium of a patient in need thereof into the normal range. The method comprises administering an effective amount of a medication that controls the serum potassium of a patient in need thereof into the normal range within two days of treatment, and in particular with chronic dosing, and further with such chronic over a period of at least one month, more specifically at least 3 months, preferably at least 6 months and more preferably at least 9 months. More specifically, the method comprises administering an effective amount of a potassium binding agent, such as 2-fluoroacrylate-divinylbenzene-1,7-octadiene copolymer crosslinked in the salt or acid form, to the patient.

[0005] Another aspect of the invention is a method of treating hypertension in a patient in need thereof, the method comprising administering an effective amount of a potassium-binding agent to the patient suffering from either hyperkalemia or proteinuria. When the potassium-binding agent is a polymer, the polymer comprises an aliphatic crosslinked cation exchange polymer and the crosslinking agent comprising 5 mol% to 15 mol% of the polymer.

[0006] Yet another aspect is a method of treating hypertension in a patient in need thereof, the method comprising administering an effective amount of a potassium-binding agent to the patient suffering from either hyperkalemia or proteinuria. When the potassium-binding

agent is a polymer, the polymer comprises a crosslinked cation exchange polymer other than a polystyrene cation exchange polymer and comprises 5 mol% to 12 mol% crosslinker.

[0007] Another aspect is a method of treating hypertension in a chronic kidney disease patient in need thereof. The patient is optionally treated with an effective amount of a renin-angiotensin-aldosterone system (RAAS) agent and the method comprising administering an effective amount of a potassium binding agent (e.g., 2-fluoroacrylate-divinylbenzene-1,7-octadiene copolymer crosslinked in the salt or acid form) to the patient to control the patient's serum potassium into the normal range.

[0008] A further aspect is a method of treating hypertension in a heart failure patient in need thereof. The patient is optionally treated with an effective amount of a renin-angiotensin-aldosterone system (RAAS) agent and the method comprises administering an effective amount of a potassium binding agent (e.g., 2-fluoroacrylate-divinylbenzene-1,7-octadiene copolymer crosslinked in the salt or acid form) to the patient to control the patient's serum potassium into the normal range.

[0009] Yet another aspect is a method of treating hypertension in a type 2 diabetes mellitus patient in need thereof. The patient is optionally treated with an effective amount of a renin-angiotensin-aldosterone system (RAAS) agent and the method comprises administering an effective amount of a potassium binding agent (e.g., 2-fluoroacrylate-divinylbenzene-1,7-octadiene copolymer crosslinked in the salt or acid form) to the patient to control the patient's serum potassium into the normal range.

[0010] Yet a further aspect is a method of treating hyperkalemia in a chronic kidney disease patient in need thereof optionally being treated with an effective amount of a renin-angiotensin-aldosterone system (RAAS) agent. The method comprises administering an effective amount of a potassium-binding agent (e.g., 2-fluoroacrylate-divinylbenzene-1,7-octadiene copolymer crosslinked in the salt or acid form) to the patient to increase or stabilize the patient's kidney function by decreasing the patient's serum creatinine level as compared to the patient's serum creatinine level before treatment with the potassium-binding agent (e.g., 2-fluoroacrylate-divinylbenzene-1,7-octadiene copolymer crosslinked in the salt or acid form).

[0011] Another aspect of the invention is a method of treating hyperkalemia in a chronic kidney disease patient in need thereof optionally being treated with an effective amount of a renin-angiotensin-aldosterone system (RAAS) agent. The method comprises administering an effective amount of a potassium-binding agent (e.g., 2-fluoroacrylate-divinylbenzene-1,7-octadiene copolymer crosslinked in the salt or acid form) to the patient to increase or stabilize

the patient's kidney function by increasing the time to progression of end stage renal disease as compared to a chronic kidney disease patient optionally treated with a RAAS agent but not treated with the potassium-binding agent.

[0012] A further aspect is a method of treating hyperkalemia in a chronic kidney disease patient in need thereof optionally being treated with an effective amount of a renin-angiotensin-aldosterone system (RAAS) agent. The method comprises administering an effective amount of a potassium-binding agent (e.g., 2-fluoroacrylate-divinylbenzene-1,7-octadiene copolymer crosslinked in the salt or acid form) to the patient to increase or stabilize the patient's kidney function by increasing survival as compared to a chronic kidney disease patient optionally treated with a RAAS agent but not treated with the potassium-binding agent.

[0013] Yet another aspect is a method of treating hyperkalemia in a chronic kidney disease patient in need thereof optionally being treated with an effective amount of a renin-angiotensin-aldosterone system (RAAS) agent. The method comprises administering an effective amount of a potassium-binding agent (e.g., 2-fluoroacrylate-divinylbenzene-1,7-octadiene copolymer crosslinked in the salt or acid form) to the patient to increase or stabilize the patient's kidney function by increasing or stabilizing estimated glomerular filtration rate (eGFR) as compared to the patient's eGFR before treatment with the potassium-binding agent.

[0014] Another aspect is a method of treating chronic kidney disease in a patient in need thereof optionally being treated with an effective amount of a renin-angiotensin-aldosterone system (RAAS) agent. The method comprises administering an effective amount of a potassium-binding agent (e.g., 2-fluoroacrylate-divinylbenzene-1,7-octadiene copolymer crosslinked in the salt or acid form) to the patient to increase or stabilize the patient's kidney function by decreasing the patient's serum creatinine level as compared to the patient's serum creatinine level before treatment with the potassium-binding agent.

[0015] A further aspect is a method of treating chronic kidney disease in a patient in need thereof optionally being treated with an effective amount of a renin-angiotensin-aldosterone system (RAAS) agent. The method comprises administering an effective amount of a potassium-binding agent (e.g., 2-fluoroacrylate-divinylbenzene-1,7-octadiene copolymer crosslinked in the salt or acid form) to the patient to increase or stabilize the patient's kidney function by increasing the time to progression of end stage renal disease as compared to a chronic kidney disease patient optionally treated with a RAAS agent but not treated with the potassium-binding agent.

[0016] Yet another aspect is a method of treating chronic kidney disease in a patient in need thereof optionally being treated with an effective amount of a renin-angiotensin-aldosterone system (RAAS) agent. The method comprises administering an effective amount of a potassium-binding agent (e.g., 2-fluoroacrylate-divinylbenzene-1,7-octadiene copolymer crosslinked in the salt or acid form) to the patient to increase or stabilize the patient's kidney function by increasing survival as compared to a chronic kidney disease patient optionally treated with a RAAS agent but not treated with the potassium-binding agent.

[0017] Another aspect is a method of treating chronic kidney disease in a patient in need thereof optionally being treated with an effective amount of a renin-angiotensin-aldosterone system (RAAS) agent. The method comprises administering an effective amount of a potassium-binding agent (e.g., 2-fluoroacrylate-divinylbenzene-1,7-octadiene copolymer crosslinked in the salt or acid form) to the patient to increase or stabilize the patient's kidney function by increasing or stabilizing estimated glomerular filtration rate (eGFR) as compared to the patient's eGFR before treatment with the potassium-binding agent.

[0018] Other objects and features will be in part apparent and in part pointed out hereinafter.

BRIEF DESCRIPTION OF THE DRAWINGS

[0019] Figure 1 is a graph of the central lab serum potassium concentration in mEq/L versus time of treatment for patients having been treated for six months with the protocol described in Example 2 and having any albumin creatinine ratio (ACR), an ACR $\geq$ 30, and ACR > 300 and an estimated glomerular filtration rate (eGFR) of 15-44 mL/min/1.73 m^2.

[0020] Figure 2 is a graph of the systolic blood pressure (SBP) in mmHg versus time of treatment for patients having been treated for six months with the protocol described in Example 2 and having any albumin creatinine ratio (ACR), an ACR $\geq$ 30, and ACR > 300 and an estimated glomerular filtration rate (eGFR) of 15-44 mL/min/1.73 m^2.

[0021] Figure 3 is a graph of the diastolic blood pressure (DBP) in mmHg versus time of treatment for patients having been treated for six months with the protocol described in Example 2 and having any albumin creatinine ratio (ACR), an ACR $\geq$ 30, and ACR > 300 and an estimated glomerular filtration rate (eGFR) of 15-44 mL/min/1.73 m^2.

[0022] Figure 4 is a graph of the urine ACR in mg/g versus time of treatment for patients having been treated for six months with the protocol described in Example 2 and having

any albumin creatinine ratio (ACR), an ACR ≥ 30, and ACR > 300 and an estimated glomerular filtration rate (eGFR) of 15-44 mL/min/1.73 m^2.

[0023] Figure 5 is a graph of the eGFR in mL/min/1.73 m^2 versus time of treatment for patients having been treated for six months with the protocol described in Example 2 and having any albumin creatinine ratio (ACR), an ACR ≥ 30, and ACR > 300 and an estimated glomerular filtration rate (eGFR) of 15-44 mL/min/1.73 m^2.

[0024] Figure 6 is a graph of eGFR versus time of treatment for a cohort of patients having pre-existing hyperkalemia on a stable dose of a RAAS inhibitor that came to the trial without a run-in period that were treated for twelve months as described in Example 2. For Figures 6-9, the data is presented at baseline (BL), one month (M1), two months (M2), six months (M6), and twelve months (M12).

[0025] Figure 7 is a graph of serum potassium versus time of treatment for a cohort of patients having pre-existing hyperkalemia on a stable dose of a RAAS inhibitor that came to the trial without a run-in period that were treated for twelve months with as described in Example 2.

[0026] Figure 8 is a graph of urine ACR versus time of treatment for a cohort of patients having pre-existing hyperkalemia on a stable dose of a RAAS inhibitor that came to the trial without a run-in period that were treated for twelve months as described in Example 2.

[0027] Figure 9 is a graph of systolic and diastolic blood pressure versus time of treatment for a cohort of patients having pre-existing hyperkalemia on a stable dose of a RAAS inhibitor that came to the trial without a run-in period that were treated for twelve months as described in Example 2.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

[0028] Hyperkalemia, which can present chronically or acutely, can lead to severe medical complications, including life-threatening cardiac arrhythmias and sudden death. Hyperkalemia is typically defined as a serum potassium level, or potassium in the blood, greater than 5.0 milliequivalents per liter (mEq/L). Patients with serum potassium levels greater than or equal to 5.5 mEq/L, which we define as moderate-to-severe hyperkalemia, were found in an independent study to have a 10-fold increase in their mortality rate within 24 hours. Hyperkalemia occurs most frequently in patients with chronic kidney disease, or CKD, where the ability of the patient's kidney to excrete potassium has been compromised. The normal range for serum potassium levels is from about 3.8 mEq/l to 5.0 mEq/L.

[0029] Potassium-binding agents can remove potassium from the gastrointestinal tract and reduce the serum potassium level and treat hyperkalemia. In particularly, potassium-binding polymers can remove potassium from the gastrointestinal tract and reduce the serum potassium level (U.S. Patent No. 7,566,799). Various studies show that an increase in serum potassium level increases the aldosterone level and a decrease in serum potassium level decreases the aldosterone level (T. Himathongkam, et al., J. Clin. Endocrinol. Metab. 1975, 41(1):153-159). These studies have shown that a small increase or decrease in serum potassium level can cause a larger change in the aldosterone level. Further, other studies show that an increase in potassium intake can reduce blood pressure (He, F.J., et al., Hypertension 2005, 45:571-574). It has now been discovered, and clinically observed, that lowering of serum potassium levels in patients also lowers blood pressure. This finding was unexpected given that the intended primary benefit of the potassium-binding polymer was to lower serum potassium. The lowering of potassium and blood pressure using a potassium-binding polymer is beneficial in patients with renal impairment, hyperkalemia and hypertension given that these patients are at significant risk of increased morbidity and mortality. Lowering of blood pressure is also beneficial in patients without such co-morbidities who suffer from hypertension.

[0030] The potassium-binding agents can be an agent that binds potassium. One class of potassium-binding agents is potassium-binding polymers. Various potassium-binding polymers can be used in the methods described herein including crosslinked cation exchange polymers. The potassium-binding agents can also be zeolites, such as zirconium silicate or zirconium germanate molecular sieves.

[0031] The crosslinked cation exchange polymers useful for the methods described herein are in the form of substantially spherical particles. As used herein, the term "substantially" means generally rounded particles having an average aspect ratio of about 1.0 to about 2.0. Aspect ratio is the ratio of the largest linear dimension of a particle to the smallest linear dimension of the particle. Aspect ratios may be easily determined by those of ordinary skill in the art. This definition includes spherical particles, which by definition have an aspect ratio of 1.0.

[0032] The particles can have an average aspect ratio of about 1.0, 1.2, 1.4, 1.6, 1.8 or 2.0. The particles may be round or elliptical when observed at a magnification wherein the field of view is at least twice the diameter of the particle.

[0033] The crosslinked cation exchange polymer particles have a mean diameter of from about 20 μm to about 200 μm. Specific ranges are where the crosslinked cation exchange

particles have a mean diameter of from about 20 μm to about 200 μm, from about 20 μm to about 150 μm, or from about 20 μm to about 125 μm. Other ranges include from about 35 μm to about 150 μm, from about 35 μm to about 125 μm, or from about 50 μm to about 125 μm. Particle sizes, including mean diameters, distributions, etc. can be determined using techniques known to those of skill in the art. For example, U.S. Pharmacopeia (USP) <429> discloses methods for determining particle sizes.

[0034] Various crosslinked cation exchange polymer particles also have less than about 4 volume percent of the particles that have a diameter of less than about 10 μm; particularly, less than about 2 volume percent of the particles that have a diameter of less than about 10 μm; more particularly, less than about 1 volume percent of the particles that have a diameter of less than about 10 μm; and even more particularly, less than about 0.5 volume percent of the particles that have a diameter of less than about 10 μm. In other cases, specific ranges are less than about 4 volume percent of the particles that have a diameter of less than about 20 μm; less than about 2 volume percent of the particles that have a diameter of less than about 20 μm; less than about 1 volume percent of the particles that have a diameter of less than about 20 μm; less than about 0.5 volume percent of the particles that have a diameter of less than about 20 μm; less than about 2 volume percent of the particles that have a diameter of less than about 30 μm; less than about 1 volume percent of the particles that have a diameter of less than about 30 μm; less than about 1 volume percent of the particles that have a diameter of less than about 30 μm; less than about 1 volume percent of the particles that have a diameter of less than about 40 μm; or less than about 0.5 volume percent of the particles that have a diameter of less than about 40 μm.

[0035] The crosslinked cation exchange polymer can have a particle size distribution wherein not more than about 5 volume% of the particles have a diameter less than about 30 μm (i.e., $D(0.05) < 30$ μm), not more than about 5 volume% of the particles have a diameter greater than about 250 μm (i.e., $D(0.05) > 250$ μm), and at least about 50 volume% of the particles have a diameter in the range from about 70 to about 150 μm.

[0036] The particle distribution of the crosslinked cation exchange polymer can be described as the span. The span of the particle distribution is defined as $(D(0.9)-D(0.1))/D(0.5)$, where $D(0.9)$ is the value wherein 90% of the particles have a diameter below that value, $D(0.1)$ is the value wherein 10% of the particles have a diameter below that value, and $D(0.5)$ is the value wherein 50% of the particles have a diameter above that value and 50% of the particles have a diameter below that value as measured by laser diffraction. The span of the particle

distribution is typically from about 0.5 to about 1, from about 0.5 to about 0.95, from about 0.5 to about 0.90, or from about 0.5 to about 0.85. Particle size distributions can be measured using Niro Method No. A 8 d (revised September 2005), available from GEA Niro, Denmark, using the Malvern Mastersizer.

[0037] Another desirable property that the crosslinked cation exchange polymers may possess is a viscosity when hydrated and sedimented of from about 10,000 Pa•s to about 1,000,000 Pa·s, from about 10,000 Pa·s to about 800,000 Pa·s, from about 10,000 Pa·s to about 600,000 Pa·s, from about 10,000 Pa·s to about 500,000 Pa·s, from about 10,000 Pa·s to about 250,000 Pa·s, or from about 10,000 Pa·s to about 150,000 Pa·s, from about 30,000 Pa·s to about 1,000,000 Pa·s, from about 30,000 Pa·s to about 500,000 Pa·s, or from about 30,000 Pa·s to about 150,000 Pa·s, the viscosity being measured at a shear rate of 0.01 sec^{-1}. This viscosity is measured using a wet polymer prepared by mixing the polymer thoroughly with a slight excess of simulated intestinal fluid (per USP <26>), allowing the mixture to sediment for 3 days at 37°C, and decanting free liquid from the sedimented wet polymer. The steady state shear viscosity of this wet polymer can be determined using a Bohlin VOR Rheometer (available from Malvern Instruments Ltd., Malvern, U.K.) or equivalent with a parallel plate geometry (upper plate of 15 mm diameter and lower plate of 30 mm diameter, and gap between plates of 1 mm) and the temperature maintained at 37°C.

[0038] The crosslinked cation exchange polymers may further have a hydrated and sedimented yield stress of from about 150 Pa to about 4000 Pa, from about 150 Pa to about 3000 Pa, from about 150 Pa to about 2500 Pa, from about 150 Pa to about 1500 Pa, from about 150 Pa to about 1000 Pa, from about 150 Pa to about 750 Pa, or from about 150 Pa to about 500 Pa, from about 200 Pa to about 4000 Pa, from about 200 Pa to about 2500 Pa, from about 200 Pa to about 1000 Pa, or from about 200 Pa to about 750 Pa. Dynamic stress sweep measurements (i.e., yield stress) can be made using a Reologica STRESSTECH Rheometer (available from Reologica Instruments AB, Lund, Sweden) or equivalent in a manner known to those of skill in the art. This rheometer also has a parallel plate geometry (upper plate of 15 mm diameter, lower plate of 30 mm diameter, and gap between plates of 1 mm) and the temperature is maintained at 37°C. A constant frequency of 1 Hz with two integration periods can be used while the shear stress is increased from 1 to 10^4 Pa.

[0039] Crosslinked cation exchange polymers useful for the methods described herein also have desirable compressibility and bulk density when in the form of a dry powder. Some of the particles of the crosslinked cation exchange polymers in the dry form have a bulk density of

from about 0.8 g/cm^3 to about 1.5 g/cm^3, from about 0.82 g/cm^3 to about 1.5 g/cm^3, from about 0.84 g/cm^3 to about 1.5 g/cm^3, from about 0.86 g/cm^3 to about 1.5 g/cm^3, from about 0.8 g/cm^3 to about 1.2 g/cm^3, or from about 0.86 g/cm^3 to about 1.2 g/cm^3. The bulk density affects the volume of crosslinked cation exchange polymer needed for administration to a patient. For example, a higher bulk density means that a lower volume will provide the same number of grams of crosslinked cation exchange polymer. This lower volume can improve patient compliance by allowing the patient to perceive they are taking a smaller amount due to the smaller volume.

[0040] A powder composed of the particles of the crosslinked cation exchange polymer in dry form has a compressibility index of from about 3 to about 15, from about 3 to about 14, from about 3 to about 13, from about 3 to about 12, from about 3 to about 11, from about 5 to about 15, from about 5 to about 13, or from about 5 to about 11. The compressibility index is defined as 100*(TD-BD)/TD, wherein BD and TD are the bulk density and tap density, respectively. The procedure for measuring bulk density and tap density is described below in Example 3. Further, the powder form of the cation exchange polymers settles into its smallest volume more easily than polymers conventionally used to treat hyperkalemia. This makes the difference between the bulk density and the tap density (measured powder density after tapping a set number of times) from about 3% to about 14%, from about 3% to about 13%, from about 3% to about 12%, from about 3% to about 11%, from about 3% to about 10%, from about 5% to about 14%, from about 5% to about 12%, or from about 5% to about 10% of the bulk density.

[0041] Generally the potassium-binding polymers in particle form are not absorbed from the gastrointestinal tract. The term "non-absorbed" and its grammatical equivalents is not intended to mean that the entire amount of administered polymer is not absorbed. It is expected that certain amounts of the polymer may be absorbed. Particularly, about 90% or more of the polymer is not absorbed, more particularly about 95% or more is not absorbed, even more particularly about 97% or more is not absorbed, and most particularly about 98% or more of the polymer is not absorbed.

[0042] The swelling ratio of the potassium-binding polymers in physiological isotonic buffer, which is representative of the gastrointestinal tract, is typically from about 1 to about 7, particularly from about 1 to about 5, more particularly from about 1 to about 3, and more specifically, from about 1 to about 2.5.

[0043] The crosslinked cation exchange polymers can have a swelling ratio of less than 5, less than about 4, less than about 3, less than about 2.5, or less than about 2. As used

herein, "swelling ratio" refers to the number of grams of solvent taken up by one gram of otherwise non-solvated crosslinked polymer when equilibrated in an aqueous environment. When more than one measurement of swelling is taken for a given polymer, the mean of the measurements is taken to be the swelling ratio. The polymer swelling can also be calculated by the percent weight gain of the otherwise non-solvated polymer upon taking up solvent. For example, a swelling ratio of 1 corresponds to polymer swelling of 100%.

[0044] Crosslinked cation exchange polymers having advantageous surface morphology are polymers in the form of substantially spherical particles with a substantially smooth surface. A substantially smooth surface is a surface wherein the average distance from the peak to the valley of a surface feature determined at random over several different surface features and over several different particles is less than about 2 μm, less than about 1 μm, or less than about 0.5 μm. Typically, the average distance between the peak and the valley of a surface feature is less than about 1 μm.

[0045] The surface morphology can be measured using several techniques including those for measuring roughness. Roughness is a measure of the texture of a surface. It is quantified by the vertical deviations of a real surface from its ideal form. If these deviations are large, the surface is rough; if they are small the surface is smooth. Roughness is typically considered to be the high frequency, short wavelength component of a measured surface. For example, roughness may be measured using contact or non-contact methods. Contact methods involve dragging a measurement stylus across the surface; these instruments include profilometers and atomic force microscopes (AFM). Non-contact methods include interferometry, confocal microscopy, electrical capacitance and electron microscopy. These methods are described in more detail in Chapter 4: Surface Roughness and Microtopography by L. Mattson in Surface Characterization, ed. by D. Brune, R. Hellborg, H.J. Whitlow, O.Hunderi, Wiley-VCH, 1997.

[0046] For three-dimensional measurements, the probe is commanded to scan over a two-dimensional area on the surface. The spacing between data points may not be the same in both directions. In this way, a side view of the surface can be obtained and the relief of the surface can be measured.

[0047] Surface roughness can be controlled in a number of ways. For example, three approaches were determined for preparing poly(α-fluoroacrylate) particles having a smoother surface. The first approach was to include a solvent that was an acceptable solvent for the monomers and the polymeric product. The second approach was to decrease the solvation of the

organic phase in the aqueous phase by a salting out process. The third approach was to increase the hydrophobicity of the starting fluoroacrylate monomer.

[0048] Dosing regimens for chronic treatment of hyperkalemia can increase compliance by patients, particularly for crosslinked cation exchange polymers that are taken in gram quantities. The present invention is also directed to methods of chronically removing potassium from a mammal in need thereof, and in particular chronically treating hyperkalemia with a potassium binder that is a crosslinked aliphatic carboxylic polymer, and preferably a salt of such polymer stabilized with a linear polyol, wherein the polymer is in the form of a substantially spherical particle.

[0049] Thus, the invention is directed to methods of treating hypertension or hyperkalemia or kidney disease in a patient in need thereof, the method comprising administering an effective amount of a potassium-binding agent, to the patient. In particular, the invention is directed to methods of treating hypertension and hyperkalemia in a patient in need thereof. In particular also, the invention is directed to methods of treating kidney disease and hyperkalemia in a patient in need thereof.

[0050] In the methods described here, the potassium-binding agent can be 2-fluoroacrylate-divinylbenzene-1,7-octadiene copolymer, crosslinked in the salt or acid form.

[0051] The methods of treating hypertension or kidney disease can include chronic administration of the potassium-binding agent. The potassium-binding agent exhibits long-term tolerability, long-term safety, and/or long-term efficacy in the patient. The long-term tolerability, long-term safety, and long-term efficacy are observed over treatment periods of 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, or more weeks. The treatment period can also be 2 years, 3 years, 4 years, 5 years, or more. Particularly, the potassium-binding agent can be administered to the patient daily for more than 8 weeks or daily for more than one year.

[0052] In particular, the 2-fluoroacrylate-divinylbenzene-1,7-octadiene copolymer crosslinked in the salt or acid form exhibits long-term tolerability, long-term safety, and/or long-term efficacy in the patient. The long-term tolerability, long-term safety, and long-term efficacy are observed over treatment periods of 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, or more weeks. The treatment period can also be 2 years, 3 years, 4 years, 5 years, or more. Particularly, the 2-fluoroacrylate-divinylbenzene-1,7-octadiene copolymer crosslinked in the salt or acid form can be administered to the patient daily for more than 8 weeks or daily for more than one year.

[0053] The methods of treating hypertension and hyperkalemia can also reduce the patient's systolic blood pressure by 5, 6, 7, 8 mmHg as compared to the patient's systolic blood

pressure before treatment with the potassium-binding agent, and/or reduce the patient's diastolic blood pressure 2, 3, 4, 5, 6 mmHg as compared to the patient's diastolic blood pressure before treatment with potassium-binding agent.

[0054] The methods of treating hypertension and hyperkalemia can also reduce the patient's systolic blood pressure by 9, 10, 11, 12, 13, 14, 15, 16, 17 mmHg or more as compared to the patient's systolic blood pressure before treatment with potassium-binding agent, and/or reduce the patient's diastolic blood pressure 7, 8, 9, 10, 11, 12, 13 mmHg or more as compared to the patient's diastolic blood pressure before treatment with potassium-binding agent.

[0055] The methods of treating hypertension and hyperkalemia can also reduce the patient's systolic blood pressure by at least 6, 7, 8, 9, 10, 11, 12, or more percent as compared to the patient's systolic blood pressure before treatment with potassium-binding agent, and/or the patient's diastolic blood pressure is reduced by at least 8, 9, 10, 11, 12, 13, 14, 15, or more percent as compared to the patient's diastolic blood pressure before treatment with potassium-binding agent.

[0056] The potassium-binding agent can be administered to a patient having a systolic blood pressure greater than 130 mmHg or ranging from 130 to 200 mmHg, 135 to 200 mmHg, 140 to 200 mmHg, 145 to 200 mmHg, or 150 to 180 mmHg before treatment with potassium-binding agent.

[0057] The potassium-binding agent can be administered to a patient having a systolic blood pressure greater than 143 mmHg or ranging from 143 to 200 mmHg or 143 to 180 mmHg before treatment with potassium-binding agent.

[0058] The systolic blood pressure of the patient can be maintained below 130, 135, or 140 mmHg over at least 90% of the period of treatment with potassium-binding agent. The diastolic blood pressure of the patient can be maintained at below 80, 85, or 90 mmHg over at least 90% of the period of treatment with potassium-binding agent.

[0059] The methods of treating hypertension can include administering an effective amount of potassium-binding agent to a heart failure patient, a type 2 diabetes mellitus patient, and/or a chronic kidney disease patient in need of hypertension treatment, the patient optionally being treated with an effective amount of a renin-angiotensin-aldosterone system (RAAS) agent.

[0060] The methods of treatment of hypertension can be administered to a patient suffering from chronic kidney disease, heart failure, type 2 diabetes mellitus or a combination thereof.

[0061] The potassium-binding agent can be administered to a patient that is not being treated with an aldosterone antagonist. Particularly, the patient is not being treated with spironolactone.

[0062] The methods of treating hypertension can include administration of potassium-binding agent to a patient that does not have another condition that causes hypertension such as Type 2 diabetes, chronic kidney disease, chronic heart failure or a combination thereof. Particularly, the patient does not have type 2 diabetes mellitus, or the patient that does not have chronic kidney disease (CKD).

[0063] The methods of treating hypertension can include administration of potassium-binding agent to a patient that does not have Class II or Class III heart failure (HF).

[0064] The methods of treating hypertension can also include administration of potassium-binding agent to a patient that is not being treated with a heart failure therapy; the heart failure therapy can be an angiotensin converting enzyme inhibitor (ACEI), an angiotensin receptor blocker (ARB), a beta blocker (BB), or a combination thereof.

[0065] The patients receiving the treatment methods of the invention need not be treated with an antihypertensive agent comprising a diuretic, a calcium channel blocker, an alpha blocker, a nervous system inhibitor, a vasodilator, an angiotensin converting enzyme inhibitor (ACEI), an angiotensin receptor blocker (ARB), a beta blocker (BB), or a combination thereof.

[0066] The methods of treating hypertension of the invention can be administered to patients that are normokalemic. Normokalemic patients have a serum potassium level of 3.5 to 5.0 mEq/L.

[0067] The present invention is directed to methods of treating hyperkalemia in a chronic kidney disease patient in need thereof optionally being treated with an effective amount of a renin-angiotensin-aldosterone system (RAAS) agent. The methods generally comprise administering an effective amount of a potassium-binding polymer to the patient to increase or stabilize the patient's kidney function.

[0068] The present invention is directed to methods of treating chronic kidney disease in a patient in need thereof optionally being treated with an effective amount of a renin-angiotensin-aldosterone system (RAAS) agent. The methods generally comprise administering an effective amount of a potassium-binding polymer to the patient to increase or stabilize the patient's kidney function.

[0069] In the methods of treating kidney disease, there are several ways in which the methods can exhibit an increase to or stabilization of the patient's kidney function, such as by

decreasing the patient's serum creatinine level as compared to the patient's serum creatinine level before treatment with a potassium-binding agent; increasing the time to progression of end stage renal disease as compared to a chronic kidney disease patient optionally treated with a RAAS agent but not treated with a potassium-binding agent; increasing survival as compared to a chronic kidney disease patient optionally treated with a RAAS agent but not treated with a potassium-binding agent; and/or increasing or stabilizing estimated glomerular filtration rate (eGFR) as compared to the patient's eGFR before treatment with a potassium-binding agent.

[0070] For all of these methods of treatment including treating hypertension, hyperkalemia, chronic kidney disease, end stage renal disease, etc. the potassium-binding agent can be a potassium-binding polymer.

[0071] For the methods of treatment described herein, the potassium-binding polymer can be a crosslinked cation exchange polymer.

[0072] For the methods of treatment described herein, the potassium-binding polymer can be an aliphatic crosslinked cation exchange polymer.

[0073] For the methods of treatment described herein, the potassium-binding polymer can be 2-fluoroacrylate-divinylbenzene-1,7-octadiene copolymer crosslinked in the salt or acid form.

[0074] For the methods of treatment described herein, the potassium-binding agent can be a zirconium silicate or a zirconium germanate molecular sieve.

[0075] For the methods of treatment described herein, the potassium-binding agent can be $Na_{2.19}ZrSi_{3.01}O_{9.11}\bullet 2.71\ H_2O$. .

[0076] As detailed in Example 2, a Phase II clinical study conducted in Type 2 diabetes mellitus (T2DM) patients with chronic kidney disease (CKD) Phase 3/4 is instructive. All patients are treated with a RAAS inhibitor, and about 40% of the patients also have heart failure (HF). And, endpoints measure changes from baseline at various time points. The trial is an 8-week, open-label, randomized, dose ranging study to determine the optimal starting dose(s) of 2-fluoroacrylate-divinylbenzene-1,7-octadiene copolymer crosslinked in the salt or acid form. In addition, the study contains a 44-week long-term safety extension component, in order to collect 1-year safety data that will support chronic use of 2-fluoroacrylate-divinylbenzene-1,7-octadiene copolymer crosslinked in the salt or acid form. Patients with normal serum K^+ levels of 4.3 – 5.0 mEq/L were enrolled in a run-in period during which they received the maximum labeled dose of losartan and/or additional spironolactone as needed. Patients with serum K^+ levels > 5.0 mEq/L at baseline entered the study without a run-in period (data from some of

these patients are shown in Figs. 6-9). For treatment of hyperkalemia (serum $K^+ > 5.0$ mEq/L), two potassium strata were chosen (stratum 1 = serum $K^+ > 5.0 – 5.5$ mEq/L; stratum 2 = serum $K^+ > 5.5 – < 6.0$ mEq/L), based on the National Kidney Foundation Kidney Disease Outcomes Quality Initiative Guideline 11 (KDOQI, 2004) definition of hyperkalemia and serum potassium cut-off points for ACEI/ARB dose modification.

[0077] This Phase II Study was enrolled with a total of 306 subjects treated for an average duration of 9.5 months. All subjects completed the trial, with 266 subjects completing 8 weeks, 226 subjects completing 6 months and 197 patients completing one year.

[0078] Several key observations can be made. Looking at interim data, and a statistically significant number of the 182 patients had an albumin creatinine ratio (ACR) of ≥ 30 mg/g and others had an ACR of > 300 mg/g and an estimated glomerular filtration rate (eGFR) of 15 to 44 mL/min/1.73 m^2 at baseline. As shown in Figure 1, for all of these patients, the patient's serum potassium concentration decreased from an average of 5.27 mEq/L at baseline to an average of 4.57 mEq/L at 24 weeks. For patients having an ACR ≥ 30 mg/g, the patient's serum potassium concentration decreased from an average of 5.28 mEq/L at baseline to an average of 4.60 mEq/L at 24 weeks. For patients having an ACR > 300 mg/g, the patient's serum potassium concentration decreased from an average of 5.35 mEq/L at baseline to an average of 4.65 mEq/L at 24 weeks. For patients having an eGFR of 15 to 44 mL/min/1.73 m^2, the patient's serum potassium concentration decreased from an average of 5.33 mEq/L at baseline to an average of 4.59 mEq/L at 24 weeks.

[0079] As shown in Figure 2, for all of these patients, the patient's systolic blood pressure decreased from an average of 154 at baseline to an average of 137 at 24 weeks; for patients having an ACR ≥ 30 mg/g, the patient's systolic blood pressure decreased from an average of 154 at baseline to an average of 138 at 24 weeks; for patients having an ACR > 300 mg/g, the patient's systolic blood pressure decreased from an average of 154 at baseline to an average of 137 at 24 weeks; and for patients having an eGFR of 15 to 44 mL/min/1.73 m^2, the patient's systolic blood pressure decreased from an average of 152 at baseline to an average of 135 at 24 weeks.

[0080] As shown in Figure 3, for all of these patients, the patient's diastolic blood pressure decreased from an average of 83 at baseline to an average of 74 at 24 weeks; for patients having an ACR ≥ 30 mg/g, the patient's diastolic blood pressure decreased from an average of 84 at baseline to an average of 74 at 24 weeks; for patients having an ACR > 300 mg/g, the patient's diastolic blood pressure decreased from an average of 86 at baseline to an

average of 73 at 24 weeks; and or patients having an eGFR of 15 to 44 mL/min/1.73 m^2, the patient's diastolic blood pressure decreased from an average of 82 at baseline to an average of 73 at 24 weeks.

[0081] As shown in Figure 4, for the patients in all groups and each group separately (e.g., ACR of ≥ 30 mg/g, ACR of > 300 mg/g, eGFR of 15 to 44 mL/min/1.73 m^2), the ACR did not significantly change over the 24 week treatment period.

[0082] As shown in Figure 5, for patients having an eGFR of 15 to 44 mL/min/1.73 m^2, the patient's eGFR increased from an average of 32 mL/min/1.73 m^2 at baseline to an average of 38 mL/min/1.73 m^2 at 24 weeks. This increase in eGFR for these patients was statistically significant.

[0083] As described above, Figures 6-9 show data from a certain cohort of patients with pre-existing hyperkalemia taking a stable dose of a RAAS inhibitor that came into the trial without a run-in period. As shown in Figure 6, the average of these patients' eGFR of 46 mL/min/1.73 m^2 at baseline did not decrease over time, as can be expected in these patients. Further data suggests that in a subset of patients, the eGFR appears to increase at one year. As shown in Figure 7, the average of these patients' serum potassium level decreased significantly from 5.3 mEq/L at baseline into the normal range (to 4.6 mEq/L) at 12 months. As shown in Figure 8, the average of these patients' urine ACR of 853 mg/g at baseline was not significantly different from the average of the patients' urine ACR at any other time point. As shown in Figure 9, the average of these patients' systolic blood pressure decreased from 157 mmHg to 134 mmHg and the average of these patients' diastolic blood pressure decreased from 85 mmHg to 77 mmHg.

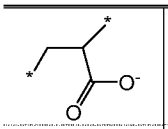
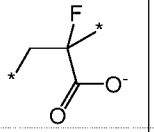
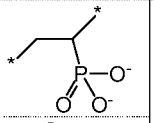
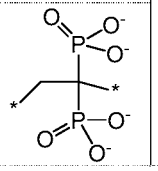
[0084] Additional observations can be made from the study results. First, the starting serum potassium is a factor in determining efficacy of 2-fluoroacrylate-divinylbenzene-1,7-octadiene copolymer crosslinked in the salt or acid form. The interim analysis of the 8-week Treatment Initiation Period performed for 304 subjects showed a mean decrease in serum potassium from baseline to week 8 in subjects in the upper serum potassium stratum (Stratum 2: serum K^+ > 5.5 to < 6.0 mEq/L) that was approximately twice that in subjects in the lower serum potassium stratum (Stratum 1: serum K^+ > 5.0 to 5.5 mEq/L) (-0.90 mEq/L versus -0.47 mEq/L, respectively). This baseline effect was seen within the first week on treatment. Second, underlying RAAS inhibitor treatment does not appear to influence the efficacy of 2-fluoroacrylate-divinylbenzene-1,7-octadiene copolymer crosslinked in the salt or acid form.

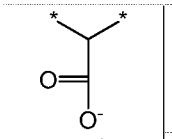
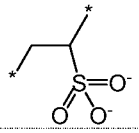
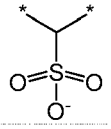
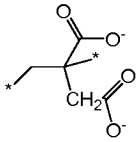
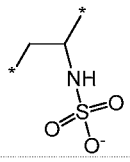
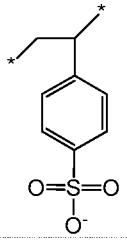
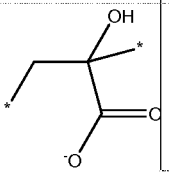
Third, the efficacy of 2-fluoroacrylate-divinylbenzene-1,7-octadiene copolymer crosslinked in the salt or acid form appears to be independent of comorbidities.

[0085] The potassium-binding polymers can be crosslinked cation exchange polymers derived from at least one crosslinker and at least one monomer containing acid groups in their protonated or ionized form, such as sulfonic, sulfuric, carboxylic, phosphonic, phosphoric, or sulfamic groups, or combinations thereof. In general, the fraction of ionization of the acid groups of the polymers used in this invention is greater than about 75% at the physiological pH (e.g., about pH 6.5) in the colon and the potassium binding capacity in vivo is greater than about 0.6 mEq/gram, more particularly greater than about 0.8 mEq/gram and even more particularly greater than about 1.0 mEq/gram. Generally the ionization of the acid groups is greater than about 80%, more particularly it is greater than about 90%, and most particularly it is about 100% at the physiological pH of the colon (e.g., about pH 6.5).

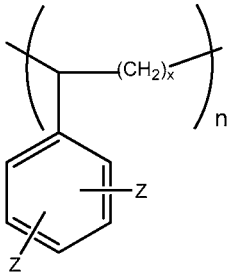
[0086] The acid containing polymers can contain more than one type of acid group. In other instances, the acid containing polymers are administered in their substantially anhydrous or salt form and generate the ionized form when contacted with physiological fluids. Representative structural units of these potassium-binding polymers are shown in Table 1 wherein the asterisk at the end of a bond indicates that bond is attached to another structural unit or to a crosslinking unit.

TABLE 1: Examples of cation exchange structural units – structures and theoretical binding capacities

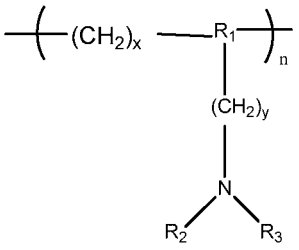
	Molar mass per charge	Theoretical capacity	Fraction of titrable H @pH 3	Fraction of titrable H @ pH 6	Expected Capacity @pH 3	Expected Capacity @pH 6
	71	14.1	0.05	.35	0.70	4.93
	87	11.49	0.2	0.95	2.3	10.92
	53	18.9	0.25	0.5	4.72	9.43
	47.5	21.1	0.25	0.5	5.26	10.53

	57	17.5	0.1	0.5	1.75	8.77
	107	9.3	1	1	9.35	9.35
	93	10.8	1	1	10.75	10.75
	63	15.9	0	0.4	0	6.35
	125	8	1	1	8	8
	183	5.5	1	1	5.46	5.46
	87	11.49	.1	.6	1.14	6.89

[0087] Other suitable cation exchange polymers contain repeat units having the following structures:



or



wherein R_1 is a bond or nitrogen, R_2 is hydrogen or Z, R_3 is Z or -$CH(Z)_2$, each Z is independently SO_3H or PO_3H, x is 2 or 3, and y is 0 or 1, n is about 50 or more, more

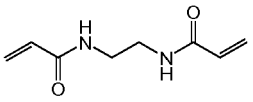
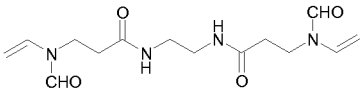
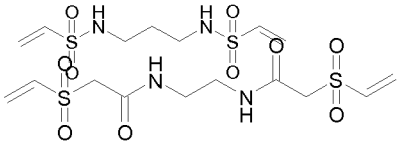
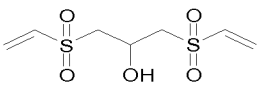
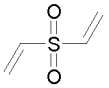
particularly n is about 100 or more, even more particularly n is about 200 or more, and most particularly n is about 500 or more.

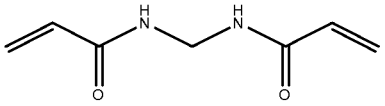
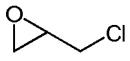
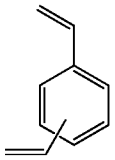
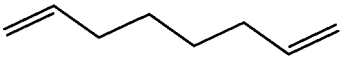
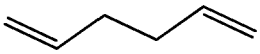
[0088] Sulfamic (i.e. when Z=SO_3H) or phosphoramidic (i.e. when Z= PO_3H) polymers can be obtained from amine polymers or monomer precursors treated with a sulfonating agent such as sulfur trioxide/amine adducts or a phosphonating agent such as P_2O_5, respectively. Typically, the acidic protons of phosphonic groups are exchangeable with cations, like sodium or potassium, at pH of about 6 to about 7.

[0089] Suitable phosphonate monomers include vinyl phosphonate, vinyl-1,1-bis phosphonate, and ethylenic derivatives of phosphonocarboxylate esters, oligo(methylenephosphonates), and hydroxyethane-1,1-diphosphonic acid. Methods of synthesis of these monomers are well known in the art.

[0090] The cation exchange structural units and repeat units containing acid groups as described above are crosslinked to form the crosslinked cation exchange polymers of the invention. Representative crosslinking monomers include those shown in Table 2.

Table 2: Crosslinker Abbreviations and Structures

Abbreviation	Chemical name	Structure	Molecular Weight
X-V-1	ethylenebisacrylamide		168.2
X-V-2	N,N'-(ethane-1,2-diyl)bis(3-(N-vinylformamido) propanamide)		310.36
X-V-3	N,N'-(propane-1,3-diyl)diethenesulfonamide		254.33
X-V-4	N,N'-bis(vinylsulfonylacetyl) ethylene diamine		324.38
X-V-5	1,3-bis(vinylsulfonyl) 2-propanol		240.3
X-V-6	vinylsulfone		118.15

X-V-7	N,N'-methylenebisacrylamide		154.17
ECH	epichlorohydrin		92.52
DVB	Divinyl benzene		130.2
ODE	1,7-octadiene		110.2
HDE	1,5-hexadiene		82.15

The ratio of repeat units to crosslinker can be chosen by those of skill in the art based on the desired physical properties of the polymer particles. For example, the swelling ratio can be used to determine the amount of crosslinking based on the general understanding of those of skill in the art that as crosslinking increases, the swelling ratio generally decreases.

[0091] The amount of crosslinker in the polymerization reaction mixture can be in the range of 3 wt. % to 15 wt. %, more specifically in the range of 5 wt. % to 15 wt.% and even more specifically in the range of 8 wt. % to 12 wt.%, based on the total weight of the monomers and crosslinkers added to the polymerization reaction. Crosslinkers can include one or a mixture of those in Table 2.

[0092] The crosslinked cation exchange polymer can also include a pKa-decreasing group, preferably an electron-withdrawing substituent, located adjacent to the acid group, preferably in the alpha or beta position of the acid group. The preferred position for the electron-withdrawing group is attached to the carbon atom alpha to the acid group. Generally, electron-withdrawing substituents are a hydroxyl group, an ether group, an ester group, an acid group, or a halide atom. More preferably, the electron-withdrawing substituent is a halide atom. Most preferably, the electron-withdrawing group is fluoride and is attached to the carbon atom alpha to the acid group. Acid groups are carboxylic, phosphonic, phosphoric, or combinations thereof.

[0093] Other particularly preferred polymers result from the polymerization of alpha-fluoro acrylic acid, difluoromaleic acid, or an anhydride thereof. Monomers for use herein include α-fluoroacrylate and difluoromaleic acid, with α-fluoroacrylate being most preferred. This monomer can be prepared from a variety of routes, see for example, Gassen et al, J. Fluorine Chemistry, 55, (1991) 149-162, KF Pittman, C. U., M. Ueda, et al. (1980). Macromolecules 13(5): 1031-1036. Difluoromaleic acid is prepared by oxidation of fluoroaromatic compounds (Bogachev et al, Zhurnal Organisheskoi Khimii, 1986, 22(12), 2578-83), or fluorinated furan derivatives (See U.S. patent 5,112,993). A mode of synthesis of α-fluoroacrylate is given in EP 415214.

[0094] Further, the potassium-binding polymer can be 2-fluoroacrylate-divinylbenzene-1,7-octadiene copolymer, crosslinked in the salt or acid form. Particularly, the 2-fluoroacrylate-divinylbenzene-1,7-octadiene copolymer crosslinked in the salt or acid form is in the salt form. The salt form comprises the sodium, calcium, magnesium, ammonium, or a combination thereof; preferably, the salt form comprises the calcium salt form.

[0095] Also, the 2-fluoroacrylate-divinylbenzene-1,7-octadiene copolymer, crosslinked in the salt form can be stabilized with a linear polyol. Particularly, the 2-fluoroacrylate-divinylbenzene-1,7-octadiene copolymer, crosslinked in the salt form can be stabilized with 10 wt.% to about 40 wt.% of a linear polyol based on the total weight of the composition.

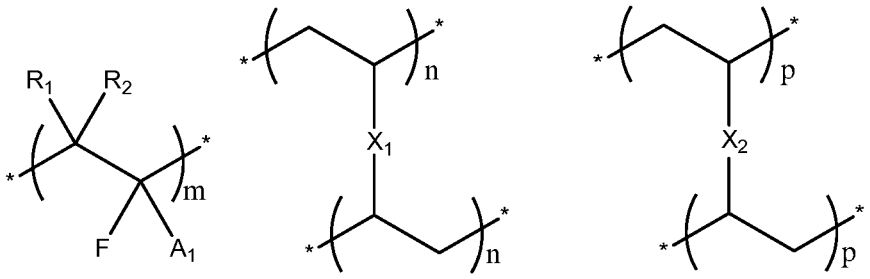
[0096] A linear polyol is added to the composition containing the salt of a potassium-binding polymer (e.g., 2-fluoroacrylate-divinylbenzene-1,7-octadiene copolymer, crosslinked in the salt form) in an amount effective to stabilize the polymer salt, and generally from about 10 wt.% to about 40 wt.% linear polyol based on the total weight of the composition.

[0097] The linear polyol is preferably a linear sugar (i.e., a linear sugar alcohol). The linear sugar alcohol is preferably selected from the group consisting of D-(+)arabitol, erythritol, glycerol, maltitol, D-mannitol, ribitol, D-sorbitol, xylitol, threitol, galactitol, isomalt, iditol, lactitol and combinations thereof, more preferably selected from the group consisting of D-(+)arabitol, erythritol, glycerol, maltitol, D-mannitol, ribitol, D-sorbitol, xylitol, and combinations thereof , and most preferably selected from the group consisting of xylitol, sorbitol, and a combination thereof.

[0098] Preferably, the pharmaceutical composition contains from about 15 wt.% to about 35 wt.% stabilizing polyol based on the total weight of the composition. This linear

polyol concentration can be sufficient to reduce the release of fluoride ion from the cation exchange polymer upon storage as compared to an otherwise identical composition containing no stabilizing polyol at the same temperature and storage time.

[0099] Further, the potassium-binding polymer can be a crosslinked cation exchange polymer comprising units having Formulae 1, 2, and 3 as represented by the following structures:



Formula 1 Formula 2 Formula 3

wherein R_1 and R_2 are independently selected from hydrogen, alkyl, cycloalkyl, or aryl; A_1 is carboxylic, phosphonic, or phosphoric in its salt or acid form; X_1 is arylene; X_2 is alkylene, an ether moiety or an amide moiety, m is in the range of from about 85 to about 93 mol%, n is in the range of from about 1 to about 10 mol% and p is in the range of from about 1 to about 10 mol% calculated based on the ratio of monomers and crosslinkers added to the polymerization mixture.

[00100] When X_2 is an ether moiety, the ether moiety can be $-(CH_2)_d-O-(CH_2)_e-$ or $-(CH_2)_d-O-(CH_2)_e-O-(CH_2)_d-$, wherein d and e are independently an integer of 1 through 5.

[00101] Preferably, d is an integer from 1 to 2 and e is an integer from 1 to 3.

[00102] When X_2 is an amide moiety, the amide moiety can be $-C(O)-NH-(CH_2)_p-NH-C(O)-$ wherein p is an integer of 1 through 8. Preferably, p is an integer of 4 to 6.

[00103] The unit corresponding to Formula 2 can be derived from a difunctional crosslinking monomer having the formula $CH_2=CH-X_1-CH=CH_2$ wherein X_1 is as defined in connection with Formula 2.

[00104] The unit corresponding to Formula 3 can be derived from a difunctional crosslinking monomer having the formula $CH_2=CH-X_2-CH=CH_2$ wherein X_2 is as defined in connection with Formula 3.

[00105] In connection with Formula 1, R_1 and R_2 are hydrogen and A_1 is carboxylic.

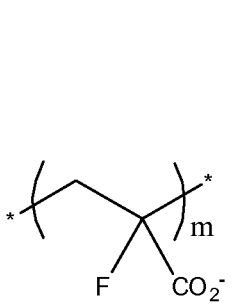
[00106] In connection with Formula 2, X_1 is an optionally substituted phenylene, and preferably phenylene.

[00107] In connection with Formula 3, X_2 is optionally substituted ethylene, propylene, butylene, pentylene, or hexylene; more specifically, X_2 is ethylene, propylene, butylene, pentylene, or hexylene; and preferably X_2 is butylene. Specifically, R_1 and R_2 are hydrogen, A_1 is carboxylic acid, X_1 is phenylene and X_2 is butylene.

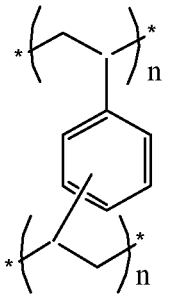
[00108] Generally, the Formulae 1, 2 and 3 structural units of the terpolymer have specific ratios, for example, wherein the structural units corresponding to Formula 1 constitute at least about 80 wt.%, particularly at least about 85 wt.%, and more particularly at least about 90 wt.% or from about 80 wt.% to about 95 wt.%, from about 85 wt.% to about 95 wt.%, from about 85 wt.% to about 93 wt.% or from about 88 wt.% to about 92 wt.% based on the total weight of structural units of Formulae 1, 2, and 3 in the polymer, calculated based on the monomers of Formulae 11, 22, and 33 used in the polymerization reaction, and the weight ratio of the structural unit corresponding to Formula 2 to the structural unit corresponding to Formula 3 is from about 4:1 to about 1:4, or about 1:1.

[00109] Further, the ratio of structural units when expressed as the mole fraction of the structural unit of Formula 1 in the polymer is at least about 0.87 or from about 0.87 to about 0.94, or from about 0.9 to about 0.92 based on the total number of moles of the structural units of Formulae 1, 2, and 3, and the mole ratio of the structural unit of Formula 2 to the structural unit of Formula 3 is from about 0.2:1 to about 7:1, from about 0.2:1 to about 3.5:1; from about 0.5:1 to about 1.3:1, from about 0.8 to about 0.9, or about 0.85:1; again these calculations are performed using the amounts of monomers of Formulae 11, 22, and 33 used in the polymerization reaction. It is not necessary to calculate conversion.

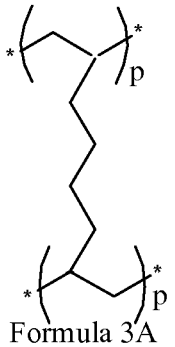
[00110] In some aspects, the crosslinked cation exchange polymer comprises units corresponding to Formulae 1A, 2A, and 3A, wherein Formula 1A, Formula 2A and Formula 3A correspond to the following structures.



Formula 1A



Formula 2A



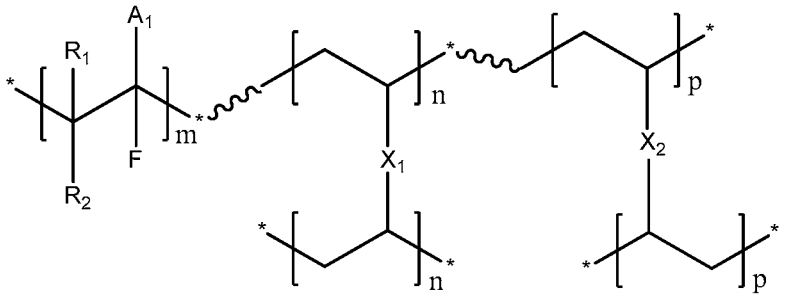
Formula 3A

[00111] In Formula 1 or 1A, the carboxylic acid can be in the acid form (i.e., balanced with hydrogen), in salt form (i.e., balanced with a counter-ion such as Ca^{2+}, Mg^{2+}, Na^{+}, NH_4^{+}, and the like) or in an ester form (i.e., balanced with an alkyl, such as methyl). Preferably, the carboxylic acid is in the salt form and balanced with a Ca^{2+} counterion.

[00112] When the carboxylic acid of the crosslinked cation exchange form is balanced with a divalent counterion, two carboxylic acid groups can be associated with the one divalent cation.

[00113] The polymers described herein are generally random polymers wherein the exact order of the structural units of Formulae 1, 2, or 3 (derived from monomers of Formulae 11, 22, or 33), or 1A, 2A, or 3A (derived from monomers of Formulae 11A, 22A, or 33A) is not predetermined.

[00114] A cation exchange polymer derived from monomers of Formulae 11, 22, and 33, followed by hydrolysis, can have the structure as follows:

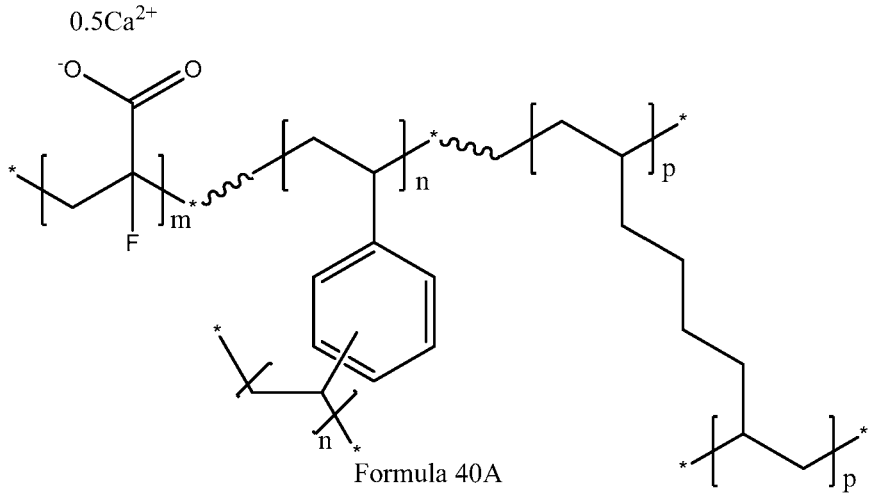


Formula 40

wherein R_1, R_2, A_1, X_1, and X_2 are as defined in connection with Formulae 1, 2, and 3 and m is in the range of from about 85 to about 93 mol%, n is in the range of from about 1 to about 10 mol% and p is in the range of from about 1 to about 10 mol% calculated based on the ratio of

monomers and crosslinkers added to the polymerization mixture. The wavy bonds in the polymer structures of Formula 40 are included to represent the random attachment of structural units to one another wherein the structural unit of Formula 1 can be attached to another structural unit of Formula 1, a structural unit of Formula 2, or a structural unit of Formula 3; the structural units of Formulae 2 and 3 have the same range of attachment possibilities.

[00115] Using the polymerization process described herein, with monomers of Formulae 11A, 22A and 33A, followed by hydrolysis and calcium ion exchange, a polymer having the general structure shown below is obtained:

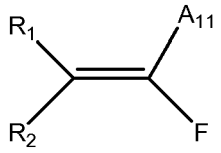


Formula 40A

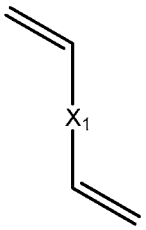
wherein m is in the range of from about 85 to about 93 mol%, n is in the range of from about 1 to about 10 mol% and p is in the range of from about 1 to about 10 mol%, calculated based on the ratios of monomers and crosslinkers added to the polymerization mixture. The wavy bonds in the polymer structures of Formula 40A are included to represent the random attachment of structural units to one another wherein the structural unit of Formula 1A can be attached to another structural unit of Formula 1A, a structural unit of Formula 2A, or a structural unit of Formula 3A; the structural units of Formulae 2A and 3A have the same range of attachment possibilities.

[00116] The crosslinked cation exchange polymer is generally a reaction product of a polymerization mixture that is subjected to polymerization conditions. The polymerization mixture may also contain components that are not chemically incorporated into the polymer. The crosslinked cation exchange polymer typically comprises a fluoro group and an acid group that is the product of the polymerization of three different monomer units where one monomer comprises a fluoro group and an acid group, another monomer is a difunctional arylene monomer and a third monomer is a difunctional alkylene, ether- or amide-containing monomer.

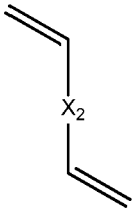
More specifically, the crosslinked cation exchange polymer can be a reaction product of a polymerization mixture comprising monomers of Formulae 11, 22, 33. The monomer of Formula 11, the monomer of Formula 22, and the monomer of Formula 33 have the general formulas:



Formula 11



Formula 22



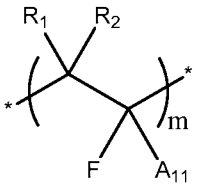
Formula 33

wherein R_1 and R_2 are as defined in connection with Formula 1, X_1 is as defined in connection with Formula 2, X_2 is as defined in connection with Formula 3, and A_{11} is an optionally protected carboxylic, phosphonic, or phosphoric.

[00117] Preferably, A_{11} is a protected carboxylic, phosphonic, or phosphoric.

[00118] The polymerization mixture typically further comprises a polymerization initiator.

[00119] The reaction product of the polymerization mixture comprising Formulae 11, 22, 33 comprises a polymer having protected acid groups and comprising units corresponding to Formula 10 and units corresponding to Formulae 2 and 3. Polymer products having protected acid groups can be hydrolyzed to form a polymer having unprotected acid groups and comprising units corresponding to Formulae 1, 2, and 3. The structural units corresponding to Formula 10 have the structure



Formula 10

wherein R_1, R_2, and A_{11} are as defined in connection with Formula 11 and m is as defined in connection with Formula 1.

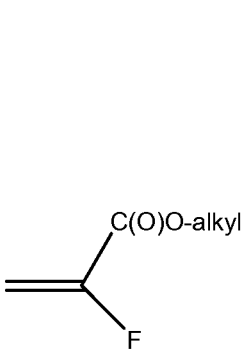
[00120] In any of the methods of the invention wherein the crosslinked cation exchange polymer is a reaction product of a polymerization mixture of monomers, A_{11} can be a protected carboxylic, phosphonic, or phosphoric. The polymer formed in the polymerization reaction contains protected carboxylic, phosphonic, or phosphoric groups. A hydrolysis agent can be

added to the polymer formed in the polymerization reaction to hydrolyze these protected groups, converting them to carboxylic, phosphonic, or phosphoric groups, or other methods of deprotection well known in the art can be used. The hydrolyzed polymer is preferably subjected to ion exchange to obtain a preferred polymer salt for therapeutic use.

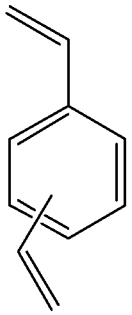
[00121] Generally, the polymerization reaction mixture comprises at least about 85 wt.% or from about 80 wt.% to about 95 wt.% of monomers corresponding to Formula 11 based on the total weight of the monomers corresponding to Formulae 11, 22, and 33; and the mixture having a weight ratio of the monomer corresponding to Formula 22 to the monomer corresponding to Formula 33 from about 4:1 to about 1:4, from about 2:1 to 1:2, or about 1:1.

[00122] The polymerization reaction mixture can comprise a unit corresponding to Formula 11 having a mole fraction of at least about 0.87 or from about 0.87 to about 0.94 based on the total number of moles of the monomers corresponding to Formulae 11, 22, and 33 and the mixture having a mole ratio of the monomer corresponding to Formula 22 to the monomer corresponding to Formula 33 of from about 0.2:1 to about 7:1, from about 0.2:1 to about 3.5:1; from about 0.5:1 to about 1.3:1, from about 0.8 to about 0.9, or about 0.85:1.

[00123] Particular crosslinked cation exchange polymers are the reaction product of a monomer corresponding to Formula 11A, a monomer corresponding to Formula 22A, a monomer corresponding to Formula 33A, and a polymerization initiator. The monomers corresponding to Formulae 11A, 22A, and 33A have the structure:



Formula 11A



Formula 22A

Formula 33A

wherein alkyl is preferably selected from methyl, ethyl, propyl, iso-propyl, butyl, iso-butyl, sec-butyl, tert-butyl, pentyl, iso-pentyl, sec-pentyl, or tert-pentyl. Most preferably, the alkyl group is methyl or tert-butyl. The -O-alkyl moiety protects the carboxyl moiety from reacting with other reactive moieties during the polymerization reaction and can be removed by hydrolysis or other deprotection methods as described in more detail below.

[00124] Further, the reaction mixture contains at least about 80 wt.%, particularly at least about 85 wt.%, and more particularly at least about 90 wt.% or from about 80 wt.% to about 95 wt.%, from about 85 wt.% to about 95 wt.%, from about 85 wt.% to about 93 wt.% or from about 88 wt.% to about 92 wt.% of monomers corresponding to Formula 11A based on the total weight of monomers of Formulae 11A, 22A, and 33A and has a weight ratio of the monomer corresponding to Formula 22A to the monomer corresponding to Formula 33A of from about 4:1 to about 1:4 or about 1:1. Additionally, the reaction mixture can have a mole fraction of at least about 0.87 or from about 0.87 to about 0.94 of the monomer of Formula 11A based on the total number of moles of the monomers of Formulae 11A, 22A, and 33A and the mixture has a mole ratio of the monomer of Formula 22A to the monomer of Formula 33A of from about 0.2:1 to about 7:1, from about 0.2:1 to about 3.5:1; from about 0.5:1 to about 1.3:1, from about 0.8 to about 0.9, or about 0.85:1.

[00125] Generally, the reaction mixture contains from about 80 wt.% to about 95 wt.% of monomers corresponding to Formula 11A based on the total weight of monomers corresponding to Formulae 11A, 22A, and 33A. Additionally, the weight ratio of the monomer corresponding to Formula 22A to the monomer corresponding to Formula 33A of from about 4:1 to about 1:4 or about 1:1. Further, the reaction mixture can have a mole fraction of from about 0.9 to about 0.92 of the monomer of Formula 11A based on the total number of moles of the monomers of Formulae 11A, 22A, and 33A. Also, the mixture has a mole ratio of the monomer of Formula 22A to the monomer of Formula 33A of from about 0.2:1 to about 7:1, from about 0.2:1 to about 3.5:1; from about 0.5:1 to about 1.3:1, from about 0.8 to about 0.9, or about 0.85:1.

[00126] An initiated polymerization reaction is employed where a polymerization initiator is used in the polymerization reaction mixture to aid initiation of the polymerization reaction. When preparing poly(methylfluoro acrylate) or (polyMeFA) or any other crosslinked cation exchange polymer of the invention in a suspension polymerization reaction, the nature of the free radical initiator plays a role in the quality of the suspension in terms of polymer particle stability, yield of polymer particles, and the polymer particle shape. Use of water-insoluble free radical initiators, such as lauroyl peroxide, can produce polymer particles in a high yield. Without being bound by any particular theory, it is believed that a water-insoluble free radical initiator initiates polymerization primarily within the dispersed phase containing the monomers of Formulae 11, 22, and 33. Such a reaction scheme provides polymer particles rather than a bulk polymer gel. Thus, the process uses free radical initiators with water solubility lower than

0.1 g/L, particularly lower than 0.01 g/L. Polymethylfluoroacrylate particles can be produced with a combination of a low water solubility free radical initiator and the presence of a salt in the aqueous phase, such as sodium chloride.

[00127] The polymerization initiator can be chosen from a variety of classes of initiators. For instance, initiators that generate polymer initiating radicals upon exposure to heat include peroxides, persulfates or azo type initiators (e.g., 2,2′-azobis(2-methylpropionitrile), lauroyl peroxide (LPO), tert-butyl hydro peroxide, dimethyl-2,2'-azobis(2-methylpropionate), 2,2'-azobis[2-methyl-N-(2-hydroxyethyl)propionamide], 2,2'-azobis[2-(2-imidazolin-2-yl)propane], (2,2"-azo bis(2,4-dimethylvaleronitrile), azobisisobutyronitrile (AIBN) or a combination thereof. Another class of polymer initiating radicals is radicals generated from redox reactions, such as persulfates and amines. Radicals can also be generated by exposing certain initiators to UV light or exposure to air.

[00128] For those polymerization reactions that contain additional components in the polymerization mixture that are not intended to be incorporated into the polymer, such additional components typically comprise surfactants, solvents, salts, buffers, aqueous phase polymerization inhibitors and/or other components known to those of skill in the art.

[00129] When the polymerization is carried out in a suspension mode, the additional components may be contained in an aqueous phase while the monomers and initiator may be contained in an organic phase. When an aqueous phase is present, the aqueous phase may be comprised of water, surfactants, stabilizers, buffers, salts, and polymerization inhibitors.

[00130] A surfactant may be selected from the group consisting of anionic, cationic, nonionic, amphoteric, zwitterionic, or a combination thereof. Anionic surfactants are typically based on sulfate, sulfonate or carboxylate anions. These surfactants include, sodium dodecyl sulfate (SDS), ammonium lauryl sulfate, other alkyl sulfate salts, sodium laureth sulfate (or sodium lauryl ether sulfate (SLES)), N-lauroylsarcosine sodium salt, lauryldimethylamine-oxide (LDAO), ethyltrimethylammoniumbromide (CTAB), bis(2-ethylhexyl)sulfosuccinate sodium salt, alkyl benzene sulfonate, soaps, fatty acid salts, or a combination thereof.

[00131] Cationic surfactants, for example, contain quaternary ammonium cations. These surfactants are cetyl trimethylammonium bromide (CTAB or hexadecyl trimethyl ammonium bromide), cetylpyridinium chloride (CPC), polyethoxylated tallow amine (POEA), benzalkonium chloride (BAC), benzethonium chloride (BZT), or a combination thereof.

[00132] Zwitterionic or amphoteric surfactants include dodecyl betaine, dodecyl dimethylamine oxide, cocamidopropyl betaine, coco ampho glycinate, or a combination thereof.

[00133] Nonionic surfactants include alkyl poly(ethylene oxide), copolymers of poly(ethylene oxide) and poly(propylene oxide) (commercially called Poloxamers or Poloxamines), alkyl polyglucosides (including octyl glucoside, decyl maltoside) fatty alcohols, cetyl alcohol, oleyl alcohol, cocamide MEA, cocamide DEA, or a combination thereof. Other pharmaceutically acceptable surfactants are well known in the art and are described in McCutcheon's Emulsifiers and Detergents, N. American Edition (2007).

[00134] Polymerization reaction stabilizers may be selected from the group consisting of organic polymers and inorganic particulate stabilizers. Examples include polyvinyl alcohol-co-vinylacetate and its range of hydrolyzed products, polyvinylacetate, polyvinylpyrolidinone, salts of polyacrylic acid, cellulose ethers, natural gums, or a combination thereof.

[00135] Buffers may be selected from the group consisting of, for example, 4-2-hydroxyethyl-1-piperazineethanesulfonic acid, 2-{[tris(hydroxymethyl)methyl]amino}ethanesulfonic acid, 3-(N-morpholino)propanesulfonic acid, piperazine-N,N′-bis(2-ethanesulfonic acid), sodium phosphate dibasic heptahydrate, sodium phosphate monobasic monohydrate or a combination thereof.

[00136] Polymerization reaction salts may be selected from the group consisting of potassium chloride, calcium chloride, potassium bromide, sodium bromide, sodium bicarbonate, ammonium peroxodisulfate, or a combination thereof.

[00137] Polymerization inhibitors may be used as known in the art and selected from the group consisting of 1,1,3-tris(2-methyl-4-hydroxy-5-tert-butylphenyl)butane, 1,3,5-trimethyl-2,4,6-tris(3,5-di-tert-butyl-4-hydroxybenzyl)benzene, 1-aza-3,7-dioxabicyclo[3.3.0]octane-5-methanol, 2,2′-ethylidene-bis(4,6-di-tert-butylphenol), 2,2′-ethylidenebis(4,6-di-tert-butylphenyl) fluorophosphite, 2,2′-methylenebis(6-tert-butyl-4-ethylphenol), 2,2′-methylenebis(6-tert-butyl-4-methylphenol), 2,5-di-tert-butyl-4-methoxyphenol, 2,6-di-tert-butyl-4-(dimethylaminomethyl)phenol, 2-heptanone oxime, 3,3′,5,5′-tetramethylbiphenyl-4,4′-diol, 3,9-bis(2,4-dicumylphenoxy)-2,4,8,10-tetraoxa-3,9-diphosphaspiro[5.5]undecane, 4,4-dimethyloxazolidine, 4-methyl-2-pentanone oxime, 5-ethyl-1-aza-3,7-dioxabicyclo[3.3.0]octane, 6,6′-dihydroxy-5,5′-dimethoxy-[1,1′-biphenyl]-3,3′-dicarboxaldehyde, distearyl-3,3′-thiodipropionate, ditetradecyl-3,3′-thiodipropionate, ditridecyl-3,3′-thiodipropionate, octadecyl-3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate, pentaerythritol tetrakis(3,5-di-tert-butyl-4-hydroxyhydrocinnamate), poly(1,2-dihydro-2,2,4-trimethylquinoline), sodium D-isoascorbate monohydrate, tetrakis(2,4-di-tert-butylphenyl)-4,4′-

biphenyldiphosphonite, tris(3,5-di-tert-butyl-4-hydroxybenzyl) isocyanurate, tris(4-tert-butyl-3-hydroxy-2,6-dimethylbenzyl) isocyanurate, sodium nitrite or a combination thereof.

[00138] Generally, the polymerization mixture is subjected to polymerization conditions. While suspension polymerization is preferred, as already discussed herein, the polymers of this invention may also be prepared in bulk, solution or emulsion polymerization processes. The details of such processes are within the skill of one of ordinary skill in the art based on the disclosure of this invention. The polymerization conditions typically include polymerization reaction temperatures, pressures, mixing and reactor geometry, sequence and rate of addition of polymerization mixtures and the like.

[00139] Polymerization temperatures are typically in the range of from about 50 to 100°C. Polymerization pressures are typically run at atmospheric pressure, but can be run at higher pressures (for example 130 PSI of nitrogen). Polymerization depends on the scale of the polymerization and the equipment used, and is within the skill of one of ordinary skill in the art. Various alpha-fluoroacrylate polymers and the synthesis of these polymers are described in U.S. Patent Application Publication No. 2005/0220752, herein incorporated by reference.

[00140] As described in more detail in connection with the examples herein, the crosslinked cation exchange polymer can be synthesized in a polymerization suspension polymerization reaction by preparing an organic phase and an aqueous phase. The organic phase typically contains a monomer of Formula 11, a monomer of Formula 22, a monomer of Formula 33, and a polymerization initiator. The aqueous phase contains a suspension stabilizer, a water soluble salt, water, and optionally a buffer. The organic phase and the aqueous phase are then combined and stirred under nitrogen. The mixture is generally heated to about 60°C to about 80°C for about 2.5 to about 3.5 hours, allowed to rise up to 95°C after polymerization is initiated, and then cooled to room temperature. After cooling, the aqueous phase is removed. Water is added to the mixture, the mixture is stirred, and the resulting solid is filtered. The solid is washed with water, alcohol or alcohol/water mixtures.

[00141] As described above, polymerization suspension stabilizers, such as polyvinyl alcohol, are used to prevent coalescence of particles during the polymerization process. Further, it has been observed that the addition of sodium chloride in the aqueous phase decreased coalescence and particle aggregation. Other suitable salts for this purpose include salts that are soluble in the aqueous phase. Water soluble salts are added at a concentration of from about 0.1 wt.% to about 10 wt.%, particularly from about 2 wt.% to about 5 wt.% and even more particularly from about 3 wt.% to about 4 wt.%.

[00142] Preferably, an organic phase of methyl 2-fluoroacrylate (90 wt.%), 1,7-octadiene (5 wt.%) and divinylbenzene (5 wt.%) is prepared and 0.5 wt.% of lauroyl peroxide is added to initiate the polymerization reaction. Additionally, an aqueous phase of water, polyvinyl alcohol, phosphates, sodium chloride, and sodium nitrite is prepared. Under nitrogen and while keeping the temperature below about 30°C, the aqueous and organic phases are mixed together. Once mixed completely, the reaction mixture is gradually heated with continuous stirring. After the polymerization reaction is initiated, the temperature of the reaction mixture is allowed to rise up to about 95°C. Once the polymerization reaction is complete, the reaction mixture is cooled to room temperature and the aqueous phase is removed. The solid can be isolated by filtration after water is added to the mixture. The resulting product is a crosslinked (methyl 2-fluoroacrylate)-divinylbenzene-1,7-octadiene terpolymer.

[00143] As discussed herein, after polymerization, the product may be hydrolyzed or otherwise deprotected by methods known in the art. For hydrolysis of the polymer having ester groups to form a polymer having carboxylic acid groups, preferably, the polymer is hydrolyzed with a strong base (e.g., NaOH, KOH, $Mg(OH)_2$, or $Ca(OH)_2$) to remove the alkyl (e.g., methyl) group and form the carboxylate salt. Depending on the pH of the hydrolysis mixture, the proton form of the (2-fluoroacrylic acid)-divinylbenzene-1,7-octadiene terpolymer is formed. Alternatively, the polymer can be hydrolyzed with a strong acid (e.g., HCl) to form the carboxylate salt. Preferably, the (methyl 2-fluoroacrylate)-divinylbenzene-1,7-octadiene terpolymer is hydrolyzed with an excess of aqueous sodium hydroxide solution at a temperature from about 30°C to about 100°C to yield (sodium 2-fluoroacrylate)-divinylbenzene-1,7-octadiene terpolymer. Typically, the hydrolysis reaction is carried out for about 15 to 25 hours. After hydrolysis, the solid is filtered and washed with water and/or an alcohol.

[00144] The cation of the polymer salt formed in the hydrolysis reaction or other deprotection step depends on the base used in that step. For example, when sodium hydroxide is used as the base, the sodium salt of the polymer is formed. This sodium ion can be exchanged for another cation by contacting the sodium salt with an excess of an aqueous metal salt to yield an insoluble solid of the desired polymer salt. After the desired ion exchange, the product is washed with an alcohol and/or water and dried directly or dried after a dewatering treatment with denatured alcohol; preferably, the product is washed with water and dried directly. For example, the sodium salt of the cation exchange polymer is converted to the calcium salt by washing with a solution that substitutes calcium for sodium, for example, by using calcium chloride, calcium acetate, calcium lactate gluconate, or a combination thereof. And, more

specifically, to exchange sodium ions for calcium ions, the (sodium 2-fluoroacrylate)-divinylbenzene-1,7-octadiene terpolymer is contacted with an excess of aqueous calcium chloride to yield an insoluble solid of crosslinked (calcium 2-fluoroacrylate)-divinylbenzene-1,7-octadiene terpolymer. If the pH of the hydrolysis mixture is sufficiently low, the proton form of the (2-fluoroacrylic acid)-divinylbenzene-1,7-octadiene terpolymer is formed.

[00145] Using this suspension polymerization process, a cross-linked polyMeFA polymer is isolated in good yield, generally above about 85%, more specifically above about 90%, and even more specifically above about 93%. The yield of the second step (i.e., hydrolysis) preferably occurs in 100%, providing an overall yield after hydrolysis of above about 85%, more specifically above about 90%, and even more specifically above about 93%.

[00146] To add the linear polyol to the composition, the salt of the polymer is slurried with an aqueous solution of polyol (e.g., sorbitol), typically with the slurry containing an excess amount of polyol based on polymer weight. Performing this step can reduce inorganic fluoride in the composition. The slurry is maintained under conditions known to those of skill in the art, such as for at least 3 hours and ambient temperature and pressure. The solids are then filtered off and dried to desired moisture content.

[00147] The methods of treatment of hypertension, hyperkalemia, and chronic kidney disease can be used for a variety of treatment periods including treatment periods of 1, 2, 4, 6, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, or more weeks. The treatment period can also be 2 years, 3 years, 4 years, 5 years, or more.

[00148] When treating the patients for hyperkalemia or chronic kidney disease using the methods of the invention, the patient can have an estimated glomerular filtration rate (eGFR) from about 15 mL/min/1.73 m^2 to about 44 mL/min/1.73 m^2.

[00149] The methods of treating hyperkalemia, methods of treating hypertension in a patient having chronic kidney disease, type 2 diabetes, heart failure or a combination thereof, and methods of treating chronic kidney disease of the invention can cause several improvements such as a decrease in the patient's serum potassium level after 48 hours, or more of treatment as compared to the patient's serum potassium level before treatment with the potassium-binding agent; an increase in the patient's eGFR after 2, 3, 4, 5, 6, months or more of treatment as compared to the patient's eGFR before treatment with the potassium-binding agent; a decrease in the patient's urine albumin:creatinine ratio (ACR) after 2, 3, 4, 5, 6, months or more of treatment as compared to the patient's urine ACR before treatment with the potassium-binding agent; a decrease in the patient's systolic and diastolic blood pressure after 1, 2, 3, 4, 5, 6, 7 days

or more of treatment as compared to the patient's systolic and diastolic blood pressure before treatment with the potassium-binding agent; a decrease in the patient's serum aldosterone level after 6, 12, 24, 48, 72, hours or more of treatment as compared to the patient's serum aldosterone level before treatment with the potassium-binding agent, or a combination thereof.

[00150] For the changes in serum potassium level, eGFR, blood pressure, and ACR, it is understood that the potassium-binding agent can be any one of the agents described herein even when the method is described relating to administration of 2-fluoroacrylate-divinylbenzene-1,7-octadiene copolymer crosslinked in the salt or acid form.

[00151] The methods of treating hyperkalemia in a chronic kidney disease patient in need thereof optionally being treated with an effective amount of a renin-angiotensin-aldosterone system (RAAS) agent comprise administering an effective amount of the potassium-binding agent to the patient and observing either (i) a decrease in the patient's serum creatinine level as compared to the patient's serum creatinine level before treatment with the potassium-binding agent, (ii) an increase in the time to progression of end stage renal disease as compared to a chronic kidney disease patient optionally treated with a RAAS agent but not treated with the potassium-binding agent, (iii) an increase in survival as compared to a chronic kidney disease patient optionally treated with a RAAS agent but not treated with the potassium-binding agent, or (iv) an increase or stabilization of estimated glomerular filtration rate (eGFR) as compared to the patient's eGFR before treatment with the potassium-binding agent, all indicating an increase or stabilization of the patient's kidney function.

[00152] The potassium-binding agent can be 2-fluoroacrylate-divinylbenzene-1,7-octadiene copolymer crosslinked in the salt or acid form.

[00153] The methods of treating hyperkalemia, methods of treating hypertension in a patient having chronic kidney disease, type 2 diabetes, heart failure or a combination thereof, and methods of treating chronic kidney disease can result in the patient's eGFR after treatment with the potassium-binding agent being increased by at least 4, 5, 6 mL/min/1.73 m^2 or more as compared to the patient's eGFR before treatment with the potassium-binding agent

[00154] When treating hypertension, hyperkalemia, or chronic kidney disease in patients in need thereof, the effective amount of the potassium-binding agent comprises up to a maximum daily dose of 60 grams. The effective amount of the potassium-binding agent can be a daily dose of from about 3 grams to about 60 grams; from about 5 grams to about 60 grams; from about 7 grams to about 60 grams; from about 10 grams to about 60 grams; from about 12 grams to about 60 grams; or from about 15 grams to about 60 grams.

[00155] The effective amount of the potassium-binding agent can be a daily dose of from about 3 grams to about 40 grams; from about 5 grams to about 40 grams; from about 10 grams to about 40 grams; or from about 15 grams to about 40 grams.

[00156] Particularly, the effective amount of the potassium-binding agent can be a daily dose of about 18 gram to about 60 grams or about 18 grams to about 40 grams.

[00157] When the potassium binding agent is 2-fluoroacrylate-divinylbenzene-1,7-octadiene copolymer crosslinked in the salt form, the dose in grams is calculated by determining the amount of the salt form of crosslinked 2-fluoroacrylate-divinylbenzene-1,7-octadiene copolymer plus the calcium counterion. So, this dose does not include the water and sorbitol that may be contained in the powder that is administered to the patient

[00158] Dosing can be once a day, twice a day or three times per day, however, once a day or twice a day is preferred, with once a day being most preferred.

[00159] The methods of treating hypertension, hyperkalemia, or chronic kidney disease of the invention can further comprise administering an effective amount of a renin-angiotensin-aldosterone system (RAAS) agent to the patient; determining the serum potassium level in the patient; and increasing the amount of the potassium-binding agent subsequently administered to the patient based on the serum potassium level if greater than or equal to 5.1 mEq/L. The methods of hypertension, hyperkalemia, or chronic kidney disease can further comprise a step wherein the amount of the potassium-binding agent was increased by 5 g or 10 g per day.

[00160] The methods of treating hypertension, hyperkalemia, or chronic kidney disease of the invention can further comprise administering an effective amount of a renin-angiotensin-aldosterone system (RAAS) agent to the patient; determining the serum potassium level in the patient; decreasing the amount of the potassium-binding agent subsequently administered to the patient based on the serum potassium level if less than 4.0 mEq/L. The method of treating hypertension, hyperkalemia, or chronic kidney disease can further comprise a step wherein the amount of the potassium-binding agent was decreased by 5 g or 10 g per day.

[00161] The methods hypertension, hyperkalemia, or chronic kidney disease of the invention can further comprise treating proteinuria.

[00162] Further, the methods of treating hypertension, hyperkalemia, proteinuria, or chronic kidney disease may include treating the patient with an effective amount of a RAAS agent, the RAAS agent being an angiotensin converting enzyme (ACE) inhibitor, an angiotensin receptor blocker (ARB), an aldosterone antagonist (AA), an aldosterone synthase inhibitor, or a

combination thereof. Particularly, the patient may be treated with an effective amount of a RAAS agent, the RAAS agent is an ACE inhibitor, an ARB, or a combination thereof.

[00163] For the methods where the patient is being treated with an effective amount of a RAAS agent, the effective amount of the RAAS agent comprises up to a maximum daily tolerated dose.

[00164] The RAAS agent comprises fosinopril, ramipril, captopril, lisinopril, trandolapril, moexipril, quinapril, enalapril, benazepril, perindopril, eprosartan, olmesartan, losartan, telmisartan, valsartan, candesartan, irbesartan, azilsartan medoxomil, spironolactone, eplerenone, or a combination thereof.

[00165] The maximum daily tolerated dose of specific RAAS agents is 4 mg/day (trandolapril), 8 mg/day (perindopril), 20 mg/day (ramipril), 30 mg/day (moexipril), 32 mg/day (candesartan), 40 mg/day (fosinopril, lisinopril, enalapril, benazepril, olmesartan), 80 mg/day (quinapril telmisartan, azilsartan, medoxomil), 100 mg/day (losartan), 300 mg/day (captopril, irbesartan), 320 mg/day (valsartan), or 800 mg/day (eprosartan).

[00166] When the RAAS agent comprises spironolactone, the maximum daily tolerated dose is 200 mg/day.

[00167] When the RAAS agent comprises eplerenone, the maximum daily tolerated dose is 50 mg/day.

[00168] Patients being treated with the methods of treating hypertension, hyperkalemia or chronic kidney disease of the invention can further be treated with an effective amount of a beta-adrenergic blocking agent. The beta-adrenergic blocking agent can comprise betaxolol, bisoprolol, atenolol, metoprolol, nebivolol, metoprolol, esmolol, acebutolol, propranolol, nadolol, carvedilol, labetalol, sotalol, timolol, carteolol, penbutolol, pindolol, or a combination thereof.

[00169] In all of the methods described above, the potassium-binding agent can be 2-fluoroacrylate-divinylbenzene-1,7-octadiene copolymer crosslinked in the salt or acid form.

[00170] The term "treating" as used herein includes achieving a therapeutic benefit. By therapeutic benefit is meant eradication, amelioration, or prevention of the underlying disorder being treated. For example, in a hyperkalemia patient, therapeutic benefit includes eradication or amelioration of the underlying hyperkalemia. Also, a therapeutic benefit is achieved with the eradication, amelioration, or prevention of one or more of the physiological symptoms associated with the underlying disorder such that an improvement is observed in the patient, notwithstanding that the patient may still be afflicted with the underlying disorder. For example,

administration of a potassium-binding polymer to a patient experiencing hyperkalemia provides therapeutic benefit not only when the patient's serum potassium level is decreased, but also when an improvement is observed in the patient with respect to other disorders that accompany hyperkalemia, like renal failure. In some treatment regimens, the crosslinked cation exchange polymer or composition of the invention may be administered to a patient at risk of developing hyperkalemia or to a patient reporting one or more of the physiological symptoms of hyperkalemia, even though a diagnosis of hyperkalemia may not have been made.

[00171] End stage renal disease is characterized by a patient being on dialysis or having a renal transplant.

[00172] Proteinuria, also known as albuminuria or urine albuminis, is a condition in which urine contains an abnormal amount of protein. Albumin is the main protein in the blood. Proteins are the building blocks for all body parts, including muscles, bones, hair, and nails. Proteins in the blood also perform a number of important functions. They protect the body from infection, help blood clot, and keep the right amount of fluid circulating throughout the body.

[00173] As blood passes through healthy kidneys, they filter out the waste products and leave in the things the body needs, like albumin and other proteins. Most proteins are too big to pass through the kidneys' filters into the urine. However, proteins from the blood can leak into the urine when the filters of the kidney, called glomeruli, are damaged.

[00174] Proteinuria is a sign of chronic kidney disease (CKD), which can result from diabetes, high blood pressure, and diseases that cause inflammation in the kidneys. For this reason, testing for albumin in the urine is part of a routine medical assessment for everyone. Kidney disease is sometimes called renal disease. If CKD progresses, it can lead to end-stage renal disease (ESRD), when the kidneys fail completely. A person with ESRD must receive a kidney transplant or regular blood-cleansing treatments called dialysis.

[00175] The potassium-binding polymers used in the methods of the invention can be administered as pharmaceutical compositions containing an effective amount, i.e., in an amount effective to achieve therapeutic or prophylactic benefit of the potassium-binding polymer and a pharmaceutically acceptable carrier. The actual amount effective for a particular application will depend on the patient (e.g., age, weight, etc.), the condition being treated, and the route of administration. Determination of an effective amount is well within the capabilities of those skilled in the art, especially in light of the disclosure herein. The effective amount for use in humans can be determined from animal models. For example, a dose for humans can be

formulated to achieve gastrointestinal concentrations that have been found to be effective in animals.

[00176] The polymers and compositions described herein can be used as food products and/or food additives. They can be added to foods prior to consumption or while packaging.

[00177] The polymers or pharmaceutically acceptable salts thereof, or compositions described herein, can be delivered to the patient using a wide variety of routes or modes of administration. The most preferred routes for administration are oral, intestinal, or rectal. Rectal routes of administration are known to those of skill in the art. Intestinal routes of administration generally refer to administration directly into a segment of the gastrointestinal tract, e.g., through a gastrointestinal tube or through a stoma. The most preferred route for administration is oral.

[00178] The polymers (or pharmaceutically acceptable salts thereof) may be administered per se or in the form of a pharmaceutical composition wherein the active compound(s) is in admixture or mixture with one or more pharmaceutically acceptable excipient. Pharmaceutical compositions for use in accordance with the present invention may be formulated in conventional manner using one or more pharmaceutically acceptable excipients comprising carriers, diluents, and auxiliaries which facilitate processing of the active compounds into preparations which can be used physiologically. Proper composition is dependent upon the route of administration chosen.

[00179] For oral administration, the polymers or compositions of the invention can be formulated readily by combining the polymer or composition with pharmaceutically acceptable excipients well known in the art. Such excipients enable the compositions of the invention to be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions, wafers, and the like, for oral ingestion by a patient to be treated.

[00180] The oral composition can not have an enteric coating.

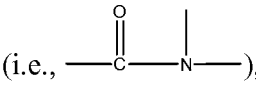
[00181] Pharmaceutical preparations for oral use can be obtained as a solid excipient, optionally grinding a resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients are, in particular, fillers such as sugars, including lactose or sucrose; cellulose preparations such as, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethyl-cellulose, sodium carboxymethylcellulose, and/or polyvinyl pyrrolidone (PVP); and various flavoring agents known in the art. If desired, disintegrating

agents may be added, such as the cross-linked polyvinyl pyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate.

[00182] The active ingredient (e.g., polymer) can constitute over about 20%, more particularly over about 40%, even more particularly over about 50%, and most particularly more than about 60% by weight of the oral dosage form, the remainder comprising suitable excipient(s). In compositions containing water and linear polyol, the polymer preferably constitutes over about 20%, more particularly over about 40%, and even more particularly over about 50% by weight of the oral dosage form.

[00183] The polymers of the invention can be provided as pharmaceutical compositions in the form of liquid compositions. The pharmaceutical composition can contain a polymer dispersed in a suitable liquid excipient. Suitable liquid excipients are known in the art; see, e.g., Remington's Pharmaceutical Sciences.

[00184] Unless otherwise indicated, an alkyl group as described herein alone or as part of another group is an optionally substituted linear saturated monovalent hydrocarbon radical containing from one to twenty carbon atoms and preferably one to eight carbon atoms, or an optionally substituted branched saturated monovalent hydrocarbon radical containing three to twenty carbon atoms, and preferably three to eight carbon atoms. Examples of unsubstituted alkyl groups include methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, n-pentyl, i-pentyl, s-pentyl, t-pentyl, and the like.

[00185] The term "amide moiety" as used herein represents a bivalent (i.e., difunctional) group including at least one amido linkage (i.e., ), such as -C(O)-NR_A-R_C-NR_B-C(O)- wherein R_A and R_B are independently hydrogen or alkyl and R_C is alkylene. For example, an amide moiety can be -C(O)-NH-$(CH_2)_p$-NH-C(O)- wherein p is an integer of 1 to 8.

[00186] The term "aryl" as used herein alone or as part of another group denotes an optionally substituted monovalent aromatic hydrocarbon radical, preferably a monovalent monocyclic or bicyclic group containing from 6 to 12 carbons in the ring portion, such as phenyl, biphenyl, naphthyl, substituted phenyl, substituted biphenyl or substituted naphthyl. Phenyl and substituted phenyl are the more preferred aryl groups. The term "aryl" also includes heteroaryl.

[00187] The terms "carboxylic acid group", "carboxylic" or "carboxyl" denote the monovalent radical -C(O)OH. Depending upon the pH conditions, the monovalent radical can

be in the form -C(O)O$^-$ Q$^+$ wherein Q$^+$ is a cation (e.g., sodium), or two of the monovalent radicals in close proximity can bond with a divalent cation Q^{2+} (e.g., calcium, magnesium), or a combination of these monovalent radicals and -C(O)OH are present.

[00188] The term "cycloalkyl" as used herein denotes optionally an optionally substituted cyclic saturated monovalent bridged or non-bridged hydrocarbon radical containing from three to eight carbon atoms in one ring and up to 20 carbon atoms in a multiple ring group. Exemplary unsubstituted cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, adamantyl, norbornyl, and the like.

[00189] The term "-ene" as used as a suffix as part of another group denotes a bivalent radical in which a hydrogen atom is removed from each of two terminal carbons of the group, or if the group is cyclic, from each of two different carbon atoms in the ring. For example, alkylene denotes a bivalent alkyl group such as methylene (-CH_2-) or ethylene (-CH_2CH_2-), and arylene denotes a bivalent aryl group such as o-phenylene, m-phenylene, or p-phenylene.

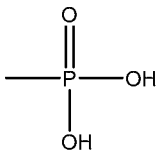
[00190] The term "ether moiety" as used herein represents a bivalent (i.e., difunctional) group including at least one ether linkage (i.e., -O-). For example, in Formulae 3 or 33 as defined herein, the ether moiety can be -R_AOR_B- or -$R_AOR_COR_B$- wherein R_A, R_B and R_C are independently alkylene.

[00191] The term "heteroaryl," as used herein alone or as part of another group, denotes an optionally substituted monovalent monocyclic or bicyclic aromatic radical of 5 to 10 ring atoms, where one or more, preferably one, two, or three, ring atoms are heteroatoms independently selected from N, O, and S, and the remaining ring atoms are carbon. Exemplary heteroaryl moieties include benzofuranyl, benzo[d]thiazolyl, isoquinolinyl, quinolinyl, thiophenyl, imidazolyl, oxazolyl, quinolinyl, furanyl, thazolyl, pyridinyl, furyl, thienyl, pyridyl, oxazolyl, pyrrolyl, indolyl, quinolinyl, isoquinolinyl, and the like.

[00192] The term "heterocyclo," as used herein alone or as part of another group, denotes a saturated or unsaturated monovalent monocyclic group of 4 to 8 ring atoms, in which one or two ring atoms are heteroatom(s), independently selected from N, O, and S, and the remaining ring atoms are carbon atoms. Additionally, the heterocyclic ring may be fused to a phenyl or heteroaryl ring, provided that the entire heterocyclic ring is not completely aromatic. Exemplary heterocyclo groups include the heteroaryl groups described above, pyrrolidino, piperidino, morpholino, piperazino, and the like.

[00193] The term "hydrocarbon" as used herein describes a compound or radical consisting exclusively of the elements carbon and hydrogen.

[00194] The term "phosphonic" or "phosphonyl" denotes the monovalent radical



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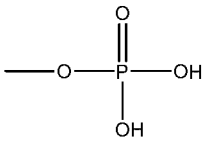
[00195] The term "phosphoric" or "phosphoryl" denotes the monovalent radical



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[00196] The term "protected" as used herein as part of another group denotes a group that blocks reaction at the protected portion of a compound while being easily removed under conditions that are sufficiently mild so as not to disturb other substituents of the compound. For example, a protected carboxylic acid group-$C(O)OP_g$ or a protected phosphoric acid group -$OP(O)(OH)OP_g$ or a protected phosphonic acid group -$P(O)(OH)OP_g$ each have a protecting group P_g associated with the oxygen of the acid group wherein P_g can be alkyl (e.g., methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, n-pentyl, i-pentyl, s-pentyl, t-pentyl, and the like), benzyl, silyl (e.g., trimethylsilyl (TMS), triethylsilyl (TES), triisopropylsilyl (TIPS), triphenylsilyl (TPS), t-butyldimethylsilyl (TBDMS), t-butyldiphenylsilyl (TBDPS) and the like. A variety of protecting groups and the synthesis thereof may be found in "Protective Groups in Organic Synthesis" by T.W. Greene and P.G.M. Wuts, John Wiley & Sons, 1999. When the term "protected" introduces a list of possible protected groups, it is intended that the term apply to every member of that group. That is, the phrase "protected carboxylic, phosphonic or phosphoric" is to be interpreted as "protected carboxylic, protected phosphonic or protected phosphoric." Likewise, the phrase "optionally protected carboxylic, phosphoric or phosphonic" is to be interpreted as "optionally protected carboxylic, optionally protected phosphonic or optionally protected phosphoric."

[00197] The term "substituted" as in "substituted aryl," "substituted alkyl," and the like, means that in the group in question (i.e., the alkyl, aryl or other group that follows the term), at least one hydrogen atom bound to a carbon atom is replaced with one or more substituent groups such as hydroxy (-OH), alkylthio, phosphino, amido (-$CON(R_A)(R_B)$, wherein R_A and R_B are independently hydrogen, alkyl, or aryl), amino(-$N(R_A)(R_B)$, wherein R_A and R_B are independently hydrogen, alkyl, or aryl), halo (fluoro, chloro, bromo, or iodo), silyl, nitro (-NO_2), an ether (-OR_A wherein R_A is alkyl or aryl), an ester (-$OC(O)R_A$ wherein R_A is alkyl or aryl),

keto (-C(O)R_A wherein R_A is alkyl or aryl), heterocyclo, and the like. When the term "substituted" introduces a list of possible substituted groups, it is intended that the term apply to every member of that group. That is, the phrase "optionally substituted alkyl or aryl" is to be interpreted as "optionally substituted alkyl or optionally substituted aryl."

[00198] Having described the invention in detail, it will be apparent that modifications and variations are possible without departing from the scope of the invention defined in the appended claims.

EXAMPLES

[00199] The following non-limiting examples are provided to further illustrate the present invention.

Example 1: Sorbitol-loaded, crosslinked (calcium 2-fluoroacrylate)-divinylbenzene-1,7-octadiene copolymer

[00200] Methyl 2-fluoroacrylate (MeFA) was purchased and was vacuum distilled before use. Divinylbenzene (DVB) was purchased from Aldrich, technical grade, 80%, mixture of isomers, and was used as received. 1,7-octadiene (ODE), lauroyl peroxide (LPO), polyvinyl alcohol (PVA) (typical molecular weight 85,000-146,000, 87-89% hydrolyzed), sodium chloride (NaCl), sodium phosphate dibasic heptahydrate ($Na_2HPO_4 \cdot 7H_2O$) and sodium phosphate monobasic monohydrate ($NaH_2PO_4 \cdot H_2O$) were purchased from commercial sources and used as received.

[00201] In an appropriately sized reactor with appropriate stirring and other equipment, a 90:5:5 weight ratio mixture of organic phase of monomers was prepared by mixing methyl 2-fluoroacrylate, 1,7-octadiene, and divinylbenzene. One-half part of lauroyl peroxide was added as an initiator of the polymerization reaction. A stabilizing aqueous phase was prepared from water, polyvinyl alcohol, phosphates, sodium chloride, and sodium nitrite. The aqueous and monomer phases were mixed together under nitrogen at atmospheric pressure, while maintaining the temperature below 30°C. The reaction mixture was gradually heated while stirring continuously. Once the polymerization reaction has started, the temperature of the reaction mixture was allowed to rise to a maximum of 95°C.

[00202] After completion of the polymerization reaction, the reaction mixture was cooled and the aqueous phase was removed. Water was added, the mixture was stirred, and the solid material was isolated by filtration. The solid was then washed with water to yield a

crosslinked (methyl 2-fluoroacrylate)-divinylbenzene-1,7-octadiene copolymer. The (methyl 2-fluoroacrylate)-divinylbenzene-1,7-octadiene copolymer was hydrolyzed with an excess of aqueous sodium hydroxide solution at 90 °C for 24 hours to yield (sodium 2-fluoroacrylate)-divinylbenzene-1,7-octadiene copolymer. After hydrolysis, the solid was filtered and washed with water. The (sodium 2-fluoroacrylate)-divinylbenzene-1,7-octadiene copolymer was exposed at room temperature to an excess of aqueous calcium chloride solution to yield insoluble cross-linked (calcium 2-fluoroacrylate)-divinylbenzene-1,7-octadiene copolymer.

[00203] After the calcium ion exchange, the wet polymer is slurried with 25-30 % w/w aqueous solution of sorbitol at ambient temperature to yield sorbitol-loaded polymer. Excess sorbitol was removed by filtration. The resulting polymer was dried at 20-30 °C until the desired moisture content (10-25 w/w/%) was reached. This provided a sorbitol-loaded, crosslinked (calcium 2-fluoroacrylate)-divinylbenzene-1,7-octadiene copolymer (5016CaS).

Example 2: Phase II Clinical Study

[00204] *Study Design Overview.* The study has two 5016CaS treatment periods: a treatment initiation period for 8 weeks, followed by a long-term maintenance period for an additional 44 weeks which allows treatment with 5016CaS for up to a total of one year (i.e., 52 weeks). Eligible non-hyperkalemic patients start a run-in period of 1 to 4 weeks in duration (Cohorts 1 and 2). Eligible hyperkalemic patients start treatment with 5016CaS immediately (Cohort 3). At the first occurrence of serum potassium (K^+) > 5.0 – < 6.0 mEq/L, eligible patients from all three cohorts are assigned to one of two strata according to baseline serum potassium and received 5016CaS treatment at randomly assigned starting doses ranging from 10 to 40 g/day. The dose amount is based on the amount of the polymer anion plus calcium (e.g., on a water and sorbitol free basis). A 10 g dose of polymer anion plus calcium is equivalent to an 8.4 g dose of the polymer anion. The study duration is up to 62 weeks per patient (including screening and follow-up procedures) and the study population is approximately 306 patients. The study variables included change in serum potassium, blood pressure, estimated GFR and ACR.

[00205] Eligible patients are assigned to one of two 5016CaS treatment strata wherein Stratum 1 includes patients with serum K^+ > 5.0 – 5.5 mEq/L, these patients are randomized in a 1:1:1 ratio to receive either 10 g/day, 20 g/day, or 30 g/day 5016CaS starting doses within each study cohort. Stratum 2 includes patients with serum K^+ > 5.5 – < 6.0 mEq/L, these patients are

randomized in a 1:1:1 ratio to receive 20 g/day, 30 g/day, or 40 g/day 5016CaS starting doses within each study cohort.

[00206] Patients start 5016CaS treatment at their assigned dose level on the evening of day 1. They continue taking losartan 100 mg/d (with or without spironolactone 25-50 mg/d) or pre-study ACEI and/or ARB with spironolactone 25-50 mg/d, (as per their Cohort 1 or 2 assignment), as well as any other protocol-allowed antihypertensive therapy. Patients in Cohort 3 continue their pre-study ACEI and/or ARB.

[00207] *Dose and Route of 5016CaS Administration.* 5016CaS was taken orally twice daily in equally divided doses for up to 52 weeks starting on day 1 (the evening dose only). Patients take 5016CaS twice a day with their regular meals (breakfast and dinner). The 5016CaS dose is adjusted as needed according to the appropriate titration algorithm (treatment initiation or long-term maintenance) starting on day 3 and up to the week 51 visit. The minimum allowed dose is 0 g/d (no 5016CaS dispensed) and the maximum dose is 60 g/d.

[00208] Figures 1-5 look at potassium reduction, blood pressure control, eGFR change and protein urea change by the following patient subtypes: (1) patients with any amount of protein in the urine (2) patients with microalbuminuria (3) patients with macroalbuminuria and (4) patients with stage 4 chronic kidney disease (CKD). Figure 1 shows that a serum potassium reduction was experienced by all of these patient types. Figures 2 and 3 showed blood pressure reductions and that 5016CaS was as effective in reducing blood pressure in all of the patient types. Figure 4 shows that there was no significant increase in protein urea levels in any of the patient types, so 5016CaS effectively stabilized the patient's protein excretion. Figure 5 shows that renal function appeared to stabilize in all patient types with a potential for improvement in renal function in patients with stage 4 CKD.

[00209] The study protocol was completed by 182 patients for the analysis following in this Example 2. A statistically significant number of these patients had an albumin creatinine ratio (ACR) of $\geq$ 30 mg/g and others had an ACR of > 300 mg/g and an estimated glomerular filtration rate (eGFR) of 15 to 44 mL/min/1.73 m^2 at baseline. For all of these patients, the patient's serum potassium concentration decreased from an average of 5.27 mEq/L at baseline to an average of 4.57 mEq/L at 24 weeks. For patients having an ACR $\geq$ 30 mg/g, the patient's serum potassium concentration decreased from an average of 5.28 mEq/L at baseline to an average of 4.60 mEq/L at 24 weeks. For patients having an ACR > 300 mg/g, the patient's serum potassium concentration decreased from an average of 5.35 mEq/L at baseline to an average of 4.65 mEq/L at 24 weeks. For patients having an eGFR of 15 to 44 mL/min/1.73 m^2,

the patient's serum potassium concentration decreased from an average of 5.33 mEq/L at baseline to an average of 4.59 mEq/L at 24 weeks.

[00210] For patients having an eGFR of 15 to 44 mL/min/1.73 m^2, the patient's eGFR increased from an average of 32 mL/min/1.73 m^2 at baseline to an average of 38 mL/min/1.73 m^2 at 24 weeks. This increase in eGFR for these patients was statistically significant.

[00211] For the patients in all groups and each group separately (e.g., ACR of $\geq$ 30 mg/g, ACR of > 300 mg/g, eGFR of 15 to 44 mL/min/1.73 m^2), the ACR did not significantly change over the 24 week treatment period.

[00212] For all of these patients, the patient's systolic blood pressure decreased from an average of 154 at baseline to an average of 137 at 24 weeks and the patient's diastolic blood pressure decreased from an average of 83 at baseline to an average of 74 at 24 weeks. For patients having an ACR $\geq$ 30 mg/g, the patient's systolic blood pressure decreased from an average of 154 at baseline to an average of 138 at 24 weeks and the patient's diastolic blood pressure decreased from an average of 84 at baseline to an average of 74 at 24 weeks. For patients having an ACR > 300 mg/g, the patient's systolic blood pressure decreased from an average of 154 at baseline to an average of 137 at 24 weeks and the patient's diastolic blood pressure decreased from an average of 86 at baseline to an average of 73 at 24 weeks. For patients having an eGFR of 15 to 44 mL/min/1.73 m^2, the patient's systolic blood pressure decreased from an average of 152 at baseline to an average of 135 at 24 weeks and the patient's diastolic blood pressure decreased from an average of 82 at baseline to an average of 73 at 24 weeks.

[00213] Figures 6-9 present one year data from a certain cohort of 90 patients with pre-existing hyperkalemia that were taking a stable dose of a RAAS inhibitor that came into the trial without a run-in period. These figures show that kidney function (Figure 6) and urinary protein excretion (Figure 8) appeared to stabilize, with reductions in serum potassium (Figure 7) and blood pressure (Figure 9). When analyzing the twelve month data for these patients, the average eGFR was 46 mL/min/1.73 m^2 at baseline (BL), 49 mL/min/1.73 m^2 at one month (M1), 51 mL/min/1.73 m^2 at two months (M2), 49 mL/min/1.73 m^2 at six months (M6) and 48 mL/min/1.73 m^2 at twelve months (M12) (Figure 6). The eGFR for these patients did not significantly change over the twelve month treatment period. These patients also experienced a significant decrease in serum potassium level. (Figure 7) For example, the average serum potassium level was 5.3 mEq/L at baseline (BL), 4.5 mEq/L at one month (M1), 4.5 mEq/L at two months (M2), 4.6 mEq/L at six months (M6), and 4.6 mEq/L at twelve months (M12).

These patients also had an average urine ACR of 853 mg/g at baseline (BL), 900 mg/g at one month (M1), 971 mg/g at two months (M2), 930 mg/g at six months (M6), and 802 mg/g at twelve months (M12). The average systolic blood pressure of these patients was 157 mmHg at baseline (BL), 138 mmHg at one month (M1), 139 mmHg at two months (M2), 138 mmHg at six months (M6), and 134 mmHg at twelve months (M12). The average diastolic blood pressure was 85 mmHg at baseline (BL), 74 mmHg at one month (M1), 73 mmHg at two months (M2), 73 mmHg at six months (M6), and 77 mmHg at twelve months (M12).

[00214] The mean change in serum potassium from baseline to week 4 or first dose titration, whichever comes first, is presented by stratum in Table 1. To be consistent with the study protocol, the most recent non-missing measurement of serum potassium was used for patients who did not titrate before the week 4 visit (last observation carried forward, i.e., LOCF). 5016CaS lowered serum potassium in all dose groups in both strata; the p-values indicate that the reduction is statistically significantly different from zero. The reference groups in both strata are the randomized starting doses chosen for the Phase III study.

Table 1. Estimated mean change from baseline in central serum K^+ to week 4 or first dose titration, by randomized starting dose withi stratum

At week 4 or prior to first titration	*Stratum 1 Local serum K^+ >5.0-5.5 mEq/L*				*Stratum 2 Local serum K^+ >5.5-<6.0 mEq/L*			
	10 g/d N=74	*20 g/d N=73*	*30 g/d N=73*	*Overall N=220*	*20 g/d N=26*	*30 g/d N=28*	*40 g/d N=30*	*Overall N=84*
Change in serum K^+ (mEq/L) from baseline								
n[a]	73	73	72	218	26	27	30	83
Least square mean ± standard error	-0.35 ± 0.066	-0.51 ± 0.066	-0.54 ± 0.066	-0.47 ± 0.038	-0.85 ± 0.136	-0.95 ± 0.132	-0.90 ± 0.127	-0.90 ± 0.076
95% confidence interval	-0.48, -0.22	-0.64, -0.38	-0.67, -0.41	-0.54, -0.39	-1.12, -0.58	-1.21, -0.68	-1.15, -0.65	-1.05, -0.75
p-value[b]	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
Comparison to reference								
Mean difference	reference	0.17	0.19		reference	0.097	0.050	
95% confidence interval		-0.018, 0.35	0.006, 0.37			-0.28, 0.48	-0.32, 0.42	
p-value[c]		0.076	0.043			0.61	0.79	

Column header counts include all randomized patients who received RLY5016 (intent-to-treat population) by each randomized starting dose within stratum. Each stratum is analyzed separately using a parallel lines analysis of covariance (ANCOVA) model where the outcome is change in serum K^+ from baseline. Each model contains a fixedeffect for randomized starting dose, cohort, and continuous baseline serum K^+. Estimates and confidence intervals for each randomized starting dose gives were generated using linear contrasts across the observed values of the covariates.

a Number of patients in the intent-to-treat population with non-missing baseline serum K^+ at baseline.

b p-values test the hypothesis that the mean change in serum K^+ from baseline is 0.

c p-values test the pairwise difference in change in serum K^+ from baseline between dose groups. Positive values indicate lager reduction from baseline as compared to the reference group.

[00215] 5016CaS lowered serum potassium in all dose groups in both strata regardless of dose titration beginning as early as Day 3 and stabilizing after approximately Week 2. Most patients were able to maintain serum potassium before and after dose titration in the range of 4.0 mEq/L to 5.0 mEq/L in all dose groups in both strata.

[00216] The primary outcome, mean change from baseline in serum K (mEq/L) at week 4 or first 5016CaS dose titration analyzed using a parallel lines ANCOVA model, was -0.47±0.038 ($p<0.001$) in S1 and -0.90±0.076 ($p<0.001$) in S2. Mean K reduction after a median 2 days of treatment was -0.29±0.03 (S1) and -0.55±0.05 mEq/L (S2). Table 2 summarizes the means and changes from baseline, allowing titration.

Table 2.

	Stratum 1 ((S1), BL K>5.0-5.5 mEq/L)			Stratum 2 ((S2), BL K>5.5-<6.0 mEq/L)		
	Baseline (n=217)	Week 4 (n=197)	Week 8 (n=185)	Baseline (N=84)	Week 4 (n=70)	Week 8 (n=70)
Mean K (SE) (mEq/L)	5.15 (0.02)	4.54 (0.03)	4.59 (0.03)	5.64 (0.04)	4.65 (0.06)	4.52 (0.06)
LS Mean change (SE) (mEq/L)	_	-0.61 (0.03)	-0.55 (0.03)	_	-0.97 (0.06)	-1.10 (0.06)

[00217] 5016CaS reduced serum K within days of treatment initiation, an effect sustained over twelve months without significant adverse effects.

Example 3: Analysis of Systolic Blood Pressure from Phase II Clinical Study

[00218] The following section contains results of the repeated measures analyses of mean systolic blood pressure during the 8-week treatment initiation period of the Phase II Clinical Study disclosed in Example 2. Table 3 through Table 6 present the analyses of mean change from baseline. Tables 3 and 4 present the results for all patients; Tables 5 and 6 present subsets of the analyses according to hyperkalemia status at screening (Cohort 3).In general, patients in Stratum 2 (patients with serum $K^+ > 5.5 - < 6.0$ mEq/L) experience smaller mean decreases in blood pressure than patients in Stratum 1 (patients with serum $K^+ > 5.0 - 5.5$ mEq/L). Patients in Cohort 3, who entered the study hyperkalemic and did not participate in the run-in phase, contributed to the reduction in mean systolic blood pressure (Tables 5 and 6) .

[00219] For Tables 3-6, column header counts include all randomized patients who received RLY5016 (intent-to-treat population) by each randomized starting dose within stratum. The data were derived from a mixed model for repeated measures where the outcome variable was a change in systolic blood pressure (SBP) from baseline. Each stratum was analyzed separately. Each model contained a fixed effect for cohort, randomized starting dose, time

(visit), continuous baseline SBP, and randomized starting dose by visit interaction. The within-patient correlation was modeled using heterogeneous Toeplitz structure. Estimates, standard errors (SE), and confidence intervals for each randomized starting dose were generated using linear contrasts across the observed values of the covariates. Overall estimates, standard errors, and confidence intervals across randomized dosing groups assume equal distribution across dosing groups. The total patients in the analysis, N, were determined by the number of randomized patients who received RLY5016, had a baseline measure, and contributed at least one post-baseline measure to this analysis. Not all patients contributed measures at each visit.

Table 3. Estimated mean change from baseline in systolic blood pressure by randomized starting dose, all patients Stratum 1

	Stratum 1 - Local serum K+ >5.0-5.5 mEq/L			
Change in SBP from baseline (mmHg)	*10 g/d N=74*	*20 g/d N=73*	*30 g/d N=73*	*Overall N=220*
Patients in analysis, N	74	73	73	220
Day 3, n	70	70	72	212
Least squares mean ± SE	-9.3 ± 1.8	-4.9 ± 1.8	-10.3 ± 1.8	-8.2 ± 1.0
95% confidence interval	-12.8, -5.7	-8.5, -1.4	-13.9, -6.8	-10.2, -6.1
Week 1, n	72	71	72	215
Least squares mean ± SE	-11.1 ± 1.9	-8.8 ± 2.0	-12.0 ± 1.9	-10.6 ± 1.1
95% confidence interval	-14.9, -7.3	-12.6, -4.9	-15.8, -8.2	-12.8, -8.4
Week 2, n	70	70	71	211
Least squares mean ± SE	-12.4 ± 2.0	-5.7 ± 2.0	-13.8 ± 2.0	-10.6 ± 1.1
95% confidence interval	-16.3, -8.5	-9.6, -1.8	-17.7, -9.9	-12.9, -8.4
Week 3, n	64	69	71	204
Least squares mean ± SE	-11.5 ± 2.1	-7.5 ± 2.0	-12.5 ± 2.0	-10.5 ± 1.2
95% confidence interval	-15.6, -7.4	-11.5, -3.5	-16.4, -8.6	-12.8, -8.2
Week 4, n	65	67	69	201
Least squares mean ± SE	-13.3 ± 2.0	-8.0 ± 2.0	-12.4 ± 2.0	-11.2 ± 1.1
95% confidence interval	-17.2, -9.3	-11.9, -4.1	-16.2, -8.5	-13.5, -9.0
Week 5, n	65	66	67	198
Least squares mean ± SE	-12.0 ± 2.0	-9.6 ± 2.0	-13.7 ± 2.0	-11.8 ± 1.2
95% confidence interval	-15.9, -8.0	-13.5, -5.7	-17.7, -9.8	-14.0, -9.5
Week 6, n	65	66	64	195
Least squares mean ± SE	-13.3 ± 2.1	-6.9 ± 2.0	-12.8 ± 2.1	-11.0 ± 1.2
95% confidence interval	-17.3, -9.3	-10.9, -2.9	-16.8, -8.7	-13.3, -8.7
Week 7, n	64	64	65	193
Least squares mean ± SE	-15.6 ± 2.0	-9.5 ± 2.0	-11.0 ± 2.0	-12.0 ± 1.2
95% confidence interval	-19.5, -11.6	-13.6, -5.5	-15.0, -7.0	-14.3, -9.7
Week 8, n	66	64	66	196
Least squares mean ± SE	-16.3 ± 2.0	-12.0 ± 2.0	-13.8 ± 2.0	-14.0 ± 1.1
95% confidence interval	-20.2, -12.5	-15.9, -8.1	-17.7, -10.0	-16.3, -11.8

Table 4. Estimated mean change from baseline in systolic blood pressure by randomized starting dose, all patients Stratum 2

	Stratum 2 - Local serum K+ >5.5-<6.0 mEq/L			
Change in SBP from baseline (mmHg)	*20 g/d N=26*	*30 g/d N=28*	*40 g/d N=30*	*Overall N=84*
Patients in analysis, N	26	28	29	83
Day 3, n	26	27	29	82
Least squares mean ± SE	-7.3 ± 3.5	-9.6 ± 3.4	-6.6 ± 3.3	-7.8 ± 2.0
95% confidence interval	-14.2, -0.4	-16.3, -2.9	-13.1, -0.08	-11.7, -4.0
Week 1, n	24	28	28	80
Least squares mean ± SE	-6.2 ± 4.2	-11.5 ± 3.9	-4.8 ± 3.9	-7.5 ± 2.3
95% confidence interval	-14.4, 1.9	-19.2, -3.9	-12.5, 2.8	-12.1, -3.0
Week 2, n	24	27	26	77
Least squares mean ± SE	-5.8 ± 4.2	-7.7 ± 4.0	-3.3 ± 4.0	-5.6 ± 2.4
95% confidence interval	-14.2, 2.5	-15.6, 0.2	-11.3, 4.6	-10.3, -1.0
Week 3, n	24	25	25	74
Least squares mean ± SE	-12.0 ± 3.8	-10.0 ± 3.6	-8.3 ± 3.6	-10.1 ± 2.1
95% confidence interval	-19.4, -4.6	-17.2, -2.9	-15.5, -1.2	-14.3, -5.9
Week 4, n	24	25	24	73
Least squares mean ± SE	-9.6 ± 3.1	-10.7 ± 3.0	-3.8 ± 3.0	-8.1 ± 1.7
95% confidence interval	-15.7, -3.5	-16.6, -4.9	-9.7, 2.1	-11.5, -4.6
Week 5, n	24	25	23	72
Least squares mean ± SE	-8.3 ± 3.6	-9.4 ± 3.5	-6.0 ± 3.5	-7.9 ± 2.0
95% confidence interval	-15.3, -1.2	-16.2, -2.7	-13.0, 0.9	-11.9, -3.9
Week 6, n	24	25	22	71
Least squares mean ± SE	-7.5 ± 3.6	-11.4 ± 3.4	-5.4 ± 3.6	-8.1 ± 2.0
95% confidence interval	-14.5, -0.5	-18.1, -4.6	-12.4, 1.6	-12.1, -4.1
Week 7, n	24	25	22	71
Least squares mean ± SE	-10.4 ± 3.4	-8.4 ± 3.3	-1.3 ± 3.4	-6.7 ± 1.9
95% confidence interval	-17.1, -3.7	-14.8, -1.9	-8.0, 5.4	-10.5, -2.9
Week 8, n	24	26	24	74
Least squares mean ± SE	-7.8 ± 3.5	-11.0 ± 3.4	-1.7 ± 3.5	-6.9 ± 2.0
95% confidence interval	-14.8, -0.9	-17.6, -4.4	-8.5, 5.1	-10.8, -3.0

Table 5. Estimated mean change from baseline in systolic blood pressure by randomized starting dose, patients who were hyperkalemic at screening Stratum 1

	Stratum 1 - Local serum K+ >5.0-5.5 mEq/L			
Change in SBP from baseline (mmHg)	*10 g/d N=57*	*20 g/d N=57*	*30 g/d N=56*	*Overall N=170*
Patients in analysis, N	57	57	56	170
Day 3, n	56	56	56	168
Least squares mean ± SE	-9.8 ± 2.0	-5.6 ± 2.0	-12.5 ± 2.0	-9.3 ± 1.2
95% confidence interval	-13.8, -5.8	-9.6, -1.6	-16.5, -8.5	-11.6, -7.0
Week 1, n	55	55	55	165
Least squares mean ± SE	-11.4 ± 2.2	-9.9 ± 2.2	-12.7 ± 2.2	-11.3 ± 1.3
95% confidence interval	-15.7, -7.1	-14.2, -5.6	-16.9, -8.4	-13.8, -8.9
Week 2, n	54	54	54	162
Least squares mean ± SE	-12.3 ± 2.3	-5.8 ± 2.3	-15.2 ± 2.3	-11.1 ± 1.3
95% confidence interval	-16.8, -7.8	-10.3, -1.3	-19.8, -10.7	-13.7, -8.5
Week 3, n	49	53	54	156
Least squares mean ± SE	-11.6 ± 2.5	-10.2 ± 2.4	-13.8 ± 2.4	-11.9 ± 1.4
95% confidence interval	-16.4, -6.7	-14.9, -5.5	-18.5, -9.1	-14.6, -9.1
Week 4, n	51	52	53	156
Least squares mean ± SE	-13.4 ± 2.3	-10.8 ± 2.3	-14.2 ± 2.3	-12.8 ± 1.3
95% confidence interval	-18.0, -8.8	-15.4, -6.3	-18.7, -9.7	-15.4, -10.2
Week 5, n	50	51	53	154
Least squares mean ± SE	-11.4 ± 2.3	-10.5 ± 2.3	-15.0 ± 2.3	-12.3 ± 1.3
95% confidence interval	-16.0, -6.8	-15.1, -5.9	-19.5, -10.5	-14.9, -9.7
Week 6, n	50	51	52	153
Least squares mean ± SE	-12.3 ± 2.2	-6.8 ± 2.2	-15.0 ± 2.2	-11.4 ± 1.3
95% confidence interval	-16.6, -7.9	-11.1, -2.5	-19.3, -10.7	-13.8, -8.9
Week 7, n	50	49	52	151
Least squares mean ± SE	-14.5 ± 2.1	-9.0 ± 2.1	-13.2 ± 2.1	-12.2 ± 1.2
95% confidence interval	-18.6, -10.3	-13.2, -4.8	-17.3, -9.1	-14.6, -9.8
Week 8, n	51	49	52	152
Least squares mean ± SE	-16.6 ± 2.2	-13.0 ± 2.3	-14.9 ± 2.2	-14.8 ± 1.3
95% confidence interval	-21.0, -12.3	-17.4, -8.6	-19.2, -10.5	-17.3, -12.3

Table 6. Estimated mean change from baseline in systolic blood pressure by randomized starting dose, patients who were hyperkalemic at screening Stratum 2

	Stratum 2 - Local serum K^+ >5.5-<6.0 mEq/L			
Change in SBP from baseline (mmHg)	*20 g/d N=24*	*30 g/d N=24*	*40 g/d N=25*	*Overall N=73*
Patients in analysis, N	24	24	24	72
Day 3, n	24	23	24	71
Least squares mean ± SE	-10.2 ± 3.6	-11.2 ± 3.7	-6.5 ± 3.7	-9.3 ± 2.1
95% confidence interval	-17.3, -3.0	-18.5, -3.9	-13.6, 0.7	-13.4, -5.1
Week 1, n	22	24	23	69
Least squares mean ± SE	-8.4 ± 4.4	-13.8 ± 4.3	-2.1 ± 4.3	-8.1 ± 2.5
95% confidence interval	-17.0, 0.3	-22.2, -5.4	-10.7, 6.4	-13.0, -3.2
Week 2, n	22	23	21	66
Least squares mean ± SE	-8.0 ± 4.3	-10.4 ± 4.2	-0.3 ± 4.3	-6.2 ± 2.5
95% confidence interval	-16.4, 0.4	-18.6, -2.1	-8.8, 8.2	-11.1, -1.4
Week 3, n	22	21	20	63
Least squares mean ± SE	-14.1 ± 3.9	-12.8 ± 3.9	-6.7 ± 4.0	-11.2 ± 2.3
95% confidence interval	-21.7, -6.4	-20.5, -5.1	-14.5, 1.2	-15.6, -6.7
Week 4, n	22	21	19	62
Least squares mean ± SE	-12.0 ± 3.2	-13.6 ± 3.2	-4.0 ± 3.3	-9.9 ± 1.9
95% confidence interval	-18.3, -5.8	-19.9, -7.3	-10.6, 2.5	-13.5, -6.2
Week 5, n	22	21	18	61
Least squares mean ± SE	-10.1 ± 3.7	-12.9 ± 3.8	-4.1 ± 4.0	-9.1 ± 2.2
95% confidence interval	-17.5, -2.8	-20.3, -5.5	-11.9, 3.7	-13.4, -4.7
Week 6, n	22	21	17	60
Least squares mean ± SE	-9.9 ± 3.5	-14.2 ± 3.6	-2.1 ± 3.8	-8.7 ± 2.1
95% confidence interval	-16.8, -3.0	-21.2, -7.2	-9.6, 5.5	-12.9, -4.6
Week 7, n	22	21	17	60
Least squares mean ± SE	-12.7 ± 3.5	-11.9 ± 3.5	1.9 ± 3.8	-7.6 ± 2.1
95% confidence interval	-19.5, -5.9	-18.8, -5.0	-5.5, 9.4	-11.6, -3.5
Week 8, n	22	22	19	63
Least squares mean ± SE	-11.4 ± 3.6	-14.4 ± 3.5	-0.3 ± 3.8	-8.7 ± 2.1
95% confidence interval	-18.4, -4.4	-21.3, -7.4	-7.7, 7.1	-12.8, -4.6

Example 4: Analysis of Diastolic Blood Pressure from Phase II Clinical Study

[00220] This section contains results of the repeated measures analyses of diastolic blood pressure during the 8-week treatment initiation period of the Phase II Clinical Study disclosed in Example 2. Table 7 through Table 10 present the analyses of mean change in diastolic blood pressure from baseline. Tables 7 and 8 present the results for all patients; Tables 9 and 10 present subsets of the analyses according to hyperkalemia status at screening (Cohort 3). Patients in both cohorts and strata experienced modest mean reductions in diastolic blood pressure.

[00221] For Tables 7-10, column header counts include all randomized patients who received RLY5016 (intent-to-treat population) by each randomized starting dose within stratum. The data were derived from a mixed model for repeated measures where the outcome variable was a change in diastolic blood pressure (DBP) from baseline. Each stratum was analyzed separately. Each model contained a fixed effect for cohort, randomized starting dose, time (visit), continuous baseline DBP, and randomized starting dose by visit interaction. The within-patient correlation was modeled using heterogeneous Toeplitz structure. Estimates, standard errors (SE), and confidence intervals for each randomized starting dose were generated using linear contrasts across the observed values of the covariates. Overall estimates, standard errors, and confidence intervals across randomized dosing groups assume equal distribution across dosing groups. The total patients in the analysis, N, were determined by the number of randomized patients who received RLY5016, had a baseline measure, and contributed at least one post-baseline measure to this analysis. Not all patients contributed measures at each visit.

Table 7. Estimated mean change from baseline in diastolic blood pressure by randomized starting dose, all patients Stratum 1

	Stratum 1 - Local serum K^+ >5.0-5.5 mEq/L			
Change in DBP from baseline (mmHg)	*10 g/d N=74*	*20 g/d N=73*	*30 g/d N=73*	*Overall N=220*
Patients in analysis, N	74	73	73	220
Day 3, n	70	70	72	212
Least squares mean ± SE	-3.8 ± 1.1	-3.1 ± 1.1	-5.8 ± 1.1	-4.2 ± 0.6
95% confidence interval	-6.0, -1.7	-5.2, -1.0	-7.9, -3.7	-5.5, -3.0
Week 1, n	72	71	72	215
Least squares mean ± SE	-6.0 ± 1.2	-5.4 ± 1.2	-7.0 ± 1.2	-6.1 ± 0.7
95% confidence interval	-8.3, -3.7	-7.7, -3.1	-9.3, -4.7	-7.4, -4.8
Week 2, n	70	70	71	211
Least squares mean ± SE	-6.6 ± 1.3	-6.1 ± 1.3	-6.1 ± 1.3	-6.3 ± 0.7
95% confidence interval	-9.0, -4.1	-8.6, -3.6	-8.6, -3.7	-7.7, -4.8
Week 3, n	64	69	71	204
Least squares mean ± SE	-5.0 ± 1.2	-6.0 ± 1.2	-8.0 ± 1.2	-6.3 ± 0.7
95% confidence interval	-7.4, -2.5	-8.4, -3.6	-10.4, -5.7	-7.7, -4.9
Week 4, n	65	67	69	201
Least squares mean ± SE	-5.8 ± 1.2	-6.5 ± 1.2	-8.0 ± 1.2	-6.7 ± 0.7
95% confidence interval	-8.1, -3.4	-8.8, -4.1	-10.3, -5.7	-8.1, -5.4
Week 5, n	65	66	67	198
Least squares mean ± SE	-6.0 ± 1.3	-5.9 ± 1.3	-8.4 ± 1.3	-6.8 ± 0.7
95% confidence interval	-8.6, -3.5	-8.5, -3.4	-10.9, -5.9	-8.2, -5.3
Week 6, n	65	66	64	195
Least squares mean ± SE	-5.7 ± 1.3	-6.4 ± 1.3	-6.6 ± 1.3	-6.2 ± 0.8
95% confidence interval	-8.3, -3.1	-9.0, -3.8	-9.2, -4.0	-7.7, -4.8
Week 7, n	64	64	65	193
Least squares mean ± SE	-6.3 ± 1.4	-6.0 ± 1.4	-6.5 ± 1.3	-6.3 ± 0.8
95% confidence interval	-8.9, -3.6	-8.7, -3.4	-9.2, -3.9	-7.8, -4.8
Week 8, n	66	64	66	196
Least squares mean ± SE	-7.6 ± 1.4	-7.3 ± 1.4	-6.8 ± 1.4	-7.2 ± 0.8
95% confidence interval	-10.3, -4.9	-10.1, -4.6	-9.5, -4.1	-8.8, -5.7

Table 8. Estimated mean change from baseline in diastolic blood pressure by randomized starting dose, all patients Stratum 2

	Stratum 2 - Local serum K^+ >5.5-<6.0 mEq/L			
Change in DBP from baseline (mmHg)	*20 g/d N=26*	*30 g/d N=28*	*40 g/d N=30*	*Overall N=84*
Patients in analysis, N	26	28	29	83
Day 3, n	26	27	29	82
Least squares mean ± SE	-1.7 ± 2.0	-3.9 ± 2.0	-5.4 ± 1.9	-3.7 ± 1.1
95% confidence interval	-5.6, 2.3	-7.8, -0.08	-9.1, -1.7	-5.9, -1.5
Week 1, n	24	28	28	80
Least squares mean ± SE	-1.4 ± 2.5	-5.3 ± 2.4	-4.4 ± 2.3	-3.7 ± 1.4
95% confidence interval	-6.4, 3.5	-9.9, -0.7	-9.0, 0.2	-6.4, -1.0
Week 2, n	24	27	26	77
Least squares mean ± SE	-7.2 ± 2.0	-3.0 ± 1.9	-5.5 ± 1.9	-5.3 ± 1.1
95% confidence interval	-11.2, -3.3	-6.8, 0.8	-9.4, -1.7	-7.5, -3.0
Week 3, n	24	25	25	74
Least squares mean ± SE	-7.0 ± 2.1	-7.1 ± 2.0	-5.9 ± 2.0	-6.7 ± 1.2
95% confidence interval	-11.1, -2.8	-11.1, -3.1	-9.9, -1.9	-9.0, -4.3
Week 4, n	24	25	24	73
Least squares mean ± SE	-7.7 ± 2.2	-6.3 ± 2.2	-1.9 ± 2.2	-5.3 ± 1.3
95% confidence interval	-12.1, -3.3	-10.6, -2.0	-6.2, 2.4	-7.8, -2.8
Week 5, n	24	25	23	72
Least squares mean ± SE	-8.2 ± 1.8	-6.8 ± 1.8	-4.4 ± 1.8	-6.5 ± 1.0
95% confidence interval	-11.8, -4.7	-10.3, -3.4	-8.0, -0.9	-8.5, -4.5
Week 6, n	24	25	22	71
Least squares mean ± SE	-7.1 ± 2.0	-8.9 ± 2.0	-4.3 ± 2.0	-6.8 ± 1.2
95% confidence interval	-11.1, -3.1	-12.8, -5.1	-8.4, -0.3	-9.1, -4.5
Week 7, n	24	25	22	71
Least squares mean ± SE	-7.3 ± 1.9	-9.0 ± 1.8	-3.4 ± 1.9	-6.6 ± 1.1
95% confidence interval	-10.9, -3.6	-12.6, -5.4	-7.1, 0.3	-8.7, -4.5
Week 8, n	24	26	24	74
Least squares mean ± SE	-4.5 ± 2.1	-7.0 ± 2.0	-1.8 ± 2.0	-4.4 ± 1.2
95% confidence interval	-8.5, -0.4	-10.9, -3.1	-5.8, 2.2	-6.7, -2.1

Table 9. Estimated mean change from baseline in diastolic blood pressure by randomized starting dose, patients who were hyperkalemic at screening Stratum 1

	Stratum 1 - Local serum K^+ >5.0-5.5 mEq/L			
Change in DBP from baseline (mmHg)	*10 g/d N=57*	*20 g/d N=57*	*30 g/d N=56*	*Overall N=170*
Patients in analysis, N	57	57	56	170
Day 3, n	56	56	56	168
Least squares mean ± SE	-3.7 ± 1.3	-4.5 ± 1.3	-7.1 ± 1.3	-5.1 ± 0.7
95% confidence interval	-6.1, -1.2	-7.0, -2.0	-9.6, -4.6	-6.5, -3.7
Week 1, n	55	55	55	165
Least squares mean ± SE	-5.8 ± 1.3	-6.6 ± 1.3	-7.5 ± 1.3	-6.6 ± 0.8
95% confidence interval	-8.4, -3.2	-9.2, -3.9	-10.2, -4.9	-8.1, -5.1
Week 2, n	54	54	54	162
Least squares mean ± SE	-7.1 ± 1.5	-7.4 ± 1.5	-6.5 ± 1.5	-7.0 ± 0.9
95% confidence interval	-10.0, -4.1	-10.4, -4.5	-9.5, -3.6	-8.7, -5.3
Week 3, n	49	53	54	156
Least squares mean ± SE	-5.2 ± 1.5	-7.4 ± 1.4	-9.7 ± 1.4	-7.4 ± 0.8
95% confidence interval	-8.1, -2.2	-10.2, -4.5	-12.5, -6.8	-9.0, -5.7
Week 4, n	51	52	53	156
Least squares mean ± SE	-5.6 ± 1.4	-8.5 ± 1.4	-10.0 ± 1.3	-8.0 ± 0.8
95% confidence interval	-8.2, -2.9	-11.2, -5.9	-12.6, -7.3	-9.6, -6.5
Week 5, n	50	51	53	154
Least squares mean ± SE	-6.5 ± 1.5	-8.3 ± 1.5	-9.5 ± 1.4	-8.1 ± 0.8
95% confidence interval	-9.4, -3.6	-11.1, -5.4	-12.3, -6.7	-9.7, -6.4
Week 6, n	50	51	52	153
Least squares mean ± SE	-5.6 ± 1.5	-7.3 ± 1.5	-7.7 ± 1.5	-6.8 ± 0.9
95% confidence interval	-8.6, -2.6	-10.3, -4.3	-10.7, -4.7	-8.6, -5.1
Week 7, n	50	49	52	151
Least squares mean ± SE	-5.5 ± 1.6	-7.1 ± 1.6	-7.7 ± 1.5	-6.8 ± 0.9
95% confidence interval	-8.6, -2.4	-10.2, -4.0	-10.8, -4.7	-8.5, -5.0
Week 8, n	51	49	52	152
Least squares mean ± SE	-7.2 ± 1.6	-8.1 ± 1.6	-8.1 ± 1.6	-7.8 ± 0.9
95% confidence interval	-10.4, -4.1	-11.4, -4.9	-11.3, -5.0	-9.7, -6.0

Table 10. Estimated mean change from baseline in diastolic blood pressure by randomized starting dose, patients who were hyperkalemic at screening Stratum 2

	Stratum 2 - Local serum K^+ >5.5-<6.0 mEq/L			
Change in DBP from baseline (mmHg)	*20 g/d N=24*	*30 g/d N=24*	*40 g/d N=25*	*Overall N=73*
Patients in analysis, N	24	24	24	72
Day 3, n	24	23	24	71
Least squares mean ± SE	-1.6 ± 2.2	-4.1 ± 2.2	-5.9 ± 2.2	-3.9 ± 1.3
95% confidence interval	-5.9, 2.6	-8.5, 0.3	-10.1, -1.6	-6.4, -1.4
Week 1, n	22	24	23	69
Least squares mean ± SE	-1.5 ± 2.7	-6.4 ± 2.7	-4.4 ± 2.7	-4.1 ± 1.6
95% confidence interval	-6.9, 3.9	-11.6, -1.2	-9.7, 0.9	-7.2, -1.1
Week 2, n	22	23	21	66
Least squares mean ± SE	-7.7 ± 2.2	-4.0 ± 2.2	-4.7 ± 2.2	-5.5 ± 1.3
95% confidence interval	-12.0, -3.4	-8.3, 0.2	-9.0, -0.3	-7.9, -3.0
Week 3, n	22	21	20	63
Least squares mean ± SE	-7.2 ± 2.3	-7.6 ± 2.3	-6.9 ± 2.3	-7.2 ± 1.3
95% confidence interval	-11.7, -2.7	-12.1, -3.1	-11.5, -2.3	-9.9, -4.6
Week 4, n	22	21	19	62
Least squares mean ± SE	-8.0 ± 2.4	-6.9 ± 2.5	-2.6 ± 2.6	-5.8 ± 1.4
95% confidence interval	-12.7, -3.2	-11.7, -2.0	-7.6, 2.4	-8.6, -3.0
Week 5, n	22	21	18	61
Least squares mean ± SE	-8.6 ± 1.9	-7.3 ± 2.0	-5.1 ± 2.1	-7.0 ± 1.1
95% confidence interval	-12.4, -4.9	-11.2, -3.5	-9.1, -1.0	-9.3, -4.8
Week 6, n	22	21	17	60
Least squares mean ± SE	-7.6 ± 2.1	-10.0 ± 2.2	-4.8 ± 2.3	-7.5 ± 1.3
95% confidence interval	-11.8, -3.4	-14.2, -5.8	-9.3, -0.2	-10.0, -5.0
Week 7, n	22	21	17	60
Least squares mean ± SE	-7.5 ± 2.0	-9.4 ± 2.1	-3.0 ± 2.2	-6.6 ± 1.2
95% confidence interval	-11.5, -3.5	-13.5, -5.4	-7.4, 1.4	-9.0, -4.3
Week 8, n	22	22	19	63
Least squares mean ± SE	-4.8 ± 2.2	-8.6 ± 2.2	-2.1 ± 2.3	-5.2 ± 1.3
95% confidence interval	-9.1, -0.4	-12.9, -4.3	-6.7, 2.5	-7.7, -2.6

Example 5: Study of Relationship Between Serum Potassium and Serum Aldosterone Levels

[00222] Male, unilaterally nephrectomized, spontaneously hypertensive rats (SHR) (N=32) were used in the experimental groups in this study. Non-manipulated SHR (N=6) were

used as a control group. Animals were acclimated on a low Ca^{2+} and Mg^{2+} diet (TD04498) for two weeks. The diet for the experimental groups was then switched to one supplemented with spironolactone (0.4% w/w, TD120436) and the drinking water was supplemented with amiloride (0.05 mM) and quinapril (30 mg/L) for the duration of the study.

[00223] Animals in the control group remained on the TD04498 diet and unsupplemented water for the duration of the study.

[00224] A baseline blood draw was performed on all animals 16 days later. The animals were randomized into 4 groups based on baseline serum potassium levels and placed on a potassium binder treatment regimen as described in the table below:

Group	Treatment	N
1	TD120436 (untreated)	8
2	TD120436 + 2% potassium binder	8
3	TD120436 + 4% potassium binder	8
4	TD120436 + 6% potassium binder	8
5	Control	6

[00225] Blood, feces, and urine were collected 9 and 15 days after the treatment regimen was started. Proximal and distal gastrointestinal segments were harvested at the end of the study. Serum, fecal, and urine potassium levels and serum aldosterone levels were determined at respective time points.

[00226] The serum potassium levels (mmol/L) for the control, untreated, and experimental groups at baseline, day 9, and day 15 were analyzed. The average serum potassium reduction levels compared to the untreated group were -9.1% (2% potassium binder), -18.2% (4% potassium binder), and -20.3% (6% potassium binder) on day 9 and -6.9% (2% potassium binder), -13.2% (4% potassium binder), and -17.4% (6% potassium binder) on day 15. A significant reduction in serum potassium levels in all groups treated with potassium binder at day 9 and at the two higher doses on day 15 was observed as compared to the untreated group. The analysis was performed using a 2-way ANOVA plus Bonferroni post hoc test (**$P<0.01$; ***$P<0.001$ vs. untreated).

[00227] The serum aldosterone levels (pg/mL) for the control, untreated, and experimental groups at baseline, day 9, and day 15 were also analyzed. The average serum aldosterone reduction levels compared to the untreated group were -22.7% (2% potassium

binder), -53.0% (4% potassium binder), and -57.6% (6% potassium binder) on day 9 and -16.6% (2% potassium binder), -37.9% (4% potassium binder), and -50.3 (6% potassium binder)% on day 15. A significant reduction in serum aldosterone levels was observed in all groups treated with potassium binder at day 9 and at the two higher doses on day 15 as compared to the untreated group. The analysis was performed using a 2-way ANOVA plus Bonferroni post-hoc test (*P<0.05; **P<0.01; ***P<0.001 vs. untreated).

[00228] There was no difference in the urine potassium excretion levels between all treatment groups.

[00229] The study showed that a reduction in serum aldosterone was observed with a reduction in serum potassium.

[00230] When introducing elements of the present invention or the preferred embodiments(s) thereof, the articles "a", "an", "the" and "said" are intended to mean that there are one or more of the elements. The terms "comprising", "including" and "having" are intended to be inclusive and mean that there may be additional elements other than the listed elements.

[00231] In view of the above, it will be seen that the several objects of the invention are achieved and other advantageous results attained.

[00232] As various changes could be made in the above methods without departing from the scope of the invention, it is intended that all matter contained in the above description and shown in the accompanying figure[s] shall be interpreted as illustrative and not in a limiting sense.

WHAT IS CLAIMED IS:

1. A method of treating hypertension in a patient in need thereof, the method comprising administering an effective amount of a potassium-binding agent to the patient suffering from either hyperkalemia or proteinuria wherein when the potassium-binding agent is a polymer, the polymer comprises an aliphatic crosslinked cation exchange polymer, the crosslinking agent comprising 5 mol% to 15 mol% of the polymer.

2. A method of treating hypertension in a patient in need thereof, the method comprising administering an effective amount of a potassium-binding agent to the patient suffering from either hyperkalemia or proteinuria wherein when the potassium-binding agent is a polymer, the polymer comprises a crosslinked cation exchange polymer other than a polystyrene cation exchange polymer and comprising 5 mol% to 12 mol% crosslinker.

3. The method of claim 1 or 2 wherein the patient suffers from hyperkalemia.

4. The method of any one of claims 1 to 3 wherein the patient suffers from proteinuria.

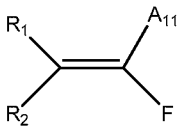
5. The method of any one of claims 1 to 4 wherein the patient suffers from chronic kidney disease.

6. The method of any one of claims 1 to 5 wherein the patient is undergoing dialysis.

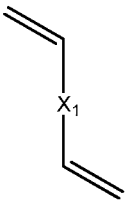
7. The method of any one of claims 1 to 6 wherein the patient is being treated with an effective amount of a renin-angiotensin-aldosterone system (RAAS) agent.

8. The method of any one of claims 1 to 7 wherein the crosslinked cation exchange polymer is in its salt or acid form and is a reaction product of a polymerization mixture comprising monomers of either (i) Formulae 11 and 22, (ii) Formulae 11 and 33, or (iii) Formulae 11, 22, and 33, wherein

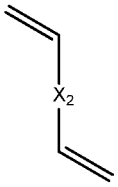
Formula 11, Formula 22, and Formula 33 are represented by the following structures:



Formula 11



Formula 22



Formula 33

and wherein

R_1 and R_2 are each independently hydrogen, alkyl, cycloalkyl, or aryl;

A_{11} is an optionally protected carboxylic, phosphonic, or phosphoric;

X_1 is arylene; and

X_2 is alkylene, an ether moiety, or an amide moiety.

9. The method of claim 8 wherein A_{11} is a protected carboxylic, phosphonic, or phosphoric.

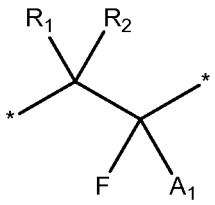
10. The method of claim 8 or 9 wherein the polymerization mixture further comprises a polymerization initiator.

11. The method of any one of claims 1 to 7 wherein the crosslinked cation exchange polymer comprising structural units corresponding to Formulae 1, 2, and 3, wherein

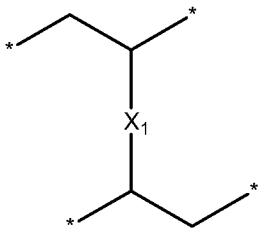
(i) the structural units corresponding to Formula 1 constitute at least about 85 wt.% based on the total weight of structural units of Formulae 1, 2, and 3 in the polymer, calculated from the amounts of monomers used in the polymerization reaction, and the weight ratio of the structural unit corresponding to Formula 2 to the structural unit corresponding to Formula 3 is from about 4:1 to about 1:4, or

(ii) the mole fraction of the structural unit of Formula 1 in the polymer is at least about 0.87 based on the total number of moles of the structural units of Formulae 1, 2, and 3, calculated from the amounts of monomers used in the polymerization reaction, and the mole ratio of the structural unit of Formula 2 to the structural unit of Formula 3 is from about 0.2:1 to about 7:1, and

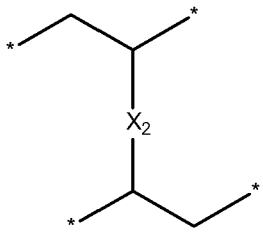
Formula 1, Formula 2, and Formula 3 correspond to the following structures:



Formula 1



Formula 2



Formula 3

wherein

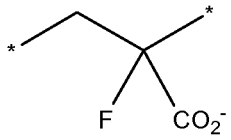
R_1 and R_2 are independently hydrogen, alkyl, cycloalkyl, or aryl;

A_1 is carboxylic, phosphonic, or phosphoric, in its salt or acid form;

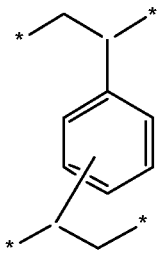
X_1 is arylene;

X_2 is alkylene, an ether moiety or an amide moiety.

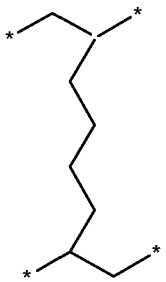
12. The method of claim 11 wherein Formula 1, Formula 2 and Formula 3 correspond to the following structures:



Formula 1A



Formula 2A



Formula 3A .

13. The method of any one of claims 8 or 11 wherein X_2 of Formulae 3 or 33 is either (a) an ether moiety selected from either $-(CH_2)_d-O-(CH_2)_e-$ or $-(CH_2)_d-O-(CH_2)_e-O-(CH_2)_d-$ wherein d and e are independently an integer of 1 through 5, or (b) an amide moiety of the formula $-C(O)-NH-(CH_2)_p-NH-C(O)-$ wherein p is an integer of 1 through 8, or (c) Formulae 3 or 33 is a mixture of structural units having the ether moiety and the amide moiety.

14. The method of claim 13 wherein X_2 is the ether moiety, d is an integer from 1 to 2, and e is an integer from 1 to 3.

15. The method of any one of claims 1 to 7 wherein the potassium-binding agent is a zeolite.

16. The method of any one of claims 1 to 14, the crosslinked cation exchange polymer being in the form of substantially spherical particles having a mean diameter of from about 20 μm to about 200 μm and less than about 4 volume percent of the particles have a diameter of less than about 10 μm, and the crosslinked cation exchange polymer having a sediment yield stress of less than about 4000 Pa, and a swelling ratio of less than 10 grams of water per gram of polymer.

17. The method of any one of claims 1 to 14, the crosslinked cation exchange polymer being in the form of substantially spherical particles having a mean diameter of less than about 250 μm and less than about 4 volume percent of the particles having a diameter of less than about 10 μm, and the crosslinked cation exchange polymer having a swelling ratio of less than 10 grams of water per gram of polymer, and a hydrated and sedimented mass of polymer particles having a viscosity of less than about 1,000,000 Pa·s, the viscosity being measured at a shear rate of 0.01 sec^{-1}.

18. The method of claims 16 or 17 wherein the mean diameter is from about 25 μm to about 150 μm.

19. The method of claims 16 or 17 wherein the mean diameter is from about 50 μm to about 125 μm.

20. The method of any one of claims 16 to 19 wherein less than about 0.5 volume percent of the particles have a diameter of less than about 10 μm.

21. The method of any one of claims 16 to 19 wherein less than about 4 volume percent of the particles have a diameter of less than about 20 μm.

22. The method of any one of claims 16 to 19 wherein less than about 0.5 volume percent of the particles have a diameter of less than about 20 μm.

23. The method of any one of claims 16 to 19 wherein less than about 4 volume percent of the particles have a diameter of less than about 30 μm.

24. The method of any one of claims 16 to 23 wherein the polymer has a swelling ratio from about 1 to about 5.

25. The method of any one of claims 16 to 23 wherein the polymer has a swelling ratio from about 1 to about 3.

26. The method of any one of claims 17 to 25 wherein the sediment yield stress is less than 4000 Pa.

27. The method of any one of claims 16 to 25 wherein the sediment yield stress is less than 3000 Pa.

28. The method of any one of claims 16 to 25 wherein the sediment yield stress is less than 2500 Pa.

29. The method of any one of claims 16 and 18 to 28 wherein a mass of the polymer particles formed by hydration and sedimentation of the polymer has a viscosity of less than about 1,000,000 Pa·s, the viscosity being measured at a shear rate of 0.01 sec^{-1}.

30. The method of claim 29 wherein the sedimented mass of particles has a viscosity of less than 800,000 Pa·s.

31. The method of claim 29 wherein the sedimented mass of particles has a viscosity of less than 500,000 Pa·s.

32. The method of any one of claims 16 to 31 wherein the polymer particles in dry form have a compressibility index of less than about 14, wherein the compressibility index is defined as 100*(TD-BD)/TD, and BD and TD are the bulk density and tap density, respectively.

33. The method of claim 32 wherein the compressibility index is less than about 10.

34. The method of any one of claims 16 to 33 wherein the particles have an average distance from peak to valley of a surface feature of less than about 2 μm.

35. The method of any one of claims 1 to 34 wherein the potassium-binding agent comprises 2-fluoroacrylate-divinylbenzene-1,7-octadiene copolymer crosslinked in the salt or acid form.

36. A method of treating hypertension in a patient in need thereof, the method comprising administering an effective amount of 2-fluoroacrylate-divinylbenzene-1,7-octadiene copolymer crosslinked in the salt or acid form to the patient.

37. The method of claim 36 wherein the 2-fluoroacrylate-divinylbenzene-1,7-octadiene copolymer crosslinked in the salt or acid form is administered chronically.

38. The method of any one of claims 1 to 37 wherein the patient's systolic blood pressure is reduced by 5, 6, 7, 8 mm Hg or more after 4 weeks of treatment with the potassium-binding agent or 2-fluoroacrylate-divinylbenzene-1,7-octadiene copolymer crosslinked in the salt or acid form as compared to the patient's systolic blood pressure before treatment with the potassium-binding agent or 2-fluoroacrylate-divinylbenzene-1,7-octadiene copolymer crosslinked in the salt or acid form.

39. The method of any one of claims 1 to 37 wherein the patient's systolic blood pressure is reduced by 9, 10, 11, 12, 13, 14, 15, 16, 17 mm Hg or more after 4 weeks of treatment with the potassium-binding agent or 2-fluoroacrylate-divinylbenzene-1,7-octadiene copolymer crosslinked in the salt or acid form as compared to the patient's systolic blood pressure before treatment with the potassium-binding agent or 2-fluoroacrylate-divinylbenzene-1,7-octadiene copolymer crosslinked in the salt or acid form.

40. The method of any one of claims 1 to 39 wherein the patient's diastolic blood pressure is reduced by 2, 3, 4, 5, 6 mm Hg as compared to the patient's diastolic blood pressure before treatment with the potassium-binding agent or 2-fluoroacrylate-divinylbenzene-1,7-octadiene copolymer crosslinked in the salt or acid form.

41. The method of any one of claims 1 to 39 wherein the patient's diastolic blood pressure is reduced by 7, 8, 9, 10, 11, 12, 13 mm Hg or more as compared to the patient's diastolic blood

pressure before treatment with the potassium-binding agent or 2-fluoroacrylate-divinylbenzene-1,7-octadiene copolymer crosslinked in the salt or acid form.

42. The method of any one of claims 1 to 41 wherein the patient's systolic blood pressure is reduced by at least 6, 7, 8, 9, 10, 11, 12, or more percent as compared to the patient's systolic blood pressure before treatment with the potassium-binding agent or 2-fluoroacrylate-divinylbenzene-1,7-octadiene copolymer crosslinked in the salt or acid form.

43. The method of any one of claims 1 to 42 wherein the patient's diastolic blood pressure is reduced by at least 8, 9, 10, 11, 12, 13, 14, 15, or more percent as compared to the patient's diastolic blood pressure before treatment with the potassium-binding agent or 2-fluoroacrylate-divinylbenzene-1,7-octadiene copolymer crosslinked in the salt or acid form.

44. The method of any one of claims 1 to 43 wherein the patient had a systolic blood pressure of from 130 mmHg to 200 mm Hg before treatment with the potassium-binding agent or 2-fluoroacrylate-divinylbenzene-1,7-octadiene copolymer crosslinked in the salt or acid form.

45. The method of any one of claims 1 to 43 wherein the patient had a systolic blood pressure of from 135 mmHg to 200 mm Hg before treatment with the potassium-binding agent or 2-fluoroacrylate-divinylbenzene-1,7-octadiene copolymer crosslinked in the salt or acid form.

46. The method of any one of claims 1 to 43 wherein the patient had a systolic blood pressure of from 140 mmHg to 200 mm Hg before treatment with the potassium-binding agent or 2-fluoroacrylate-divinylbenzene-1,7-octadiene copolymer crosslinked in the salt or acid form.

47. The method of any one of claims 1 to 43 wherein the patient had a systolic blood pressure of from 143 mmHg to 200 mm Hg before treatment with the potassium-binding agent or 2-fluoroacrylate-divinylbenzene-1,7-octadiene copolymer crosslinked in the salt or acid form.

48. The method of any one of claims 1 to 43 wherein the patient had a systolic blood pressure of from 145 mmHg to 180 mmHg before treatment with the potassium-binding agent or 2-fluoroacrylate-divinylbenzene-1,7-octadiene copolymer crosslinked in the salt or acid form.

49. The method of any one of claims 1 to 43 wherein the patient had a systolic blood pressure of from 148 mmHg to 180 mmHg before treatment with the potassium-binding agent or 2-fluoroacrylate-divinylbenzene-1,7-octadiene copolymer crosslinked in the salt or acid form.

50. The method of any one of claims 1 to 49 wherein the systolic blood pressure of the patient is maintained below 130 mm Hg over at least 90% of the period of treatment with the potassium-binding agent or 2-fluoroacrylate-divinylbenzene-1,7-octadiene copolymer crosslinked in the salt or acid form.

51. The method of any one of claims 1 to 50 wherein the diastolic blood pressure of the patient is maintained at below 80 mm Hg over at least 90% of the period of treatment with the potassium-binding agent or 2-fluoroacrylate-divinylbenzene-1,7-octadiene copolymer crosslinked in the salt or acid form.

52. The method of any one of claims 1 to 50 wherein the patient is not being treated with an aldosterone antagonist.

53. The method of any one of claims 1 to 52 wherein the patient does not have another condition that causes hypertension.

54. The method of claim 53 wherein the patient does not have Type 2 diabetes.

55. The method of claim 53 wherein the patient does not have Class II or Class III heart failure (HF).

56. The method of any one of claims 1 to 55 wherein the patient is not being treated with a heart failure therapy.

57. The method of claim 56 wherein the heart failure therapy is an angiotensin converting enzyme inhibitor (ACEI), an angiotensin receptor blocker (ARB), a beta blocker (BB), or a combination thereof.

58. The method of any one of claims 1 to 57 wherein the patient is not being treated with an antihypertensive agent comprising a diuretic, a calcium channel blocker, an alpha blocker, a nervous system inhibitor, a vasodilator, an angiotensin converting enzyme inhibitor (ACEI), an angiotensin receptor blocker (ARB), a beta blocker (BB), or a combination thereof.

59. The method of any one of claims 1, 2, and 4 to 58 wherein the patient is normokalemic.

60. A method of treating hypertension in a chronic kidney disease patient in need thereof, the patient optionally being treated with an effective amount of a renin-angiotensin-aldosterone system (RAAS) agent, the method comprising administering an effective amount of a potassium-binding agent to the patient.

61. A method of treating hypertension in a heart failure patient in need thereof, the patient optionally being treated with an effective amount of a renin-angiotensin-aldosterone system (RAAS) agent, the method comprising administering an effective amount of a potassium-binding agent to the patient.

62. A method of treating hypertension in a type 2 diabetes mellitus patient in need thereof, the patient optionally being treated with an effective amount of a renin-angiotensin-aldosterone system (RAAS) agent, the method comprising administering an effective amount of a potassium-binding agent to the patient.

63. The method of any one of claims 60 to 62 wherein the potassium-binding agent is 2-fluoroacrylate-divinylbenzene-1,7-octadiene copolymer crosslinked in the salt or acid form.

64. The method of claim 60 and 63 wherein the patient further suffers from heart failure and type 2 diabetes mellitus.

65. The method of any one of claims 61 to 63 wherein the patient further suffers from chronic kidney disease.

66. The method of claim 62 or 63 wherein the patient further suffers from heart failure.

67. The method of any one of claims 60 to 66 wherein the patient's systolic blood pressure is reduced by 5, 6, 7, 8 mm Hg as compared to the patient's systolic blood pressure before treatment with the potassium-binding agent.

68. The method of any one of claims 60 to 66 wherein the patient's systolic blood pressure is reduced by 9, 10, 11, 12, 13, 14, 15, 16, 17 mm Hg or more as compared to the patient's systolic blood pressure before treatment with the potassium-binding agent.

69. The method of any one of claims 60 to 68 wherein the patient's diastolic blood pressure is reduced by 2, 3, 4, 5, 6 mm Hg as compared to the patient's diastolic blood pressure before treatment with the potassium-binding agent.

70. The method of any one of claims 60 to 68 wherein the patient's diastolic blood pressure is reduced by 7, 8, 9, 10, 11, 12, 13 mm Hg or more as compared to the patient's diastolic blood pressure before treatment with 2-fluoroacrylate-divinylbenzene-1,7-octadiene copolymer crosslinked in the salt or acid form.

71. The method of any one of claims 60 to 66 and 68 to 70 wherein the patient's systolic blood pressure is reduced by at least 6, 7, 8, 9, 10, 11, 12, or more percent as compared to the patient's systolic blood pressure before treatment with the potassium-binding agent.

72. The method of any one of claims 60 to 68, 70, and 71 wherein the patient's diastolic blood pressure is reduced by at least 8, 9, 10, 11, 12, 13, 14, 15, or more percent as compared to the patient's diastolic blood pressure before treatment with 2-fluoroacrylate-divinylbenzene-1,7-octadiene copolymer crosslinked in the salt or acid form.

73. A method of treating hyperkalemia in a chronic kidney disease patient in need thereof optionally being treated with an effective amount of a renin-angiotensin-aldosterone system (RAAS) agent, the method comprising:

administering an effective amount of a potassium-binding agent to the patient and observing a decrease in the patient's serum creatinine level as compared to the patient's serum creatinine level before treatment with the potassium-binding agent indicating an increase or stabilization of the patient's kidney function.

74. A method of treating hyperkalemia in a chronic kidney disease patient in need thereof optionally being treated with an effective amount of a renin-angiotensin-aldosterone system (RAAS) agent, the method comprising:

administering an effective amount of a potassium-binding agent to the patient and observing an increase in the time to progression of end stage renal disease as compared to a chronic kidney disease patient optionally treated with a RAAS agent but not treated with the potassium-binding agent indicating an increase or stabilization of the patient's kidney function.

75. A method of treating hyperkalemia in a chronic kidney disease patient in need thereof optionally being treated with an effective amount of a renin-angiotensin-aldosterone system (RAAS) agent, the method comprising:

administering an effective amount of a potassium-binding agent to the patient and observing an increase in survival as compared to a chronic kidney disease patient optionally treated with a RAAS agent but not treated with the potassium-binding agent indicating an increase or stabilization of the patient's kidney function.

76. A method of treating hyperkalemia in a chronic kidney disease patient in need thereof optionally being treated with an effective amount of a renin-angiotensin-aldosterone system (RAAS) agent, the method comprising:

administering an effective amount of a potassium-binding agent to the patient and observing an increase or stabilization of estimated glomerular filtration rate (eGFR) as compared to the patient's eGFR before treatment with the potassium-binding agent indicating an increase or stabilization of the patient's kidney function.

77. A method of treating chronic kidney disease in a patient in need thereof optionally being treated with an effective amount of a renin-angiotensin-aldosterone system (RAAS) agent, the method comprising:

administering an effective amount of a potassium-binding agent to the patient to increase or stabilize the patient's kidney function by decreasing the patient's serum creatinine level as compared to the patient's serum creatinine level before treatment with the potassium-binding agent.

78. A method of treating chronic kidney disease in a patient in need thereof optionally being treated with an effective amount of a renin-angiotensin-aldosterone system (RAAS) agent, the method comprising:

administering an effective amount of a potassium-binding agent to the patient to increase or stabilize the patient's kidney function by increasing the time to progression of end stage renal disease as compared to a chronic kidney disease patient optionally treated with a RAAS agent but not treated with the potassium-binding agent.

79. A method of treating chronic kidney disease in a patient in need thereof optionally being treated with an effective amount of a renin-angiotensin-aldosterone system (RAAS) agent, the method comprising:

administering an effective amount of a potassium-binding agent to the patient to increase or stabilize the patient's kidney function by increasing survival as compared to a chronic kidney disease patient optionally treated with a RAAS agent but not treated with the potassium-binding agent.

80. A method of treating chronic kidney disease in a patient in need thereof optionally being treated with an effective amount of a renin-angiotensin-aldosterone system (RAAS) agent, the method comprising:

administering an effective amount of a potassium-binding agent to the patient to increase or stabilize the patient's kidney function by increasing or stabilizing estimated glomerular filtration rate (eGFR) as compared to the patient's eGFR before treatment with the potassium-binding agent.

81. The method of any one of claims 73 to 80 wherein the potassium-binding agent is 2-fluoroacrylate-divinylbenzene-1,7-octadiene copolymer crosslinked in the salt or acid form.

82. The method of any one of claims 77 to 80 further comprising treating hyperkalemia in a patient in need thereof.

83. The method of any one of claims 1 to 82 wherein the treatment period is 1, 2, 4, 6, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, or more weeks.

84. The method of any one of claims 1 to 83 wherein the patient has a baseline estimated glomerular filtration rate (eGFR) of from about 15 mL/min/1.73 m^2 to about 44 mL/min/1.73 m^2.

85. The method of any one of claims 1 to 84 wherein the patient's eGFR after treatment with the potassium-binding agent is not significantly different from the patient's eGFR before treatment with the potassium-binding agent.

86. The method of any one of claims 1 to 85 wherein the patient's eGFR is increased after 2, 3, 4, 5, 6 months or more of treatment as compared to the patient's eGFR before treatment with the potassium-binding agent.

87. The method of claim 86 wherein the patient's eGFR after treatment with the potassium-binding agent increased by at least 4, 5, 6 mL/min/1.73 m^2 or more as compared to the patient's eGFR before treatment with the potassium-binding agent.

88. The method of any one of claims 1 to 87 wherein the patient's serum potassium level is decreased after 1, 2, 3, 4, 5, 6, 7 days or more of treatment as compared to the patient's serum potassium level before treatment with the potassium-binding agent.

89. The method of any one of claims 1 to 88 wherein the patient's urine albumin:creatinine ratio (ACR) is not significantly different after 2, 3, 4, 5, 6 months or more of treatment as compared to the patient's urine ACR before treatment with the potassium-binding agent.

90. The method of any one of claims 60 to 89 wherein the patient's systolic and diastolic blood pressure is decreased after 1, 2, 3, 4, 5, 6, 7 days or more of treatment as compared to the patient's systolic and diastolic blood pressure before treatment with the potassium-binding agent.

91. The method of claim 90 wherein the patient's systolic blood pressure is reduced by 5, 6, 7, 8 mm Hg or more as compared to the patient's systolic blood pressure before treatment with the potassium-binding agent.

92. The method of claim 90 wherein the patient's systolic blood pressure is reduced by 9, 10, 11, 12, 13, 14, 15, 16, 17 mm Hg or more as compared to the patient's systolic blood pressure before treatment with the potassium-binding agent.

93. The method of any one of claims 90 to 92 wherein the patient's diastolic blood pressure is reduced by 2, 3, 4, 5, 6 mm Hg as compared to the patient's diastolic blood pressure before treatment with the potassium-binding agent.

94. The method of any one of claims 90 or 92 wherein the patient's diastolic blood pressure is reduced by 7, 8, 9, 10, 11, 12, 13 mm Hg or more as compared to the patient's diastolic blood pressure before treatment with the potassium-binding agent.

95. The method of any one of claims 90 and 92 to 94 wherein the patient's systolic blood pressure is reduced by at least 6, 7, 8, 9, 10, 11, 12, or more percent as compared to the patient's systolic blood pressure before treatment with the potassium-binding agent.

96. The method of any one of claims 90 to 92, 94, and 95 wherein the patient's diastolic blood pressure is reduced by at least 8, 9, 10, 11, 12, 13, 14, 15, or more percent as compared to the patient's diastolic blood pressure before treatment with the potassium-binding agent.

97. The method of any one of claims 1 to 96 wherein the patient's serum aldosterone level is decreased after four weeks or more of treatment as compared to the patient's serum aldosterone level before treatment with the potassium-binding agent.

98. The method of any one of claims 1 to 97 wherein the effective amount of the potassium-binding agent comprises up to a maximum daily dose of 60 grams.

99. The method of claim 98 wherein the effective amount of the potassium-binding agent comprises a daily dose of from 10 grams to 60 grams.

100. The method of claim 98 wherein the effective amount of the potassium-binding agent comprises a daily dose of from 18 grams to 40 grams.

101. The method of any one of claims 1 to 100 wherein the dose is adjusted to maintain the patient's serum potassium level in the normal range.

102. The method of any one of claims 35 to 59, 63 to 72, and 81 to 101 wherein 2-fluoroacrylate-divinylbenzene-1,7-octadiene copolymer crosslinked in the salt or acid form is in the salt form.

103. The method of claim 102 wherein the salt form comprises the sodium, calcium, magnesium, ammonium, or a combination thereof.

104. The method of claim 103 wherein the salt form comprises the calcium salt form.

105. The method of any one of claims 102 to 104 wherein the 2-fluoroacrylate-divinylbenzene-1,7-octadiene copolymer crosslinked in the salt form is stabilized with a linear polyol.

106. The method of claim 105 wherein the 2-fluoroacrylate-divinylbenzene-1,7-octadiene copolymer crosslinked in the salt form is stabilized with sorbitol.

107. The method of any one of claims 1 to 106 wherein the potassium-binding agent or 2-fluoroacrylate-divinylbenzene-1,7-octadiene copolymer crosslinked in the salt or acid form exhibits long-term tolerability in the patient.

108. The method of any one of claims 1 to 107 wherein the potassium-binding agent or 2-fluoroacrylate-divinylbenzene-1,7-octadiene copolymer crosslinked in the salt or acid form exhibits long-term safety in the patient.

109. The method of any one of claims 1 to 108 wherein the potassium-binding agent or 2-fluoroacrylate-divinylbenzene-1,7-octadiene copolymer crosslinked in the salt or acid form exhibits long-term efficacy in the patient.

110. The method of any one of claims 1 to 109 wherein the potassium-binding agent or 2-fluoroacrylate-divinylbenzene-1,7-octadiene copolymer crosslinked in the salt or acid form is administered to the patient daily for more than 8 weeks.

111. The method of any one of claims 1 to 109 wherein the potassium-binding agent or 2-fluoroacrylate-divinylbenzene-1,7-octadiene copolymer crosslinked in the salt or acid form is administered to the patient daily for more than one year.

112. The method of any one of claims 1 to 51, 53 to 55, and 59 to 111 wherein the patient is being treated or further treated with an effective amount of a RAAS agent, the RAAS agent being an angiotensin converting enzyme (ACE) inhibitor, an angiotensin receptor blocker (ARB), an aldosterone antagonist (AA), an aldosterone synthase inhibitor, or a combination thereof.

113. The method of claim 112 wherein the RAAS agent is the ACE inhibitor, the ARB, or a combination thereof.

114. The method of claim 112 or 113 wherein the effective amount of the RAAS agent comprises up to a maximum daily tolerated dose.

115. The method of any one of claims 112 to 114 wherein the RAAS agent comprises fosinopril, ramipril, captopril, lisinopril, trandolapril, moexipril, quinapril, enalapril, benazepril, perindopril, eprosartan, olmesartan, losartan, telmisartan, valsartan, candesartan, irbesartan, azilsartan medoxomil, spironolactone, eplerenone, or a combination thereof.

116. The method of claim 115 wherein the RAAS agent comprises fosinopril and the maximum daily tolerated dose is 40 mg/day.

117. The method of claim 115 wherein the RAAS agent comprises ramipril and the maximum daily tolerated dose is 20 mg/day.

118. The method of claim 115 wherein the RAAS agent comprises captopril and the maximum daily tolerated dose is 300 mg/day.

119. The method of claim 115 wherein the RAAS agent comprises lisinopril and the maximum daily tolerated dose is 40 mg/day.

120. The method of claim 115 wherein the RAAS agent comprises trandolapril and the maximum daily tolerated dose is 4 mg.

121. The method of claim 115 wherein the RAAS agent comprises moexipril and the maximum daily tolerated dose is 30 mg/day.

122. The method of claim 115 wherein the RAAS agent comprises quinapril and the maximum daily tolerated dose is 80 mg/day.

123. The method of claim 115 wherein the RAAS agent comprises enalapril and the maximum daily tolerated dose is 40 mg/day.

124. The method of claim 115 wherein the RAAS agent comprises benazepril and the maximum daily tolerated dose is 40 mg/day.

125. The method of claim 115 wherein the RAAS agent comprises perindopril and the maximum daily tolerated dose is 8 mg/day.

126. The method of claim 115 wherein the RAAS agent comprises eprosartan and the maximum daily tolerated dose is 800 mg/day.

127. The method of claim 115 wherein the RAAS agent comprises olmesartan and the maximum daily tolerated dose is 40 mg/day.

128. The method of claim 115 wherein the RAAS agent comprises losartan and the maximum daily tolerated dose is 100 mg/day.

129. The method of claim 115 wherein the RAAS agent comprises telmisartan and the maximum daily tolerated dose is 80 mg/day.

130. The method of claim 115 wherein the RAAS agent comprises valsartan and the maximum daily tolerated dose is 320 mg/day.

131. The method of claim 115 wherein the RAAS agent comprises candesartan and the maximum daily tolerated dose is 32 mg/day.

132. The method of claim 115 wherein the RAAS agent comprises irbesartan and the maximum daily tolerated dose is 300 mg/day.

133. The method of claim 115 wherein the RAAS agent comprises azilsartan medoxomil and the maximum daily tolerated dose is 80 mg/day.

134. The method of claim 115 wherein the RAAS agent comprises spironolactone and the maximum daily tolerated dose is 200 mg/day.

135. The method of claim 115 wherein the RAAS agent comprises eplerenone and the maximum daily tolerated dose is 50 mg/day.

136. The method of any one of claims 1 to 55 and 59 to 135 wherein the patient is further being treated with an effective amount of a beta-adrenergic blocking agent.

137. The method of claim 136 wherein the beta-adrenergic blocking agent comprises betaxolol, bisoprolol, atenolol, metoprolol, nebivolol, metoprolol, esmolol, acebutolol, propranolol, nadolol, carvedilol, labetalol, sotalol, timolol, carteolol, penbutolol, pindolol, or a combination thereof.

FIG. 1

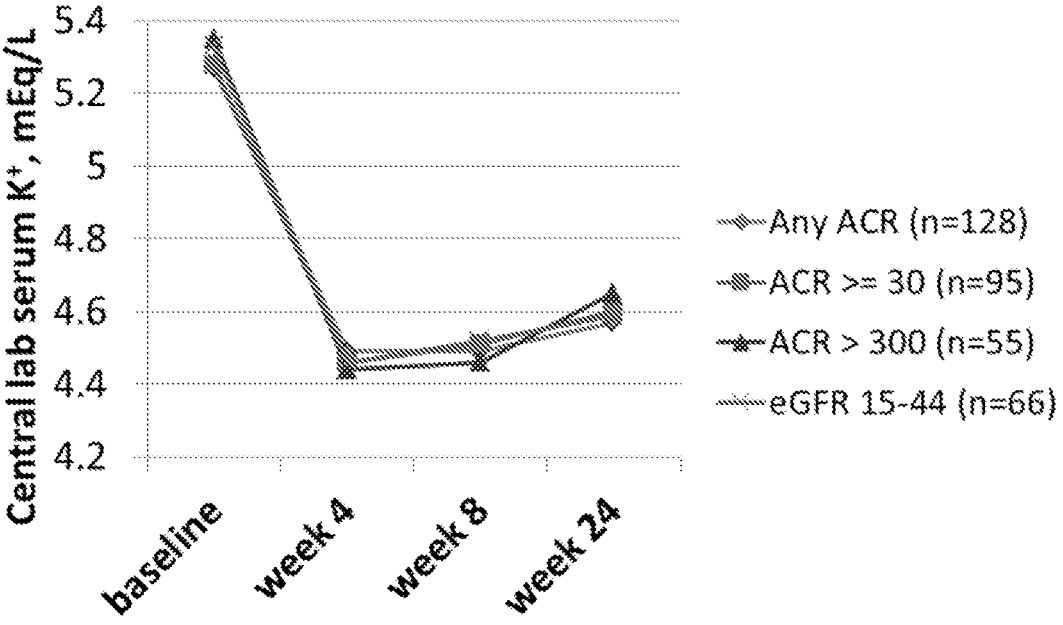

Central lab serum K+, mEq/L
5.4
5.2
5
4.8
4.6
4.4
4.2
baseline
week 4
week 8
week 24
Any ACR (n=128)
ACR >= 30 (n=95)
ACR > 300 (n=55)
eGFR 15-44 (n=66)

FIG. 2

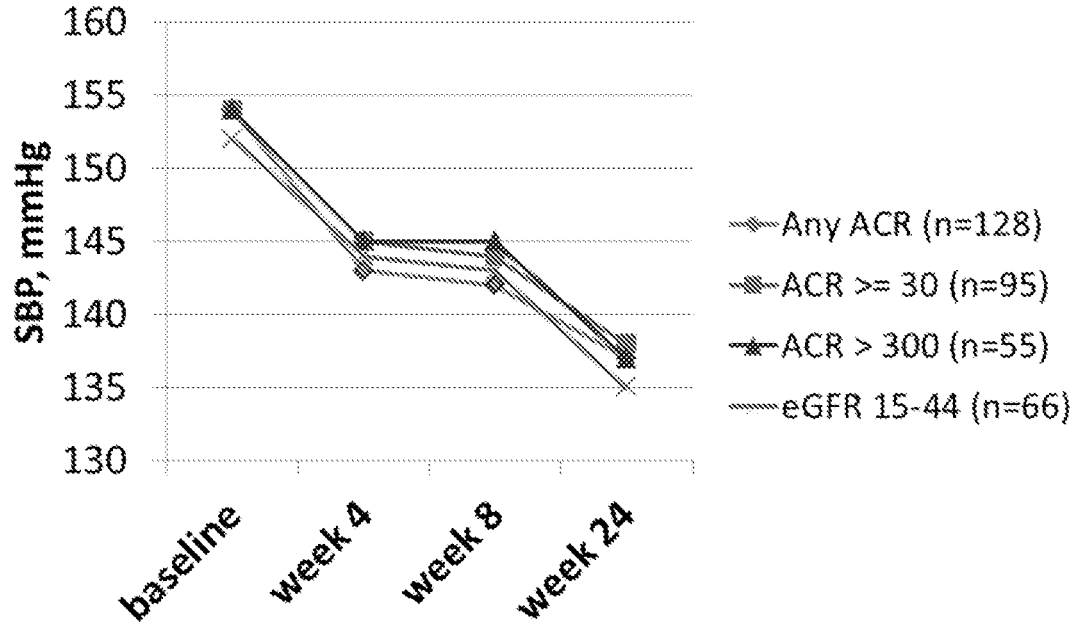

SBP, mmHg
160
155
150
145
140
135
130
baseline
week 4
week 8
week 24
Any ACR (n=128)
ACR >= 30 (n=95)
ACR > 300 (n=55)
eGFR 15-44 (n=66)

FIG. 3

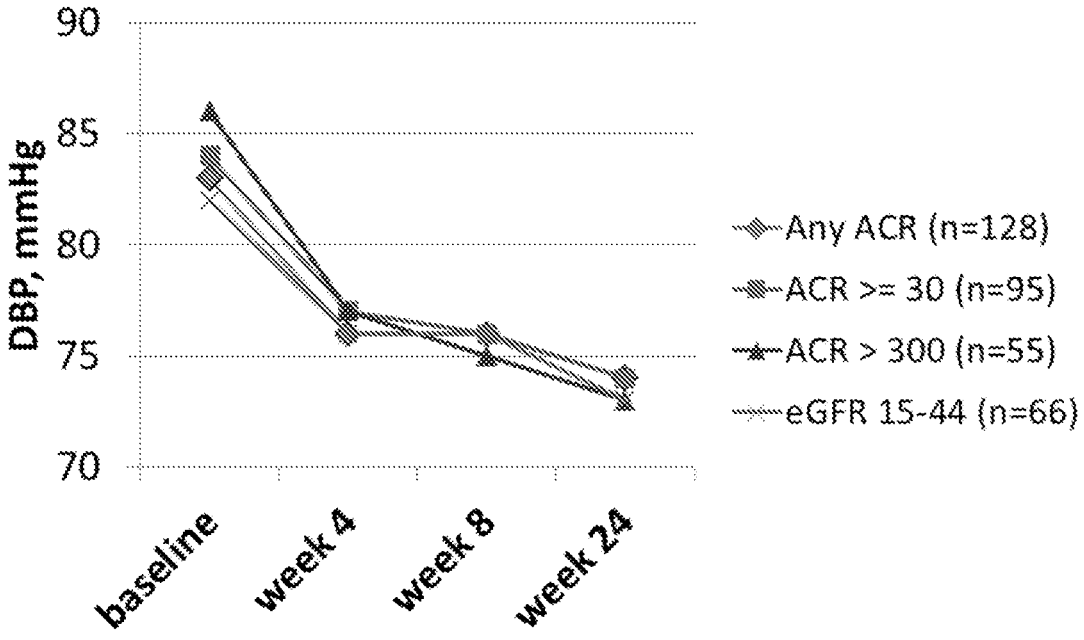

90
85
80
75
70
DBP, mmHg
baseline
week 4
week 8
week 24
Any ACR (n=128)
ACR >= 30 (n=95)
ACR > 300 (n=55)
eGFR 15-44 (n=66)

FIG. 4

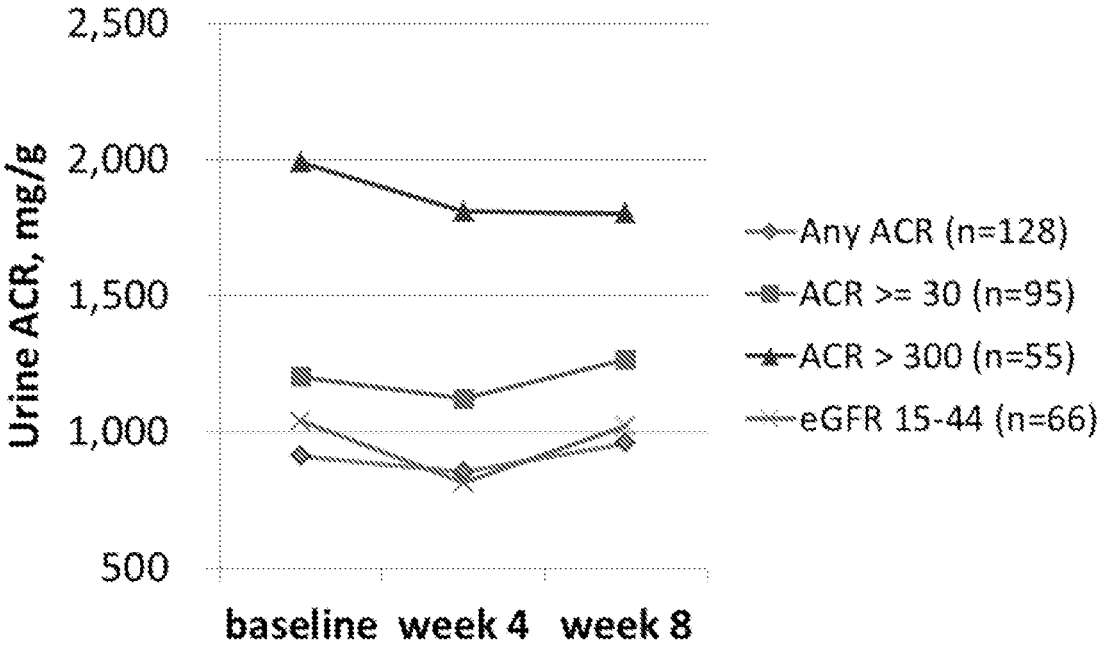

2,500
2,000
1,500
1,000
500
Urine ACR, mg/g
baseline
week 4
week 8
Any ACR (n=128)
ACR >= 30 (n=95)
ACR > 300 (n=55)
eGFR 15-44 (n=66)

FIG. 5

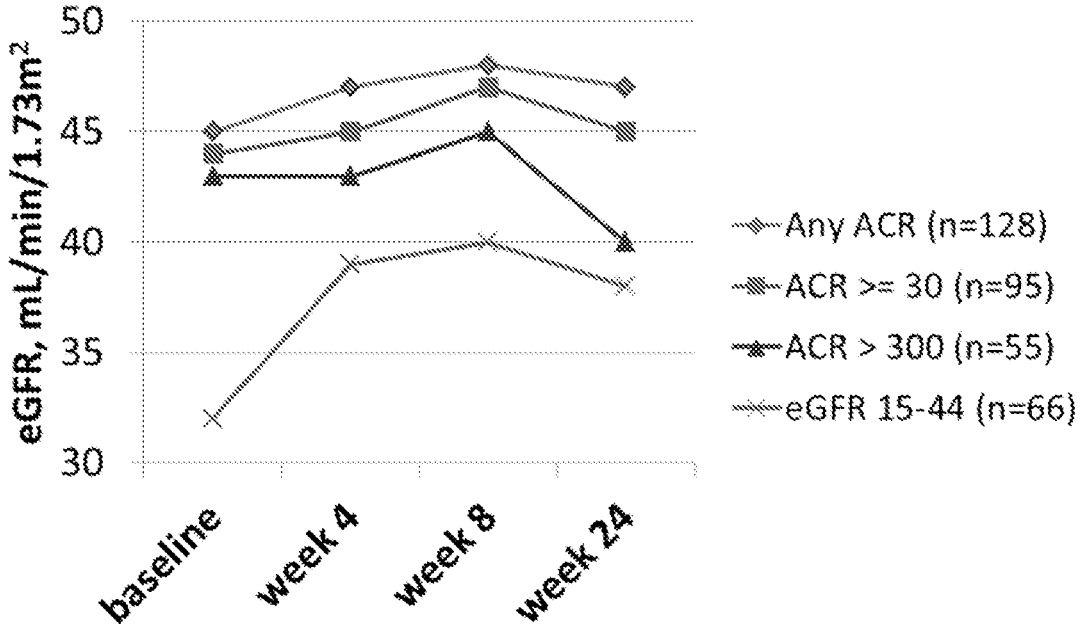

50
45
40
35
30
eGFR, mL/min/1.73m²
baseline
week 4
week 8
week 24
Any ACR (n=128)
ACR >= 30 (n=95)
ACR > 300 (n=55)
eGFR 15-44 (n=66)

FIG. 6

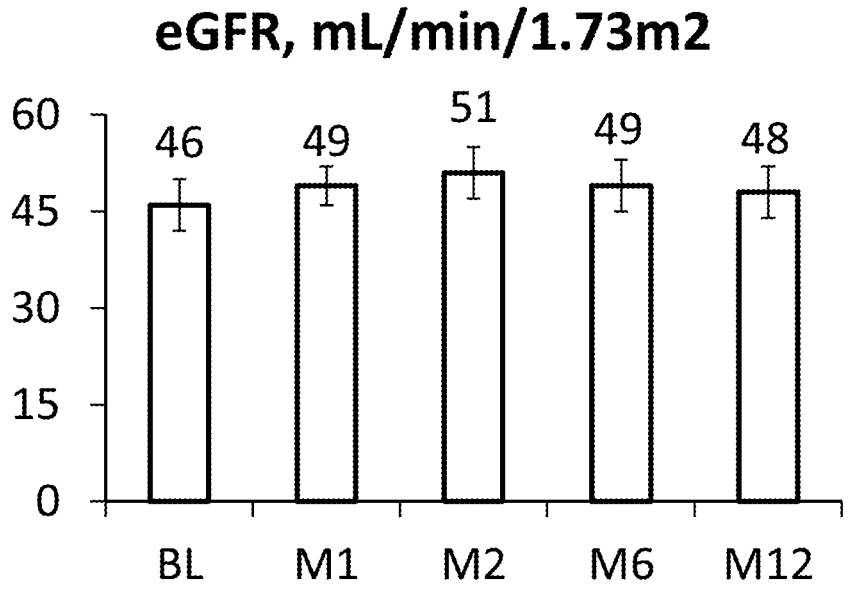

eGFR, mL/min/1.73m2
60
45
30
15
0
46
49
51
49
48
BL
M1
M2
M6
M12

FIG. 7

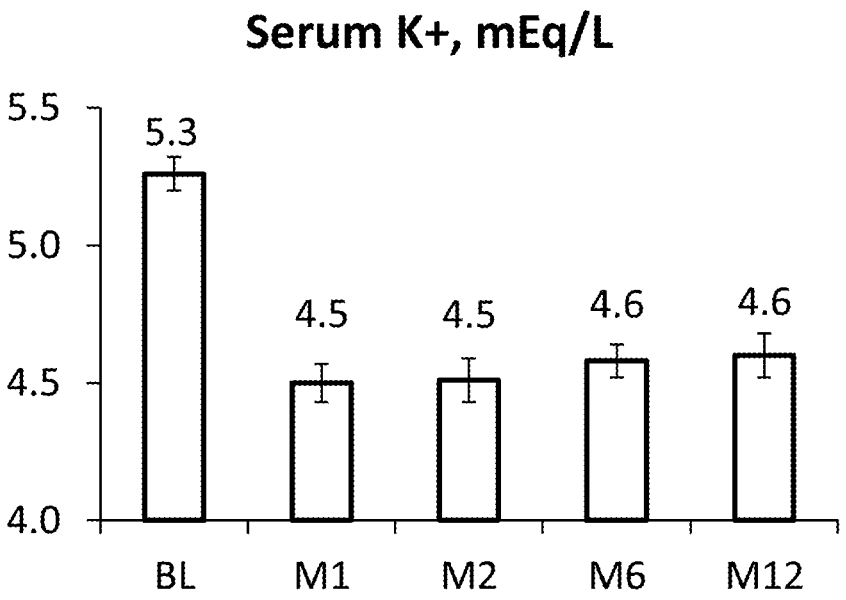

Serum K+, mEq/L
5.5
5.0
4.5
4.0
5.3
4.5
4.5
4.6
4.6
BL
M1
M2
M6
M12

FIG. 8

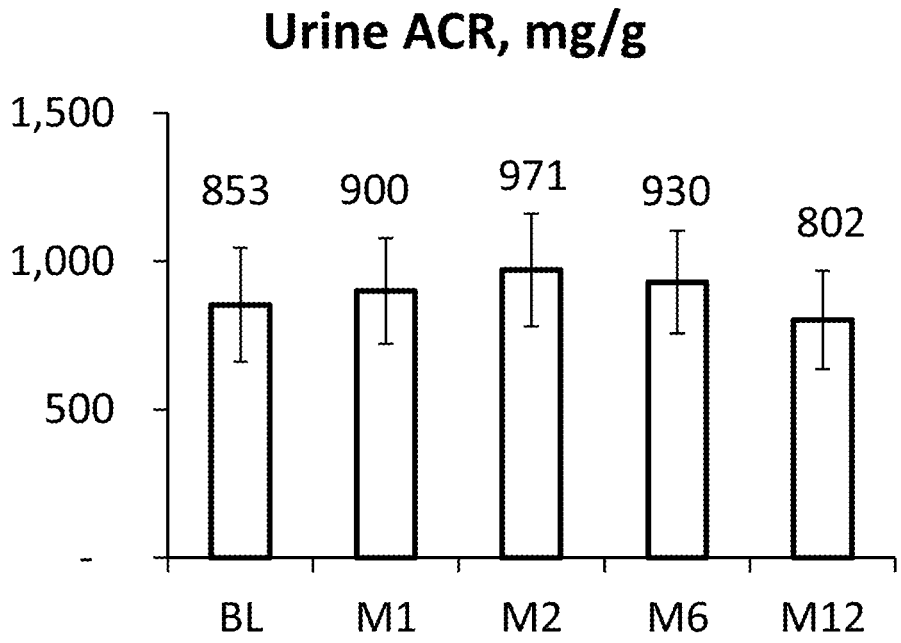
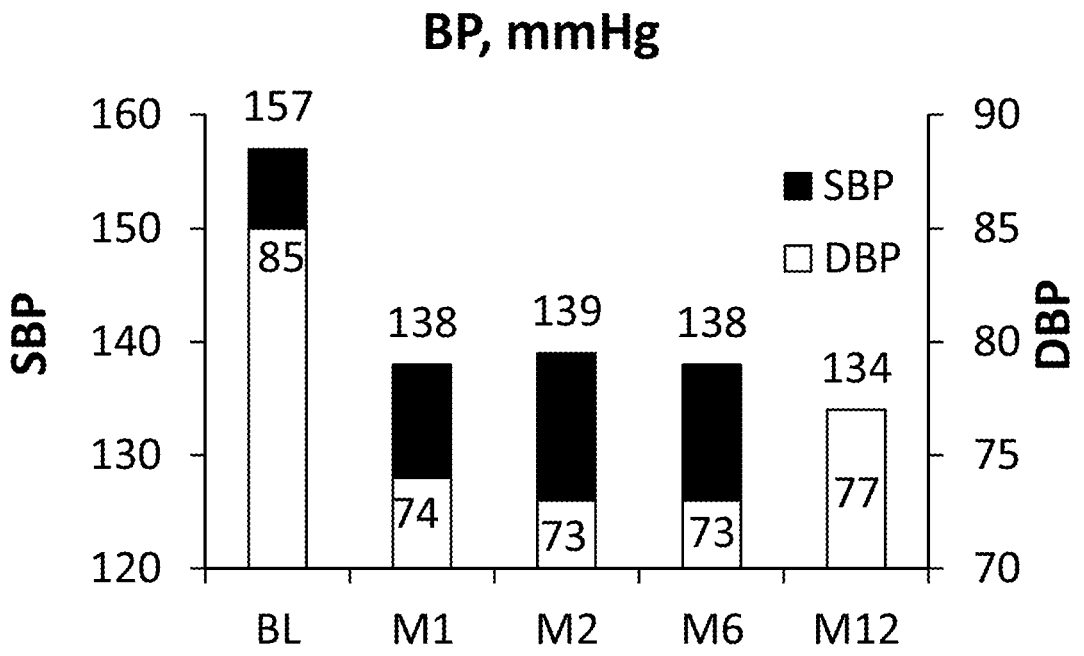

Urine ACR, mg/g
1,500
1,000
500
-
853
900
971
930
802
BL
M1
M2
M6
M12

FIG. 9


BP, mmHg
SBP
DBP
160
150
140
130
120
90
85
80
75
70
157
85
138
74
139
73
138
73
134
77
BL
M1
M2
M6
M12

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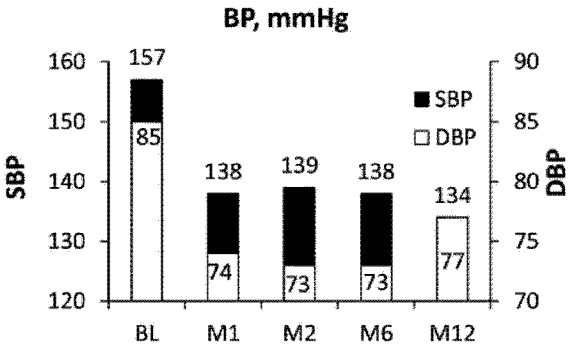
(54)发明名称

治疗高血压和高血钾症的钾结合剂

(57)摘要

本发明总体上涉及在有需要的患者中治疗高血压(HTN)的方法，其中所述患者任选还患有慢性肾病(CKD)或II型糖尿病(T2DM)。本发明还涉及在有需要的患者中治疗高血钾症的方法，其中所述患者患有CKD、T2DM或HTN并且任选地用有效量的肾素-血管紧张素-醛固酮系统(RAAS)试剂治疗。本发明还涉及在有需要的患者中治疗肾病的方法，其中所述患者任选地用有效量的肾素-血管紧张素-醛固酮系统(RAAS)试剂治疗。所述方法可包括向所述患者施用有效量的钾结合剂以降低所述患者的血压和/或增强或稳定所述患者的肾功能。



CN 104822383 A

1. 一种在有需要的患者中治疗高血压 (HTN) 的方法，所述方法包括向患有高血钾症或蛋白尿症的患者施用有效量的钾结合剂，其中当所述钾结合剂为聚合物时，所述聚合物包含脂肪族交联阳离子交换聚合物、占所述聚合物的 5 摩尔％至 15 摩尔％的交联剂。

2. 一种在有需要的患者中治疗高血压的方法，所述方法包括向患有高血钾症或蛋白尿症的患者施用有效量的钾结合剂，其中当所述钾结合剂为聚合物时，所述聚合物包含除聚苯乙烯阳离子交换聚合物外的交联阳离子交换聚合物并且包含 5 摩尔％至 12 摩尔％的交联剂。

3. 根据权利要求 1 或 2 所述的方法，其中所述患者患有高血钾症。

4. 根据权利要求 1-3 中任一项所述的方法，其中所述患者患有蛋白尿症。

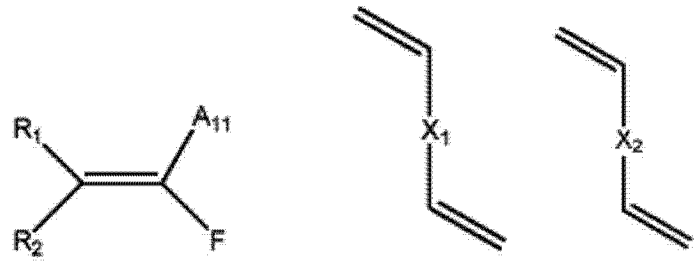
5. 根据权利要求 1-4 中任一项所述的方法，其中所述患者患有慢性肾病。

6. 根据权利要求 1-5 中任一项所述的方法，其中所述患者在接受透析。

7. 根据权利要求 1-6 中任一项所述的方法，其中所述患者在用有效量的肾素 - 血管紧张素 - 醛固酮系统 (RAAS) 试剂治疗。

8. 根据权利要求 1-7 中任一项所述的方法，其中所述交联阳离子交换聚合物呈其盐或酸形式并且是包含 (i) 式 11 和 22、(ii) 式 11 和 33 或 (iii) 式 11、22 和 33 的单体的聚合混合物的反应产物，其中

式 11、式 22 和式 33 由以下结构表示：



式 11　　式 22　　式 33

并且其中

R_1和 R_2各自独立地为氢、烷基、环烷基或芳基；

A_{11}为任选受保护的羧酸基、膦酸基或磷酸基；

X_1为亚芳基；并且

X_2为亚烷基、醚部分或酰胺部分。

9. 根据权利要求 8 所述的方法，其中 A_{11}为受保护的羧酸基、膦酸基或磷酸基。

10. 根据权利要求 8 或 9 所述的方法，其中所述聚合混合物还包含聚合引发剂。

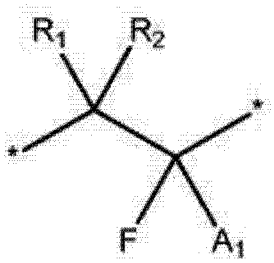
11. 根据权利要求 1-7 中任一项所述的方法，其中所述交联阳离子交换聚合物包含与式 1、2 和 3 相对应的结构单元，其中

(i) 按所述聚合物中式 1、2 和 3 结构单元的总重量计，由所述聚合反应中所用单体的量计算，与式 1 相对应的结构单元构成至少约 85 重量％，并且与式 2 相对应的结构单元和与式 3 相对应的结构单元的重量比为约 4:1 至约 1:4，或

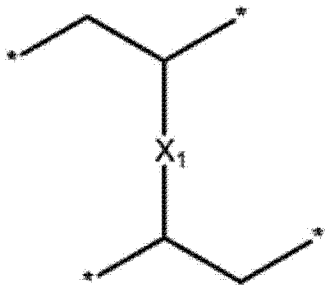
(ii) 按式 1、2 和 3 结构单元的总摩尔数计，由所述聚合反应中所用单体的量计算，所述聚合物中式 1 结构单元的摩尔分数为至少约 0.87，并且式 2 结构单元与式 3 结构单元的摩

尔比为约 0.2:1 至约 7:1，并且

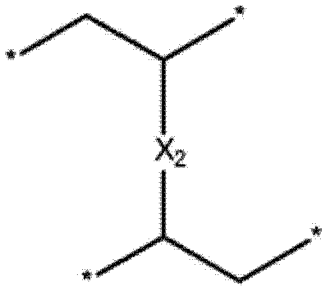
式 1、式 2 和式 3 与以下结构相对应：



式 1



式 2



式 3

其中

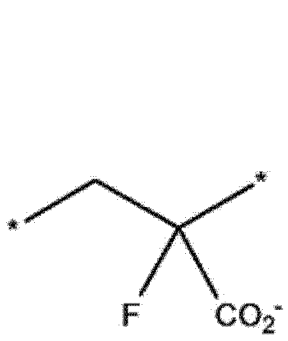
R_1和 R_2各自独立地为氢、烷基、环烷基或芳基；

A_{11}为呈其盐或酸形式的羧酸基、膦酸基或磷酸基；

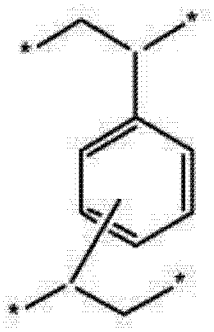
X_1为亚芳基；

X_2为亚烷基、醚部分或酰胺部分。

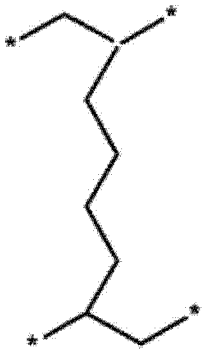
12. 根据权利要求 11 所述的方法，其中式 1、式 2 和式 3 与以下结构相对应：



式 1A



式 2A



式 3A。

13. 根据权利要求 8 或 11 中任一项所述的方法，其中式 3 或 33 的 X_2为 (a) 选自 $-(CH_2)_d-O-(CH_2)_e-$ 或 $-(CH_2)_d-O-(CH_2)_e-O-(CH_2)_d-$的醚部分，其中 d 和 e 独立地为 1 至 5 的整数，或 (b) 式 $-C(O)-NH-(CH_2)_p-NH-C(O)-$ 的酰胺部分，其中 p 为 1 至 8 的整数，或 (c) 式 3 或 33 为具有醚部分和酰胺部分的结构单元的混合物。

14. 根据权利要求 13 所述的方法，其中 X_2为醚部分，d 为 1 至 2 的整数，并且 e 为 1-3 的整数。

15. 根据权利要求 1-7 中任一项所述的方法，其中所述钾结合剂为沸石。

16. 根据权利要求 1-14 中任一项所述的方法，所述交联阳离子交换聚合物呈平均直径约 20 μm 至约 200 μm 的大体球形颗粒形式并且小于约 4 体积％的所述颗粒的直径小于约 10 μm，并且所述交联阳离子交换聚合物的沉积屈服应力小于约 4000Pa 且溶胀比小于 10 克水 / 克聚合物。

17. 根据权利要求 1-14 中任一项所述的方法，所述交联阳离子交换聚合物呈平均直径小于约 250 μm 的大体球形颗粒形式并且小于约 4 体积％的所述颗粒的直径小于约 10 μm，

并且所述交联阳离子交换聚合物的溶胀比小于 10 克水 / 克聚合物，并且聚合物颗粒的水合和沉积团块的粘度小于约 1,000,000Pa·s，所述粘度在 0.01sec^{-1}的剪切速率下测得。

18. 根据权利要求 16 或 17 所述的方法，其中所述平均直径为约 25μm 至约 150μm。

19. 根据权利要求 16 或 17 所述的方法，其中所述平均直径为约 50μm 至约 125μm。

20. 根据权利要求 16-19 中任一项所述的方法，其中小于约 0.5 体积％的所述颗粒的直径小于约 10μm。

21. 根据权利要求 16-19 中任一项所述的方法，其中小于约 4 体积％的所述颗粒的直径小于约 20μm。

22. 根据权利要求 16-19 中任一项所述的方法，其中小于约 0.5 体积％的所述颗粒的直径小于约 20μm。

23. 根据权利要求 16-19 中任一项所述的方法，其中小于约 4 体积％的所述颗粒的直径小于约 30μm。

24. 根据权利要求 16-23 中任一项所述的方法，其中所述聚合物的溶胀比为约 1 至约 5。

25. 根据权利要求 16-23 中任一项所述的方法，其中所述聚合物的溶胀比为约 1 至约 3。

26. 根据权利要求 17-25 中任一项所述的方法，其中所述沉积屈服应力小于 4000Pa。

27. 根据权利要求 16-25 中任一项所述的方法，其中所述沉积屈服应力小于 3000Pa。

28. 根据权利要求 16-25 中任一项所述的方法，其中所述沉积屈服应力小于 2500Pa。

29. 根据权利要求 16 和 18-28 中任一项所述的方法，其中通过所述聚合物水合和沉积形成的所述聚合物颗粒的团块的粘度小于约 1,000,000Pa·s，所述粘度在 0.01sec^{-1}的剪切速率下测得。

30. 根据权利要求 29 所述的方法，其中所述颗粒的沉积团块的粘度小于 800,000Pa·s。

31. 根据权利要求 29 所述的方法，其中所述颗粒的沉积团块的粘度小于 500,000Pa·s。

32. 根据权利要求 16-31 中任一项所述的方法，其中呈干燥形式的所述聚合物颗粒的压缩指数小于约 14，其中所述压缩指数定义为 100*(TD-BD)/TD，并且 BD 和 TD 分别为堆积密度和振实密度。

33. 根据权利要求 32 所述的方法，其中所述压缩指数小于约 10。

34. 根据权利要求 16-33 中任一项所述的方法，其中所述颗粒的表面特征的从峰到谷的平均距离小于约 2μm。

35. 根据权利要求 1-34 中任一项所述的方法，其中所述钾结合剂包含呈盐或酸形式的交联的 2- 氟代丙烯酸酯 - 二乙烯基苯 -1,7- 辛二烯共聚物。

36. 一种在有需要的患者中治疗高血压的方法，所述方法包括向所述患者施用有效量的呈盐或酸形式的交联的 2- 氟代丙烯酸酯 - 二乙烯基苯 -1,7- 辛二烯共聚物。

37. 根据权利要求 36 所述的方法，其中长期施用呈盐或酸形式的交联的所述 2- 氟代丙烯酸酯 - 二乙烯基苯 -1,7- 辛二烯共聚物。

38. 根据权利要求 1-37 中任一项所述的方法，其中与用所述钾结合剂或呈盐或酸形式的交联的 2- 氟代丙烯酸酯 - 二乙烯基苯 -1,7- 辛二烯共聚物治疗之前的所述患者的收缩压相比，在用所述钾结合剂或呈盐或酸形式的交联的 2- 氟代丙烯酸酯 - 二乙烯基

苯 -1,7- 辛二烯共聚物治疗 4 周后，所述患者的收缩压降低 5、6、7、8mm Hg 或更多。

39. 根据权利要求 1-37 中任一项所述的方法，其中与用所述钾结合剂或呈盐或酸形式的交联的 2- 氟代丙烯酸酯 - 二乙烯基苯 -1,7- 辛二烯共聚物治疗之前的所述患者的收缩压相比，在用所述钾结合剂或呈盐或酸形式的交联的 2- 氟代丙烯酸酯 - 二乙烯基苯 -1,7- 辛二烯共聚物治疗 4 周后，所述患者的收缩压降低 9、10、11、12、13、14、15、16、17mm Hg 或更多。

40. 根据权利要求 1-39 中任一项所述的方法，其中与用所述钾结合剂或呈盐或酸形式的交联的 2- 氟代丙烯酸酯 - 二乙烯基苯 -1,7- 辛二烯共聚物治疗之前的所述患者的舒张压相比，所述患者的舒张压降低 2、3、4、5、6mm Hg。

41. 根据权利要求 1-39 中任一项所述的方法，其中与用所述钾结合剂或呈盐或酸形式的交联的 2- 氟代丙烯酸酯 - 二乙烯基苯 -1,7- 辛二烯共聚物治疗之前的所述患者的舒张压相比，所述患者的舒张压降低 7、8、9、10、11、12、13mm Hg 或更多。

42. 根据权利要求 1-41 中任一项所述的方法，其中与用所述钾结合剂或呈盐或酸形式的交联的 2- 氟代丙烯酸酯 - 二乙烯基苯 -1,7- 辛二烯共聚物治疗之前的所述患者的收缩压相比，所述患者的收缩压降低至少 6、7、8、9、10、11、12 或更多百分比。

43. 根据权利要求 1-42 中任一项所述的方法，其中与用所述钾结合剂或呈盐或酸形式的交联的 2- 氟代丙烯酸酯 - 二乙烯基苯 -1,7- 辛二烯共聚物治疗之前的所述患者的舒张压相比，所述患者的舒张压降低至少 8、9、10、11、12、13、14、15 或更多百分比。

44. 根据权利要求 1-43 中任一项所述的方法，其中在用所述钾结合剂或呈盐或酸形式的交联的 2- 氟代丙烯酸酯 - 二乙烯基苯 -1,7- 辛二烯共聚物治疗之前，所述患者的收缩压为 130mmHg 至 200mm Hg。

45. 根据权利要求 1-43 中任一项所述的方法，其中在用所述钾结合剂或呈盐或酸形式的交联的 2- 氟代丙烯酸酯 - 二乙烯基苯 -1,7- 辛二烯共聚物治疗之前，所述患者的收缩压为 135mmHg 至 200mm Hg。

46. 根据权利要求 1-43 中任一项所述的方法，其中在用所述钾结合剂或呈盐或酸形式的交联的 2- 氟代丙烯酸酯 - 二乙烯基苯 -1,7- 辛二烯共聚物治疗之前，所述患者的收缩压为 140mmHg 至 200mm Hg。

47. 根据权利要求 1-43 中任一项所述的方法，其中在用所述钾结合剂或呈盐或酸形式的交联的 2- 氟代丙烯酸酯 - 二乙烯基苯 -1,7- 辛二烯共聚物治疗之前，所述患者的收缩压为 143mmHg 至 200mm Hg。

48. 根据权利要求 1-43 中任一项所述的方法，其中在用所述钾结合剂或呈盐或酸形式的交联的 2- 氟代丙烯酸酯 - 二乙烯基苯 -1,7- 辛二烯共聚物治疗之前，所述患者的收缩压为 145mmHg 至 180mm Hg。

49. 根据权利要求 1-43 中任一项所述的方法，其中在用所述钾结合剂或呈盐或酸形式的交联的 2- 氟代丙烯酸酯 - 二乙烯基苯 -1,7- 辛二烯共聚物治疗之前，所述患者的收缩压为 148mmHg 至 180mm Hg。

50. 根据权利要求 1-49 中任一项所述的方法，其中在历经用所述钾结合剂或呈盐或酸形式的交联的 2- 氟代丙烯酸酯 - 二乙烯基苯 -1,7- 辛二烯共聚物治疗的周期的至少 90％后，所述患者的收缩压维持在 130mm Hg 以下。

51. 根据权利要求 1-50 中任一项所述的方法，其中在历经用所述钾结合剂或呈盐或酸形式的交联的 2- 氟代丙烯酸酯 - 二乙烯基苯 -1,7- 辛二烯共聚物治疗的周期的至少 90％后，所述患者的舒张压维持在 80mm Hg 以下。

52. 根据权利要求 1-50 中任一项所述的方法，其中所述患者未用醛固酮拮抗剂治疗。

53. 根据权利要求 1-52 中任一项所述的方法，其中所述患者无引起高血压的其它病状。

54. 根据权利要求 53 所述的方法，其中所述患者无 2 型糖尿病。

55. 根据权利要求 53 所述的方法，其中所述患者无 II 类或 III 类心力衰竭 (HF)。

56. 根据权利要求 1-55 中任一项所述的方法，其中所述患者未用心力衰竭疗法治疗。

57. 根据权利要求 56 所述的方法，其中所述心力衰竭疗法为血管紧张素转化酶抑制剂 (ACEI)、血管紧张素受体阻断剂 (ARB)、β 阻断剂 (BB) 或其组合。

58. 根据权利要求 1-57 中任一项所述的方法，其中所述患者未用包含利尿剂、钙通道阻断剂、α 阻断剂、神经系统抑制剂、血管扩张剂、血管紧张素转化酶抑制剂 (ACEI)、血管紧张素受体阻断剂 (ARB)、β 阻断剂 (BB) 或其组合的抗高血压剂治疗。

59. 根据权利要求 1、2 和 4-58 中任一项所述的方法，其中所述患者血钾量正常。

60. 一种在有需要的慢性肾病患者中治疗高血压的方法，所述患者任选地用有效量的肾素 - 血管紧张素 - 醛固酮系统 (RAAS) 试剂治疗，所述方法包括向所述患者施用有效量的钾结合剂。

61. 一种在有需要的心力衰竭患者中治疗高血压的方法，所述患者任选地用有效量的肾素 - 血管紧张素 - 醛固酮系统 (RAAS) 试剂治疗，所述方法包括向所述患者施用有效量的钾结合剂。

62. 一种在有需要的 2 型糖尿病患者中治疗高血压的方法，所述患者任选地用有效量的肾素 - 血管紧张素 - 醛固酮系统 (RAAS) 试剂治疗，所述方法包括向所述患者施用有效量的钾结合剂。

63. 根据权利要求 60-62 中任一项所述的方法，其中所述钾结合剂为呈盐或酸形式的交联的 2- 氟代丙烯酸酯 - 二乙烯基苯 -1,7- 辛二烯共聚物。

64. 根据权利要求 60 和 63 所述的方法，其中所述患者还患有心力衰竭和 2 型糖尿病。

65. 根据权利要求 61-63 中任一项所述的方法，其中所述患者还患有慢性肾病。

66. 根据权利要求 62 或 63 所述的方法，其中所述患者还患有心力衰竭。

67. 根据权利要求 60-66 中任一项所述的方法，其中与用所述钾结合剂治疗之前的所述患者的收缩压相比，所述患者的收缩压降低 5、6、7、8mm Hg。

68. 根据权利要求 60-66 中任一项所述的方法，其中与用所述钾结合剂治疗之前的所述患者的收缩压相比，所述患者的收缩压降低 9、10、11、12、13、14、15、16、17mm Hg 更多。

69. 根据权利要求 60-68 中任一项所述的方法，其中与用所述钾结合剂治疗之前的所述患者的舒张压相比，所述患者的舒张压降低 2、3、4、5、6mm Hg。

70. 根据权利要求 60-68 中任一项所述的方法，其中与用呈盐或酸形式的交联的 2- 氟代丙烯酸酯 - 二乙烯基苯 -1,7- 辛二烯共聚物治疗之前的所述患者的舒张压相比，所述患者的舒张压降低 7、8、9、10、11、12、13mm Hg 或更多。

71. 根据权利要求 60-66 和 68-70 中任一项所述的方法，其中与用所述钾结合剂治疗之

前的所述患者的收缩压相比，所述患者的收缩压降低至少 6、7、8、9、10、11、12 或更多百分比。

72. 根据权利要求 60-68、70 和 71 中任一项所述的方法，其中与用呈盐或酸形式的交联的 2- 氟代丙烯酸酯 - 二乙烯基苯 -1,7- 辛二烯共聚物治疗之前的所述患者的舒张压相比，所述患者的舒张压降低至少 8、9、10、11、12、13、14、15 或更多百分比。

73. 一种在有需要的慢性肾病患者中治疗高血钾症的方法，所述患者任选地用有效量的肾素 - 血管紧张素 - 醛固酮系统 (RAAS) 试剂治疗，所述方法包括：

向所述患者施用有效量的钾结合剂并观察到与用所述钾结合剂治疗之前的所述患者的血清肌酐水平相比，所述患者的血清肌酐水平降低，表明所述患者的肾功能增强或稳定。

74. 一种在有需要的慢性肾病患者中治疗高血钾症的方法，所述患者任选地用有效量的肾素 - 血管紧张素 - 醛固酮系统 (RAAS) 试剂治疗，所述方法包括：

向所述患者施用有效量的钾结合剂并观察到与任选地用 RAAS 试剂治疗但未用所述钾结合剂治疗的慢性肾病患者相比，终末期肾病的进展时间增加，表明所述患者的肾功能增强或稳定。

75. 一种在有需要的慢性肾病患者中治疗高血钾症的方法，所述患者任选地用有效量的肾素 - 血管紧张素 - 醛固酮系统 (RAAS) 试剂治疗，所述方法包括：

向所述患者施用有效量的钾结合剂并观察到与任选地用 RAAS 试剂治疗但未用所述钾结合剂治疗的慢性肾病患者相比，存活率增加，表明所述患者的肾功能增强或稳定。

76. 一种在有需要的慢性肾病患者中治疗高血钾症的方法，所述患者任选地用有效量的肾素 - 血管紧张素 - 醛固酮系统 (RAAS) 试剂治疗，所述方法包括：

向所述患者施用有效量的钾结合剂并观察到与用所述钾结合剂治疗之前的所述患者的 eGFR 相比，估计肾小球滤过率 (eGFR) 增大或稳定，表明所述患者的肾功能增强或稳定。

77. 一种在有需要的患者中治疗慢性肾病的方法，所述患者任选地用有效量的肾素 - 血管紧张素 - 醛固酮系统 (RAAS) 试剂治疗，所述方法包括：

向所述患者施用有效量的钾结合剂以通过与用所述钾结合剂治疗之前的所述患者的血清肌酐水平相比降低所述患者的血清肌酐水平来增强或稳定所述患者的肾功能。

78. 一种在有需要的患者中治疗慢性肾病的方法，所述患者任选地用有效量的肾素 - 血管紧张素 - 醛固酮系统 (RAAS) 试剂治疗，所述方法包括：

向所述患者施用有效量的钾结合剂以通过与任选用 RAAS 试剂治疗但未用所述钾结合剂治疗的慢性肾病患者相比增加终末期肾病的进展时间来增强或稳定所述患者的肾功能。

79. 一种在有需要的患者中治疗慢性肾病的方法，所述患者任选地用有效量的肾素 - 血管紧张素 - 醛固酮系统 (RAAS) 试剂治疗，所述方法包括：

向所述患者施用有效量的钾结合剂以通过与任选用 RAAS 试剂治疗但未用所述钾结合剂治疗的慢性肾病患者相比增加存活率来增强或稳定所述患者的肾功能。

80. 一种在有需要的患者中治疗慢性肾病的方法，所述患者任选地用有效量的肾素 - 血管紧张素 - 醛固酮系统 (RAAS) 试剂治疗，所述方法包括：

向所述患者施用有效量的钾结合剂以通过与用所述钾结合剂治疗之前的患者的 eGFR 相比增大或稳定估计肾小球滤过率 (eGFR) 来增强或稳定所述患者的肾功能。

81. 根据权利要求 73-80 中任一项所述的方法，其中所述钾结合剂为呈盐或酸形式的

交联的 2- 氟代丙烯酸酯 - 二乙烯基苯 -1,7- 辛二烯共聚物。

82. 根据权利要求 77-80 中任一项所述的方法，还包括在有需要的患者中治疗高血钾症。

83. 根据权利要求 1-82 中任一项所述的方法，其中所述治疗期为 1、2、4、6、8、12、16、20、24、28、32、36、40、44、48、52 周或更多周数。

84. 根据权利要求 1-83 中任一项所述的方法，其中所述患者的基线估计肾小球滤过率 (eGFR) 为约 15mL/min/1.73m^{2}至约 44mL/min/1.73m^2。

85. 根据权利要求 1-84 中任一项所述的方法，其中用所述钾结合剂治疗之后的所述患者的 eGFR 与用所述钾结合剂治疗之前的所述患者的 eGFR 无明显不同。

86. 根据权利要求 1-85 中任一项所述的方法，其中在治疗 2、3、4、5、6 个月或更长之后，与用所述钾结合剂治疗之前的所述患者的 eGFR 相比，所述患者的 eGFR 增加。

87. 根据权利要求 86 所述的方法，其中与用所述钾结合剂治疗之前的所述患者的 eGFR 相比，用所述钾结合剂治疗之后的所述患者的 eGFR 增加至少 4、5、6mL/min/1.73m^2。

88. 根据权利要求 1-87 中任一项所述的方法，其中在治疗 1、2、3、4、5、6、7 天或更长之后，与用所述钾结合剂治疗之前的所述患者的血清钾水平相比，所述患者的血清钾水平降低。

89. 根据权利要求 1-88 中任一项所述的方法，其中在治疗 2、3、4、5、6 个月或更长之后，与用所述钾结合剂治疗之前的所述患者的尿 ACR 相比，所述患者的尿白蛋白 : 肌酐比 (ACR) 无明显不同。

90. 根据权利要求 60-89 中任一项所述的方法，其中在治疗 1、2、3、4、5、6、7 天或更长之后，与用所述钾结合剂治疗之前的所述患者的收缩压和舒张压相比，所述患者的收缩压和舒张压降低。

91. 根据权利要求 90 所述的方法，其中与用所述钾结合剂治疗之前的所述患者的收缩压相比，所述患者的收缩压降低 5、6、7、8mmHg 或更多。

92. 根据权利要求 90 所述的方法，其中与用所述钾结合剂治疗之前的所述患者的收缩压相比，所述患者的收缩压降低 9、10、11、12、13、14、15、16、17mm Hg 或更多。

93. 根据权利要求 90-92 中任一项所述的方法，其中与用所述钾结合剂治疗之前的所述患者的舒张压相比，所述患者的舒张压降低 2、3、4、5、6mm Hg。

94. 根据权利要求 90-92 中任一项所述的方法，其中与用所述钾结合剂治疗之前的所述患者的舒张压相比，所述患者的舒张压降低 7、8、9、10、11、12、13mm Hg 或更多。

95. 根据权利要求 90 和 92-94 中任一项所述的方法，其中与用所述钾结合剂治疗之前的所述患者的收缩压相比，所述患者的收缩压降低至少 6、7、8、9、10、11、12 或更多百分比。

96. 根据权利要求 90-92、94 和 95 中任一项所述的方法，其中与用所述钾结合剂治疗之前的所述患者的舒张压相比，所述患者的舒张压降低至少 8、9、10、11、12、13、14、15 或更多百分比。

97. 根据权利要求 1-96 中任一项所述的方法，其中在治疗 4 周或更长之后，与用所述钾结合剂治疗之前的所述患者的血清醛固酮水平相比，所述患者的血清醛固酮水平降低。

98. 根据权利要求 1-97 中任一项所述的方法，其中所述钾结合剂的有效量包含高达 60g 的最大日剂量。

99. 根据权利要求 98 所述的方法，其中所述钾结合剂的有效量包含 10g-60g 的日剂量。

100. 根据权利要求 98 所述的方法，其中所述钾结合剂的有效量包含 18g-40g 的日剂量。

101. 根据权利要求 1-100 中任一项所述的方法，其中调节所述剂量以将所述患者的血清钾水平维持在正常范围内。

102. 根据权利要求 35-59、63-72 和 81-101 中任一项所述的方法，其中呈盐或酸形式的交联的 2- 氟代丙烯酸酯 - 二乙烯基苯 -1,7- 辛二烯共聚物呈盐形式。

103. 根据权利要求 102 所述的方法，其中所述盐形式包括钠、钙、镁、铵或其组合。

104. 根据权利要求 103 所述的方法，其中所述盐形式包括钙盐形式。

105. 根据权利要求 102-104 中任一项所述的方法，其中用直链多元醇来稳定所述呈盐形式的交联的 2- 氟代丙烯酸酯 - 二乙烯基苯 -1,7- 辛二烯共聚物。

106. 根据权利要求 105 所述的方法，其中用山梨糖醇来稳定所述呈盐形式的交联的 2- 氟代丙烯酸酯 - 二乙烯基苯 -1,7- 辛二烯共聚物。

107. 根据权利要求 1-106 中任一项所述的方法，其中所述钾结合剂或呈盐或酸形式的交联的 2- 氟代丙烯酸酯 - 二乙烯基苯 -1,7- 辛二烯共聚物在所述患者中表现出长期耐受性。

108. 根据权利要求 1-107 中任一项所述的方法，其中所述钾结合剂或呈盐或酸形式的交联的 2- 氟代丙烯酸酯 - 二乙烯基苯 -1,7- 辛二烯共聚物在所述患者中表现出长期安全性。

109. 根据权利要求 1-108 中任一项所述的方法，其中所述钾结合剂或呈盐或酸形式的交联的 2- 氟代丙烯酸酯 - 二乙烯基苯 -1,7- 辛二烯共聚物在所述患者中表现出长期功效。

110. 根据权利要求 1-109 中任一项所述的方法，其中每天向所述患者施用所述钾结合剂或呈盐或酸形式的交联的 2- 氟代丙烯酸酯 - 二乙烯基苯 -1,7- 辛二烯共聚物 8 周以上。

111. 根据权利要求 1-109 中任一项所述的方法，其中每天向所述患者施用所述钾结合剂或呈盐或酸形式的交联的 2- 氟代丙烯酸酯 - 二乙烯基苯 -1,7- 辛二烯共聚物一年以上。

112. 根据权利要求 1-51、53-55 和 59-111 中任一项所述的方法，其中所述患者在用或进一步用有效量的 RAAS 试剂治疗，所述 RAAS 试剂为管紧张素转化酶 (ACE) 抑制剂、血管紧张素受体阻断剂 (ARB)、醛固酮拮抗剂 (AA)、醛固酮合酶抑制剂或其组合。

113. 根据权利要求 112 所述的方法，其中所述 RAAS 试剂为 ACE 抑制剂、ARB 或其组合。

114. 根据权利要求 112 或 113 所述的方法，其中所述 RAAS 试剂的有效量包含最大日耐受剂量。

115. 根据权利要求 112-114 中任一项所述的方法，其中所述 RAAS 试剂包含福辛普利、雷米普利、卡托普利、赖诺普利、群多普利、莫西普利、喹那普利、依那普利、贝那普利、培哚普利、依普沙坦、奥美沙坦、氯沙坦、替米沙坦、缬沙坦、坎地沙坦、厄贝沙坦、阿齐沙坦酯、安体舒通、依普利酮或其组合。

116. 根据权利要求 115 所述的方法，其中所述 RAAS 试剂包含福辛普利且最大日耐受剂量为 40mg/ 日。

117. 根据权利要求 115 所述的方法，其中所述 RAAS 试剂包含雷米普利且最大日耐受剂量为 20mg/ 日。

118. 根据权利要求 115 所述的方法，其中所述 RAAS 试剂包含卡托普利且最大日耐受剂量为 300mg/ 日。

119. 根据权利要求 115 所述的方法，其中所述 RAAS 试剂包含赖诺普利且最大日耐受剂量为 40mg/ 日。

120. 根据权利要求 115 所述的方法，其中所述 RAAS 试剂包含群多普利且最大日耐受剂量为 4mg。

121. 根据权利要求 115 所述的方法，其中所述 RAAS 试剂包含莫西普利且最大日耐受剂量为 30mg/ 日。

122. 根据权利要求 115 所述的方法，其中所述 RAAS 试剂包含喹那普利且最大日耐受剂量为 80mg/ 日。

123. 根据权利要求 115 所述的方法，其中所述 RAAS 试剂包含依那普利且最大日耐受剂量为 40mg/ 日。

124. 根据权利要求 115 所述的方法，其中所述 RAAS 试剂包含贝那普利且最大日耐受剂量为 40mg/ 日。

125. 根据权利要求 115 所述的方法，其中所述 RAAS 试剂包含培哚普利且最大日耐受剂量为 8mg/ 日。

126. 根据权利要求 115 所述的方法，其中所述 RAAS 试剂包含依普沙坦且最大日耐受剂量为 800mg/ 日。

127. 根据权利要求 115 所述的方法，其中所述 RAAS 试剂包含奥美沙坦且最大日耐受剂量为 40mg/ 日。

128. 根据权利要求 115 所述的方法，其中所述 RAAS 试剂包含氯沙坦且最大日耐受剂量为 100mg/ 日。

129. 根据权利要求 115 所述的方法，其中所述 RAAS 试剂包含替米沙坦且最大日耐受剂量为 80mg/ 日。

130. 根据权利要求 115 所述的方法，其中所述 RAAS 试剂包含缬沙坦且最大日耐受剂量为 320mg/ 日。

131. 根据权利要求 115 所述的方法，其中所述 RAAS 试剂包含坎地沙坦且最大日耐受剂量为 32mg/ 日。

132. 根据权利要求 115 所述的方法，其中所述 RAAS 试剂包含厄贝沙坦且最大日耐受剂量为 300mg/ 日。

133. 根据权利要求 115 所述的方法，其中所述 RAAS 试剂包含阿齐沙坦酯且最大日耐受剂量为 80mg/ 日。

134. 根据权利要求 115 所述的方法，其中所述 RAAS 试剂包含安体舒通且最大日耐受剂量为 200mg/ 日。

135. 根据权利要求 115 所述的方法，其中所述 RAAS 试剂包含依普利酮且最大日耐受剂量为 50mg/ 日。

136. 根据权利要求 1-55 和 59-135 中任一项所述的方法，其中所述患者在进一步用有效量的 β- 肾上腺素能阻断剂治疗。

137. 根据权利要求 136 所述的方法，其中所述 β- 肾上腺素能阻断剂包含倍他索洛尔、

比索洛尔、阿替洛尔、美托洛尔、奈比洛尔、美托洛尔、艾司洛尔、醋丁洛尔、普萘洛尔、纳多洛尔、卡维地洛、拉贝洛尔、索他洛尔、噻吗洛尔、卡替洛尔、喷布洛尔、吲哚洛尔或其组合。

治疗高血压和高血钾症的钾结合剂

发明领域

[0001] 本发明总体上涉及在有需要的患者中治疗高血压 (HTN) 的方法，其中所述患者任选还患有慢性肾病 (CKD) 或 II 型糖尿病 (T2DM)。本发明还涉及在有需要的患者中治疗肾病的方法，其中所述患者在任选地用有效量的肾素 - 血管紧张素 - 醛固酮系统 (RAAS) 试剂治疗。本发明还涉及在有需要的患者中治疗高血钾症的方法，其中所述患者患有 CKD、T2DM 或 HTN 并且在任选地用有效量的肾素 - 血管紧张素 - 醛固酮系统 (RAAS) 试剂治疗。所述方法可包括向所述患者施用有效量的钾结合剂以降低所述患者的血压和 / 或增强或稳定所述患者的肾功能。

[0002] 发明背景

[0003] 正常的肾功能对钾稳态的维持至关重要。肾脏维持钾稳态的能力取决于几个因素，包括醛固酮正常生成、钠递送到远侧肾单位和皮质集合管内充分的钠钾交换 (Palmer, B.F., N.Engl.J.Med.2004,351 :585-92)。在这些因素中，醛固酮生成和作用受肾素 - 血管紧张素 - 醛固酮系统 (RAAS)，控制血压、血量和心血管功能的调节组分的要素严密控制。因此为限制醛固酮生成和功能设计的 RAAS 抑制是对高血压、糖尿病、慢性肾病和心力衰竭的重要治疗策略。几项研究已经证明了血管紧张素受体阻断剂 (ARB) 例如氯沙坦或厄贝沙坦的肾保护作用 (Brenner, B.M. 等，N.Engl.J.Med.2001,345 :861-869 ;de Zeeuw, D. 等 Kidney Intl.2004,65 :2309-2320 ;Miao, Y. 等，Diabetologia 2010 ;Lewis, E.J. 等，N.Engl.J.Med.2001,345 :851-860 ;Atkins, R.C. 等，Am.J.Kidney Dis.2005, 45 :281-287)，而使用对 RAAS 的双重阻滞，向血管紧张素转化酶抑制剂 (ACEI) 或 ARB 疗法添加醛固酮拮抗剂（安体舒通或依普利酮）的研究经证实在心力衰竭或心肌梗塞后患者中实质上减少了心血管终点 (Pitt, B. 等，N.Engl.J.Med.1999,341 :709-717 ;Pitt, B., Molecular&Cellular Endocrinol.2004,217 :53-58 ;Zannad, F. 等，European J.Heart Failure 2010)。

[0004] 尽管已证实 RAAS 抑制剂的临床效益，但药物的基本作用模式扰乱了肾小管中的钠钾交换。因此，钾潴留可促成定义为血清钾值＞ 5.0mEq/L 的高血钾症。这在由慢性肾病和常见共病例如高血压、糖尿病和心力衰竭引起肾功能减退的患者中尤其成问题。在这种情况下，RAAS 抑制和肾功能减退的组合可使初生正钾平衡恶化并引发高钾血事件。RAAS 抑制剂剂量的停止或减少是对服用 RAAS 抑制剂，显示出血清钾水平异常升高的患者而言是常见干预，血清钾水平异常升高使患者失去 RAAS 抑制剂效益。因此，需要控制患者的血压并治疗高血钾症。

[0005] 发明概述

[0006] 本发明的一方面是一种在有需要的患者中治疗高血压的方法。所述方法包括施用将有需要的患者的血清钾控制在正常范围内的有效量的药剂。所述方法包括施用在两天治疗时间内将有需要的患者的血清钾控制在正常范围内的有效量的药剂，并且尤其长期用药，且进一步地经至少 1 个月，更特别地至少 3 个月，优选至少 6 个月且更优选至少 9 个月这样长期用药。更具体地，所述方法包括向患者施用有效量的钾结合剂，例如呈盐或酸形式

的交联的 2- 氟代丙烯酸酯 - 二乙烯基苯 -1,7- 辛二烯共聚物。

[0007] 本发明的另一方面是一种在有需要的患者中治疗高血压的方法，所述方法包括向患有高血钾症或蛋白尿症的患者施用有效量的钾结合剂。当所述钾结合剂为聚合物时，所述聚合物包含脂肪族交联阳离子交换聚合物和占所述聚合物的 5 摩尔％至 15 摩尔％的交联剂。

[0008] 本发明的再一方面是一种在有需要的患者中治疗高血压的方法，所述方法包括向患有高血钾症或蛋白尿症的患者施用有效量的钾结合剂。当所述钾结合剂为聚合物时，所述聚合物包含除聚苯乙烯阳离子交换聚合物外的交联阳离子交换聚合物且包含 5 摩尔％至 12 摩尔％的交联剂。

[0009] 另一方面是一种在有需要的慢性肾病患者中治疗高血压的方法。所述患者任选地用有效量的肾素 - 血管紧张素 - 醛固酮系统 (RAAS) 试剂治疗并且所述方法包括向患者施用有效量的钾结合剂（例如，呈盐或酸形式的交联的 2- 氟代丙烯酸酯 - 二乙烯基苯 -1,7- 辛二烯共聚物）以将所述患者的血清钾水平控制在正常范围内。

[0010] 再一方面是一种在有需要的心力衰竭患者中治疗高血压的方法。所述患者任选地用有效量的肾素 - 血管紧张素 - 醛固酮系统 (RAAS) 试剂治疗并且所述方法包括向患者施用有效量的钾结合剂（例如，呈盐或酸形式的交联的 2- 氟代丙烯酸酯 - 二乙烯基苯 -1,7- 辛二烯共聚物）以将所述患者的血清钾水平控制在正常范围内。

[0011] 又一方面是一种在有需要的 2 型糖尿病患者中治疗高血压的方法。所述患者任选地用有效量的肾素 - 血管紧张素 - 醛固酮系统 (RAAS) 试剂治疗并且所述方法包括向患者施用有效量的钾结合剂（例如，呈盐或酸形式的交联的 2- 氟代丙烯酸酯 - 二乙烯基苯 -1,7- 辛二烯共聚物）以将所述患者的血清钾水平控制在正常范围内。

[0012] 再一方面是一种在有需要的慢性肾病患者中治疗高血钾症的方法，所述患者任选地用有效量的肾素 - 血管紧张素 - 醛固酮系统 (RAAS) 试剂治疗。所述方法包括向患者施用有效量的钾结合剂（例如，呈盐或酸形式的交联的 2- 氟代丙烯酸酯 - 二乙烯基苯 -1,7- 辛二烯共聚物）以通过与用钾结合剂（例如，呈盐或酸形式的交联的 2- 氟代丙烯酸酯 - 二乙烯基苯 -1,7- 辛二烯共聚物）治疗之前的患者的血清肌酐水平相比降低患者的血清肌酐水平来增强或稳定患者的肾功能。

[0013] 本发明的另一方面是一种在有需要的慢性肾病患者中治疗高血钾症的方法，所述患者任选地用有效量的肾素 - 血管紧张素 - 醛固酮系统 (RAAS) 试剂治疗。所述方法包括向患者施用有效量的钾结合剂（例如，呈盐或酸形式的交联的 2- 氟代丙烯酸酯 - 二乙烯基苯 -1,7- 辛二烯共聚物）以通过与任选地用 RAAS 试剂治疗但未用钾结合剂治疗的慢性肾病患者相比增加终末期肾病的进展时间来增强或稳定患者的肾功能。

[0014] 再一方面是一种在有需要的慢性肾病患者中治疗高血钾症的方法，所述患者任选地用有效量的肾素 - 血管紧张素 - 醛固酮系统 (RAAS) 试剂治疗。所述方法包括向患者施用有效量的钾结合剂（例如，呈盐或酸形式的交联的 2- 氟代丙烯酸酯 - 二乙烯基苯 -1,7- 辛二烯共聚物）以通过与任选地用 RAAS 试剂治疗但未用钾结合剂治疗的慢性肾病患者相比增加存活率来增强或稳定患者的肾功能。

[0015] 又一方面是一种在有需要的慢性肾病患者中治疗高血钾症的方法，所述患者任选地用有效量的肾素 - 血管紧张素 - 醛固酮系统 (RAAS) 试剂治疗。所述方法包括向患者施用

有效量的钾结合剂（例如，呈盐或酸形式的交联的 2- 氟代丙烯酸酯 - 二乙烯基苯 -1,7- 辛二烯共聚物）以通过与用钾结合剂治疗之前的患者的 eGFR 相比增大或稳定估计肾小球滤过率 (eGFR) 来增强或稳定患者的肾功能。

[0016] 另一方面是一种在有需要的患者中治疗慢性肾病的方法，所述患者任选地用有效量的肾素 - 血管紧张素 - 醛固酮系统 (RAAS) 试剂治疗。所述方法包括向患者施用有效量的钾结合剂（例如，呈盐或酸形式的交联的 2- 氟代丙烯酸酯 - 二乙烯基苯 -1,7- 辛二烯共聚物）以通过与用钾结合剂治疗之前的患者的血清肌酐水平相比降低患者的血清肌酐水平来增强或稳定患者的肾功能。

[0017] 再一方面是一种在有需要的患者中治疗慢性肾病的方法，所述患者任选地用有效量的肾素 - 血管紧张素 - 醛固酮系统 (RAAS) 试剂治疗。所述方法包括向患者施用有效量的钾结合剂（例如，呈盐或酸形式的交联的 2- 氟代丙烯酸酯 - 二乙烯基苯 -1,7- 辛二烯共聚物）以通过与任选地用 RAAS 试剂治疗但未用钾结合剂治疗的慢性肾病患者相比增加终末期肾病的进展时间来增强或稳定患者的肾功能。

[0018] 又一方面是一种在有需要的患者中治疗慢性肾病的方法，所述患者任选地用有效量的肾素 - 血管紧张素 - 醛固酮系统 (RAAS) 试剂治疗。所述方法包括向患者施用有效量的钾结合剂（例如，呈盐或酸形式的交联的 2- 氟代丙烯酸酯 - 二乙烯基苯 -1,7- 辛二烯共聚物）以通过与任选地用 RAAS 试剂治疗但未用钾结合剂治疗的慢性肾病患者相比增加存活率来增强或稳定患者的肾功能。

[0019] 另一方面是一种在有需要的患者中治疗慢性肾病的方法，所述患者任选地用有效量的肾素 - 血管紧张素 - 醛固酮系统 (RAAS) 试剂治疗。所述方法包括向患者施用有效量的钾结合剂（例如，呈盐或酸形式的交联的 2- 氟代丙烯酸酯 - 二乙烯基苯 -1,7- 辛二烯共聚物）以通过与用钾结合剂治疗之前的患者的 eGFR 相比增大或稳定估计肾小球滤过率 (eGFR) 来增强或稳定患者的肾功能。

[0020] 其它目的和特征将部分将显而易见并且部分将在下文指出。

[0021] 附图简述

[0022] 图 1 为已经用实施例 2 中所述方案治疗 6 个月且具有任何白蛋白肌酐比 (ACR)，ACR ≥ 30 和 ACR > 300 且估计肾小球滤过率 (eGFR) 为 15-44mL/min/1.73m^{2}的患者的中心实验室血清钾浓度 (mEq/L) 相对于治疗时间的图。

[0023] 图 2 为已经用实施例 2 中所述方案治疗 6 个月且具有任何白蛋白肌酐比 (ACR)，ACR ≥ 30 和 ACR > 300 且估计肾小球滤过率 (eGFR) 为 15-44mL/min/1.73m^{2}的患者的收缩压 (SBP)(mmHg) 相对于治疗时间的图。

[0024] 图 3 为已经用实施例 2 中所述方案治疗 6 个月且具有任何白蛋白肌酐比 (ACR)，ACR ≥ 30 和 ACR > 300 且估计肾小球滤过率 (eGFR) 为 15-44mL/min/1.73m^{2}的患者的舒张压 (DBP)(mmHg) 相对于治疗时间的图。

[0025] 图 4 为已经用实施例 2 中所述方案治疗 6 个月且具有任何白蛋白肌酐比 (ACR)，ACR ≥ 30 和 ACR > 300 且估计肾小球滤过率 (eGFR) 为 15-44mL/min/1.73m^{2}的患者的尿 ACR(mg/g) 相对于治疗时间的图。

[0026] 图 5 为已经用实施例 2 中所述方案治疗 6 个月且具有任何白蛋白肌酐比 (ACR)，ACR ≥ 30 和 ACR > 300 且估计肾小球滤过率 (eGFR) 为 15-44mL/min/1.73m^{2}的患者的

eGFR(mL/min/1.73m^2) 相对于治疗时间的图。

[0027] 图 6 为具有预先存在的高血钾症，服用稳定剂量的 RAAS 抑制剂，未经导入期 (run-in period) 进行试验，如实施例 2 所述治疗 12 个月的一组患者的 eGFR 相对于治疗时间的图。对于图 6-9，提供在基线 (BL)、1 个月 (M1)、2 个月 (M2)、6 个月 (M6) 和 12 个月 (M12) 的数据。

[0028] 图 7 为具有预先存在的高血钾症，服用稳定剂量的 RAAS 抑制剂，未经导入期进行试验，如实施例 2 所述治疗 12 个月的一组患者的血清钾相对于治疗时间的图。

[0029] 图 8 为具有预先存在的高血钾症，服用稳定剂量的 RAAS 抑制剂，未经导入期进行试验，如实施例 2 所述治疗 12 个月的一组患者的尿 ACR 相对于治疗时间的图。

[0030] 图 9 为具有预先存在的高血钾症，服用稳定剂量的 RAAS 抑制剂，未经导入期进行试验，如实施例 2 所述治疗 12 个月的一组患者的收缩压和舒张压相对于治疗时间的图。

[0031] 优选实施方案描述

[0032] 可慢性或急性呈现的高血钾症可导致几种医疗并发症，包括危及生命的心律失常和猝死。高血钾症通常定义为血清钾水平或血液中的钾高于 5.0 毫当量 / 升 (mEq/L)。在独立研究中发现血清钾水平高于或等于 5.5mEq/L，我们将其定义为中度至重度高血钾症的患者的死亡率在 24h 内增加 10 倍。高血钾症最常在慢性肾病或 CKD 患者中出现，其中患者肾脏分泌钾的能力已经受损。血清钾水平的正常范围为约 3.8mEq/l 至 5.0mEq/L。

[0033] 钾结合剂可从胃肠道将钾去除并降低血清钾水平且治疗高血钾症。具体而言，钾结合聚合物可从胃肠道将钾去除并降低血清钾水平 (美国专利第 7,566,799 号)。各项研究证实，血清钾水平升高使醛固酮水平升高而血清钾水平降低使醛固酮水平降低 (T.Himathongkam 等，J.Clin.Endocrinol.Metab.1975,41(1) :153-159)。这些研究已经证实，血清钾水平的小量升高或降低可引起醛固酮水平的较大变化。另外，其它研究证实钾摄取量增加可降低血压 (He，F.J. 等，Hypertension 2005,45 :571-574)。现已发现，并且在临床上观察到，患者血清钾水平降低也使血压降低。考虑到钾结合聚合物的主要预期效益是降低血清钾，这项发现出乎意料。在有肾损害、高血钾症和高血压的患者中，鉴于这些患者有发病率和死亡率增加的重大风险，使用钾结合聚合物降低钾和血压有益。在患有高血压，无此类共病的患者中，降低血压也有益。

[0034] 钾结合剂可以是结合钾的试剂。一类钾结合剂为钾结合聚合物。各种钾结合聚合物均可用于本文所述方法中，包括交联阳离子交换聚合物。钾结合剂也可为沸石，例如硅酸锆或锗酸锆分子筛。

[0035] 用于本文所述方法的交联阳离子交换聚合物呈大体球形颗粒形式。如本文所使用，术语“大体”意为平均纵横比约 1.0 至约 2.0 的大致圆形颗粒。纵横比是颗粒最大线性尺寸与颗粒最小线性尺寸之比。纵横比可易于由本领域的普通技术人员测定。该定义包括按照定义纵横比为 1.0 的球形颗粒。

[0036] 所述颗粒可具有约 1.0、1.2、1.4、1.6、1.8 或 2.0 的平均纵横比。当在其中视野为颗粒直径的至少 2 倍的放大倍数下观察时，颗粒可为圆形或椭圆形。

[0037] 交联阳离子交换聚合物颗粒的平均直径为约 20 μm 至约 200 μm。特定范围是交联阳离子交换颗粒的平均直径为约 20 μm 至约 200 μm，约 20 μm 至约 150 μm，或约 20 μm 至约 125 μm 的范围。其它范围包括约 35 μm 至约 150 μm，约 35 μm 至约 125 μm，或约 50 μm

至约 125 μm。可使用本领域技术人员已知的技术测定粒度，包括平均直径、分布等。例如，美国药典 (USP)<429> 公开了测定粒度的方法。

[0038] 各种交联阳离子交换聚合物颗粒也具有小于约 4 体积％的直径小于约 10 μm 的颗粒；特别地，小于约 2 体积％的直径小于约 10 μm 的颗粒；更特别地，小于约 1 体积％的直径小于约 10 μm 的颗粒；甚至更特别地，小于约 0.5 体积％的直径小于约 10 μm 的颗粒。在其它情况下，特定范围为小于约 4 体积％的直径小于约 20 μm 的颗粒；小于约 2 体积％的直径小于约 20 μm 的颗粒；小于约 1 体积％的直径小于约 20 μm 的颗粒；小于约 0.5 体积％的直径小于约 20 μm 的颗粒；小于约 2 体积％的直径小于约 30 μm 的颗粒；小于约 1 体积％的直径小于约 30 μm 的颗粒；小于约 1 体积％的直径小于约 30 μm 的颗粒；小于约 1 体积％的直径小于约 40 μm 的颗粒；或小于约 0.5 体积％的直径小于约 40 μm 的颗粒。

[0039] 交联阳离子交换聚合物可具有其中不超过约 5 体积％的所述颗粒的直径小于约 30 μm(即，D(0.05) ＜ 30 μm)，不超过约 5 体积％的所述颗粒的直径大于约 250 μm(即，D(0.05) ＞ 250 μm)，和至少约 50 体积％的所述颗粒的直径在约 70 至约 150 μm 范围内的粒度分布。

[0040] 可以将交联阳离子交换聚合物的颗粒分布描述为跨度。将颗粒分布的跨度定义为 (D(0.9)-D(0.1))/D(0.5)，其中 D(0.9) 是其中 90％的颗粒的直径低于该值的值，D(0.1) 是其中 10％的颗粒的直径低于该值的值，并且 D(0.5) 是其中 50％的颗粒的直径高于该值而 50％的颗粒的直径低于该值的值，所述值通过激光衍射法测得。颗粒分布的跨度通常为约 0.5 至约 1，约 0.5 至约 0.95，约 0.5 至约 0.90，或约 0.5 至约 0.85。可使用可从 GEA Niro 获得的 Niro 法 No.A 8d(2005 年 9 月修订)，使用 Malvem Mastersizer 测量粒度分布。

[0041] 交联阳离子交换聚合物可能具有的另一种理想特性是在水合和沉积时粘度为约 10,000Pa•s 至约 1,000,000Pa•s，约 10,000Pa•s 至约 800,000Pa•s，约 10,000Pa•s 至约 600,000Pa•s，约 10,000Pa•s 至约 500,000Pa•s，约 10,000Pa•s 至约 250,000Pa•s，或约 10,000Pa•s 至约 150,000Pa•s，约 30,000Pa•s 至约 1,000,000Pa•s，约 30,000Pa•s 至约 500,000Pa•s，或约 30,000Pa•s 至约 150,000Pa•s，所述粘度在 0.01sec^{-1}的剪切速率下测得。使用通过使聚合物与稍过量的模拟肠液充分混合（按照 USP<26>)，使混合物在 37℃下沉积 3 天，并且从沉积湿聚合物轻轻倒出游离液体制备的湿聚合物测量该粘度。可使用 Bohlin VOR 流变仪（可从 Malvern Instruments Ltd.，Malvern，U.K. 获得）或等效物，采用平行板几何形状（上板直径 15mm，下板直径 30mm，板间间隙 1mm) 在维持在 37℃的温度下来测定该湿聚合物的稳态剪切粘度。

[0042] 交联阳离子交换聚合物可能还具有约 150Pa 至约 4000Pa、约 150Pa 至约 3000Pa、约 150Pa 至约 2500Pa、约 150Pa 至约 1500Pa、约 150Pa 至约 1000Pa、约 150Pa 至约 750Pa 或约 150Pa 至约 500Pa、约 200Pa 至约 4000Pa、约 200Pa 至约 2500Pa、约 200Pa 至约 1000Pa 或约 200Pa 至约 750Pa 的水合和沉积屈服应力。可使用 Reologica STRESSTECH 流变仪（可从 Reologica Instruments AB，Lund，Sweden 获得）或本领域中技术人员已知的等效方式进行动态应力扫描测量（即，屈服应力）。这种流变仪还具有平行板几何形状（上板直径 15mm，下板直径 30mm，板间间隙 1mm) 并且温度维持在 37℃下。当剪切应力从 1Pa 增加到 10^4Pa 时可使用 1Hz 的固定频率和双积分周期。

[0043] 用于本文所述方法的交联阳离子交换聚合物在呈干粉形式时还具有理想压缩性

和堆积密度。呈干燥形式的一些交联阳离子交换聚合物颗粒具有约 0.8g/cm^{3}至约 1.5g/cm^3、约 0.82g/cm^{3}至约 1.5g/cm^3、约 0.84g/cm^{3}至约 1.5g/cm^3、约 0.86g/cm^{3}至约 1.5g/cm^3、约 0.8g/cm^{3}至约 1.2g/cm^{3}或约 0.86g/cm^{3}至约 1.2g/cm^{3}的堆积密度。堆积密度会影响需要向患者施用的交联阳离子交换聚合物的体积。例如，堆积密度较高意味着较小体积将提供相同克数的交联阳离子交换聚合物。由于体积较小，这种较小体积通过使患者感到其正服用较小的量，从而可提高患者依从性。

[0044] 呈干燥形式的交联阳离子交换聚合物颗粒组成的粉末的压缩指数为约 3 至约 15、约 3 至约 14、约 3 至约 13、约 3 至约 12、约 3 至约 11、约 5 至约 15、约 5 至约 13 或约 5 至约 11。将压缩指数定义为 100*(TD-BD)/TD，其中 BD 和 TD 分别为堆积密度和振实密度。下面在实施例 3 中描述了测量堆积密度和振实密度的程序。另外，粉末形式的阳离子交换聚合物比通常用于治疗高血钾症的聚合物更易于沉淀为其最小体积。这使得堆积密度和振实密度（在振实固定数量的次数之后测量的粉末密度）之间的差异为堆积密度的约 3％至约 14％、约 3％至约 13％、约 3％至约 12％、约 3％至约 11％、约 3％至约 10％、约 5％至约 14％、约 5％至约 12％或约 5％至约 10％。

[0045] 通常，呈颗粒形式的钾结合聚合物不从胃肠道被吸收。术语“未被吸收”及其语法等同体并非意欲表示全部量的施用聚合物均未被吸收。预计一定量的聚合物可吸收。特别地，约 90％或更多的聚合物未被吸收，更特别地约 95％或更多未被吸收，更特别地约 97％或更多未被吸收，并且最特别地约 98％或更多聚合物未被吸收。

[0046] 代表胃肠道的生理等渗缓冲液中钾结合聚合物的溶胀比通常为约 1 至约 7，特别地为约 1 至约 5，更特别地为约 1 至约 3，并且更具体地，为约 1 至约 2.5。

[0047] 交联阳离子交换聚合物的溶胀比可小于 5，小于约 4，小于约 3，小于约 2.5，或小于约 2。如本文所使用，“溶胀比”指在水环境中平衡时，1g 其它非溶剂化交联聚合物吸收的溶剂克数。当对指定聚合物进行一次以上溶胀测量时，取测量平均值为溶胀比。也可通过其它非溶剂化交联聚合物吸收溶剂后的增重百分比计算聚合物溶胀。例如，溶胀比 1 对应于 100％聚合物溶胀。

[0048] 具有有利表面形态的交联阳离子交换聚合物呈具有大体光滑表面的大体球形颗粒形式。大体光滑表面是其中在几个不同表面特征处和在几个不同颗粒上随机测定的表面特征的从峰到谷的平均距离小于约 2μm、小于约 1μm 或小于约 0.5μm 的表面。通常，表面特征的峰谷之间的平均距离小于约 1μm。

[0049] 可使用几种技术，包括测量粗糙度的技术，测量表面形态。粗糙度是对表面纹理的度量。其通过实际表面与其理想形式的垂向偏差来量化。如果这些偏差大，则表面粗糙；如果偏差小，则表面光滑。通常将粗糙度视为所测表面的高频率、短波长的组成。例如，可使用接触或非接触法测量粗糙度。接触法包括将测量用触针拖拽过表面；这些仪器包括表面光度仪和原子力显微镜 (AFM)。非接触法包括干涉量度法、共聚焦显微镜术、电容和电子显微镜术。在 1997 年 D.Brune、R.Hellborg、H.J.Whitlow、O.Hunderi、Wiley-VCH 编辑的 Surface Characterization 中，第 4 章：L.Mattson 的 Surface Roughness and Microtopography，更加详细地描述了这些方法。

[0050] 对于三维测量，探针被控制在表面上的二维区域上进行扫描。两个方向上的数据点间的间距可不同。这样，可获得表面的侧视图并且可测量表面的浮凸。

[0051] 可按许多方式控制表面粗糙度。例如，确定将三种方法用于制备具有更加光滑的表面的聚（α－氟代丙烯酸酯）颗粒。第一种方法是包括溶剂，其为单体和聚合产物的可接受溶剂。第二种方法是通过盐析过程减少有机相在水相中的溶剂化。第三种方法是增加起始氟丙烯酸酯单体的疏水性。

[0052] 高血钾症长期治疗的给药方案可增加患者依从性，特别是对于按克数服用的交联阳离子交换聚合物而言。本发明还涉及通过用直链多元醇稳定的钾结合剂来从有需要的哺乳动物长期除钾的方法，特别是长期治疗高血钾症的方法，所述钾结合剂为交联脂肪族羧酸聚合物并且优选为此类聚合物的盐，其中所述聚合物呈大体球形颗粒形式。

[0053] 因此，本发明涉及在有需要的患者中治疗高血压或高血钾症或肾病的方法，所述方法包括向患者施用有效量的钾结合剂。具体而言，本发明涉及在有需要的患者中治疗高血压和高血钾症的方法。具体而言，本发明还涉及在有需要的患者中治疗肾病和高血钾症的方法。

[0054] 在本文所述方法中，钾结合剂可为呈盐或酸形式的交联的 2- 氟代丙烯酸酯 - 二乙烯基苯 -1,7- 辛二烯共聚物。

[0055] 治疗高血压或肾病的方法可包括长期施用钾结合剂。钾结合剂在患者中表现出长期耐受性、长期安全性和 / 或长期功效。在 12、16、20、24、28、32、36、40、44、48、52 周或更多周数的治疗期观察到长期耐受性、长期安全性和长期功效。治疗期也可为 2 年、3 年、4 年、5 年或更长。特别地，可向患者每日施用钾结合剂 8 周以上或每日施用一年以上。

[0056] 具体而言，呈盐或酸形式的交联的 2- 氟代丙烯酸酯 - 二乙烯基苯 -1,7- 辛二烯共聚物在患者中表现出长期耐受性、长期安全性和 / 或长期功效。在 12、16、20、24、28、32、36、40、44、48、52 周或更多周数的治疗期观察到长期耐受性、长期安全性和长期功效。治疗期也可为 2 年、3 年、4 年、5 年或更长。特别地，可向患者每日施用呈盐或酸形式的交联的 2- 氟代丙烯酸酯 - 二乙烯基苯 -1,7- 辛二烯共聚物达 8 周以上或每日施用达一年以上。

[0057] 治疗高血压和高血钾症的所述方法也可使患者的收缩压与用钾结合剂治疗之前的患者的收缩压相比降低 5、6、7、8mmHg，和 / 或使患者的舒张压与用钾结合剂治疗之前的患者的舒张压相比降低 2、3、4、5、6mmHg。

[0058] 治疗高血压和高血钾症的所述方法也可使患者的收缩压与用钾结合剂治疗之前的患者的收缩压相比降低 9、10、11、12、13、14、15、16、17mmHg 或更多，和 / 或使患者的舒张压与用钾结合剂治疗之前的患者的舒张压相比降低 7、8、9、10、11、12、13mmHg 或更多。

[0059] 治疗高血压和高血钾症的所述方法也可使患者的收缩压与用钾结合剂治疗之前的患者的收缩压相比降低至少 6、7、8、9、10、11、12％或更多百分比，和 / 或使患者的舒张压与用钾结合剂治疗之前的患者的舒张压相比降低至少 8、9、10、11、12、13、14、15 或更多百分比。

[0060] 可向用钾结合剂治疗之前收缩压高于 130mmHg 或范围从 130 至 220mmHg、135 至 200mmHg、140 至 200mmHg，145 至 200mmHg 或 150 至 180mmHg 的患者施用钾结合剂。

[0061] 可向用钾结合剂治疗之前收缩压高于 143mmHg 或范围从 143 至 200mmHg 或 143 至 180mmHg 的患者施用钾结合剂。

[0062] 在历经用钾结合剂治疗的周期的至少 90％后，患者的收缩压维持在 130、135 或 140mmHg 以下。在历经用钾结合剂治疗的周期的至少 90％后，患者的舒张压维持在 80、85

或 90mmHg 以下。

[0063] 治疗高血压的方法可包括向需要高血压治疗的心力衰竭患者、2 型糖尿病患者和 / 或慢性肾病患者施用有效量的钾结合剂，所述患者在任选地用有效量的肾素 - 血管紧张素 - 醛固酮系统 (RAAS) 试剂治疗。

[0064] 可向患有慢性肾病、心力衰竭、2 型糖尿病或其组合的患者施用治疗高血压的方法。

[0065] 可向未用醛固酮拮抗剂治疗的患者施用钾结合剂。特别地，所述患者未用安体舒通治疗。

[0066] 治疗高血压的方法可包括向没有引起高血压的另一种病状，例如 2 型糖尿病、慢性肾病、慢性心力衰竭或其组合的患者施用钾结合剂。特别地，患者无 2 型糖尿病，或患者无慢性肾病 (CKD)。

[0067] 治疗高血压的方法可包括向无 II 类或 III 类心力衰竭 (HF) 的患者施用钾结合剂。

[0068] 治疗高血压的方法还可包括向未用心力衰竭疗法治疗的患者施用钾结合剂，所述心力衰竭疗法可为血管紧张素转化酶抑制剂 (ACEI)、血管紧张素受体阻断剂 (ARB)、β 阻断剂 (BB) 或其组合。

[0069] 接受本发明治疗方法的患者不需要用包含利尿剂、钙通道阻断剂、α 阻断剂、神经系统抑制剂、血管扩张剂、血管紧张素转化酶抑制剂 (ACEI)、血管紧张素受体阻断剂 (ARB)、β 阻断剂 (BB) 或其组合的抗高血压剂来治疗。

[0070] 可向血压正常的患者施用本发明治疗高血压的方法。血压正常的患者的血清钾水平为 3.5-5.0mEq/L。

[0071] 本发明涉及在有需要的慢性肾病患者中治疗高血钾症的方法，所述患者任选地用有效量肾素 - 血管紧张素 - 醛固酮系统 (RAAS) 试剂治疗。所述方法通常包括向所述患者施用有效量的钾结合聚合物以增加或稳定患者的肾功能。

[0072] 本发明涉及在有需要的患者中治疗慢性肾病的方法，所述患者任选地用有效量肾素 - 血管紧张素 - 醛固酮系统 (RAAS) 试剂治疗。所述方法通常包括向所述患者施用有效量的钾结合聚合物以增加或稳定患者的肾功能。

[0073] 在治疗肾病的方法中，存在若干种方式，其中所述方法例如通过与用钾结合剂治疗之前的患者的血清肌酐水平相比，降低患者的血清肌酐水平；与任选地用 RAAS 试剂治疗但未用钾结合剂治疗的慢性肾病患者相比，增加终末期肾病的进展时间；与任选地用 RAAS 试剂治疗但未用钾结合剂治疗的慢性肾病患者相比，增加存活率；和 / 或与用钾结合剂治疗之前的患者的 eGFR 相比，增加或稳定估计肾小球滤过率 (eGFR)，可表现出患者肾功能增强或稳定。

[0074] 对于所有这些治疗方法，包括治疗高血压、高血钾症、慢性肾病、终末期肾病等的方法而言，钾结合剂可为钾结合聚合物。

[0075] 对于本文所述的治疗方法而言，钾结合聚合物可为交联阳离子交换聚合物。

[0076] 对于本文所述的治疗方法而言，钾结合聚合物可为脂肪族交联阳离子交换聚合物。

[0077] 对于本文所述的治疗方法而言，钾结合聚合物可为呈盐或酸形式的交联的 2- 氟

代丙烯酸酯 - 二乙烯基苯 -1,7- 辛二烯共聚物。

[0078] 对于本文所述的治疗方法而言，钾结合剂可为硅酸锆或锗酸锆分子筛。

[0079] 对于本文所述的治疗方法而言，钾结合剂可为 $Na_{2.19}ZrSi_{3.01}O_{9.11} \cdot 2.71H_2O$。

[0080] 如实施例 2 中所详述，在有 3/4 期慢性肾病 (CKD) 的 2 型糖尿病 (T2DM) 患者中进行的 II 期临床研究是有益的。所有患者用 RAAS 抑制剂治疗，并且约 40％的患者还有心力衰竭 (HF)。并且，终点测量在不同时间点从基线的变化。试验为 8 周、开放标签、随机、剂量范围研究，以测定呈盐或酸形式的交联的 2- 氟代丙烯酸酯 - 二乙烯基苯 -1,7- 辛二烯共聚物的最佳起始剂量。另外，研究含 44 周长期安全性延长组成，以便收集将支持长期使用呈盐或酸形式的交联的 2- 氟代丙烯酸酯 - 二乙烯基苯 -1,7- 辛二烯共聚物的 1 年安全性数据。具有 4.3-5.0mEq/L 的正常血清 K^+ 水平的患者加入导入期，在此期间根据需要其接受最大标记剂量的氯沙坦和 / 或附加安体舒通。在基线时血清 K^+ 水平 ＞ 5.0mEq/L 的患者未经导入期就进入研究 (图 6-9 中示出了来自这些患者中的一些的数据)。为治疗高血钾症 (血清 K^+ ＞ 5.0mEq/L)，根据国家肾脏基金会肾脏病预后质量倡议指南 11(KDOQI,2004) 关于 ACEI/ARB 剂量变更的高血钾症和血清钾分界点的定义，选择两个钾层组 (层组 1 ＝血清 K^+ ＞ 5.0-5.5mEq/L ；层组 2 ＝血清 K^+ ＞ 5.5- ＜ 6.0mEq/L)。

[0081] 该 II 期研究总共登记了治疗平均持续时间为 9.5 个月的 306 名受试者。所有受试者均完成试验，266 名受试者 8 周完成，226 名受试者 6 周完成而 197 名受试者一年完成。

[0082] 进行几项关键观察。查看临时数据，在基线时统计显著量的 182 名患者的白蛋白肌酐比 (ACR) ≥ 30mg/g，其它患者的 ACR ＞ 300mg/g 且估计肾小球滤过率 (eGFR) 为 15-44mL/min/1.73m^2。如图 1 所示，对于所有这些患者而言，在 24 周时患者的血清钾浓度从基线的平均 5.27mEq/L 降到平均 4.57mEq/L。对于 ACR ≥ 30mg/g 的患者而言，在 24 周时患者的血清钾浓度从基线的平均 5.28mEq/L 降到平均 4.60mEq/L。对于 ACR ＞ 300mg/g 的患者而言，在 24 周时患者的血清钾浓度从基线的平均 5.35mEq/L 降到平均 4.65mEq/L。对于 eGFR 为 15-44mL/min/1.73m^2 的患者而言，在 24 周时患者的血清钾浓度从基线的平均 5.33mEq/L 降到平均 4.59mEq/L。

[0083] 如图 2 所示，对于所有这些患者而言，在 24 周时患者的收缩压从基线的平均 154 降到平均 137 ；对于 ACR ≥ 30mg/g 的患者而言，在 24 周时患者的收缩压从基线的平均 154 降到平均 138 ；对于 ACR ＞ 300mg/g 的患者而言，在 24 周时患者的收缩压从基线的平均 154 降到平均 137 ；并且对于 eGFR 为 15-44mL/min/1.73m^2 的患者而言，在 24 周时患者的收缩压从基线的平均 152 降到平均 135。

[0084] 如图 3 所示，对于所有这些患者而言，在 24 周时患者的舒张压从基线的平均 83 降到平均 74 ；对于 ACR ≥ 30mg/g 的患者而言，在 24 周时患者的舒张压从基线的平均 84 降到平均 74 ；对于 ACR ＞ 300mg/g 的患者而言，在 24 周时患者的舒张压从基线的平均 86 降到平均 73 ；并且对于 eGFR 为 15-44mL/min/1.73m^2 的患者而言，在 24 周时患者的舒张压从基线的平均 82 降到平均 73。

[0085] 如图 4 所示，分别对于所有组和每个组的患者而言 (例如，ACR ≥ 30mg/g，ACR ＞ 300mg/g，eGFR 为 15-44mL/min/1.73m^2)，在 24 周治疗期后 ACR 未显著变化。

[0086] 如图 5 所示，对于 eGFR 为 15-44mL/min/1.73m^2 的患者而言，在 24 周时患者的 eGFR 从基线的平均 32mL/min/1.73m^2 增加到平均 38mL/min/1.73m^2。对于这些患者而言 eGFR 的

这种增加具有统计显著性。

[0087] 如上所述，图 6-9 示出了来自具有预先存在的高血钾症，服用稳定剂量的 RAAS 抑制剂，未经导入期进行试验的某一组患者的数据。如图 6 所示，正如在这些患者中预料的那样，基线时这些患者的 eGFR 平均值为 46mL/min/1.73m^2 随时间推移未下降。更多数据表明，在一个亚组的患者中，eGFR 似乎在一年时增大。如图 7 所示，在 12 个月时这些患者的血清钾水平平均值从基线的 5.3mEq/L 明显降低到正常范围（降到 4.6mEq/L）。如图 8 所示，这些患者在基线的尿 ACR 平均值为 853mg/g，与患者在任何时间点的尿 ACR 平均值无明显不同。如图 9 所示，这些患者的收缩压平均值从 157mmHg 降到 134mmHg 而这些患者的舒张压平均值从 85mmHg 降到 77mmHg。

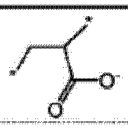
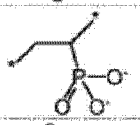
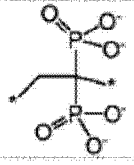
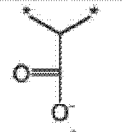
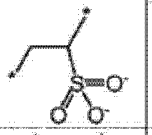
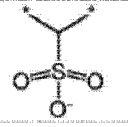
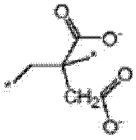
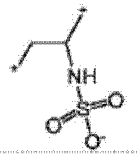
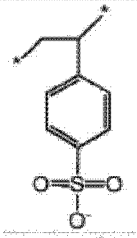
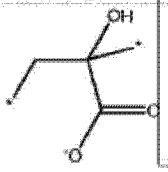
[0088] 可从研究结果进行另外的观察。第一，起始血清钾是决定呈盐或酸形式的交联的 2- 氟代丙烯酸酯 - 二乙烯基苯 -1,7- 辛二烯共聚物的功效的因素。对 304 名受试者进行的 8 周治疗起始期的期中分析显示了血清钾从基线到第 8 周的平均下降量，在受试者中血清钾上层组（层组 2 ：血清 K^+ ＞ 5.5 至＜ 6.0mEq/L）的平均下降量大致为受试者中血清钾下层组（层组 1 ：血清 K^+ ＞ 5.0 至 5.5mEq/L）的两倍（分别为 -0.90mEq/L 与 -0.47mEq/L）。在治疗第一周内观察到这种基线效应。第二，基础的 RAAS 抑制剂治疗似乎不影响呈盐或酸形式的交联的 2- 氟代丙烯酸酯 - 二乙烯基苯 -1,7- 辛二烯共聚物的功效。第三，呈盐或酸形式的交联的 2- 氟代丙烯酸酯 - 二乙烯基苯 -1,7- 辛二烯共聚物的功效似乎与共病无关。

[0089] 钾结合聚合物可为源自至少一种交联剂和至少一种单体的交联阳离子交换聚合物，所述单体含有呈其质子化或离子化形式的酸基，例如磺酸基、硫酸基、羧酸基、膦酸基、磷酸基或胺磺酰基或其组合。一般而言，用于本发明的聚合物的酸基的离子化分数在结肠的生理 pH（例如，约 pH 6.5）下高于约 75％并且体内钾结合容量高于约 0.6mEq/g，更特别地高于约 0.8mEq/g 并且甚至更特别地高于约 1.0mEq/g。通常，酸基的离子化在结肠的生理 pH（例如，约 pH 6.5）下高于约 80％，更特别地高于约 90％，并且最特别地为约 100％。

[0090] 所述含酸聚合物可含有一种以上类型的酸基。在其它情况下，所述含酸聚合物以其基本上无水或盐的形式施用并且当与生理性流体接触时产生离子化形式。表 1 示出了这些钾结合聚合物的代表性结构单元，其中键末端的星号表示键与另一结构单元或交联单元相连。

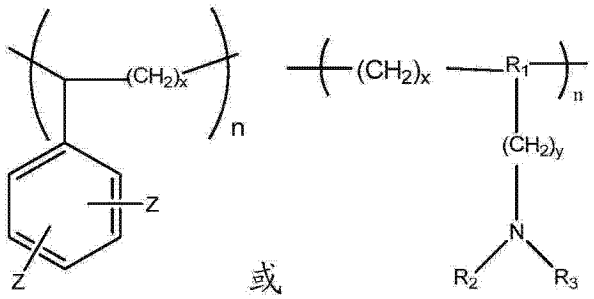
[0091] 表 1 ：阳离子交换结构单元的实例 - 结构和理论结合容量

[0092]

	摩尔质量/电荷	理论容量	在pH 3下可滴定H的分数	在pH 6下可滴定H的分数	在pH 3下的预期容量	在pH 6下的预期容量
	71	14.1	0.05	.35	0.70	4.93
	87	11.49	0.2	0.95	2.3	10.92
	53	18.9	0.25	0.5	4.72	9.43
	47.5	21.1	0.25	0.5	5.26	10.53
	57	17.5	0.1	0.5	1.75	8.77
	107	9.3	1	1	9.35	9.35
	93	10.8	1	1	10.75	10.75
	63	15.9	0	0.4	0	6.35
	125	8	1	1	8	8
	183	5.5	1	1	5.46	5.46
	87	11.49	.1	.6	1.14	6.89

[0093] 其它适合的阳离子交换聚合物含具有以下结构的重复单元：

[0094]



[0095] 其中 R_1为键或氮，R_2为氢或 Z，R_3为 Z 或 $-CH(Z)_2$，每个 Z 独立地为 SO_3H 或 PO_3H，x 为 2 或 3，并且 y 为 0 或 1，n 为约 50 或更大，更特别地 n 为约 100 或更多，甚至更特别地 n 为约 200 或更大，并且最特别地 n 为约 500 或更大。

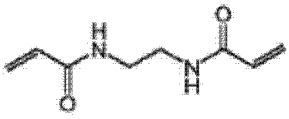
[0096] 可由分别用磺化剂例如三氧化硫 / 胺加合物或膦酸化试剂例如 P_2O_5处理的胺聚合物或单体前体获得胺磺酰基（即当 Z ＝ SO_3H 时）或磷酰胺基（即当 Z ＝ PO_3H 时）聚合物。通常，在约 6 至约 7 的 pH 下，膦酸基的酸性质子可与阳离子，如钠或钾交换。

[0097] 适合的膦酸酯单体包括膦酸乙烯酯、乙烯基 -1，1- 双膦酸酯以及膦酰羧酸酯、寡聚（亚甲基膦酸酯）和羟基乙烷 -1，1- 二膦酸的乙烯衍生物。这些单体的合成方法在本领域众所周知。

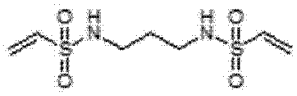
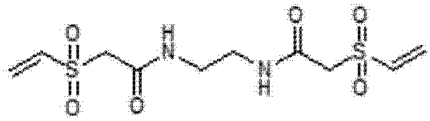
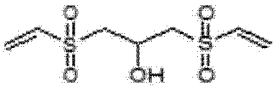
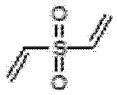
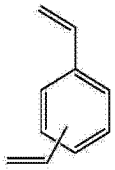
[0098] 使如上所述含酸基的的阳离子交换结构单元和重复单元交联，形成本发明的交联阳离子交换聚合物。代表性交联单体包括表 2 所示交联单体。

[0099] 表 2 :交联剂缩写及结构

[0100]

缩写	化学名称	结构	分子量
X-V-1	乙烯基双丙烯酰胺		168.2

[0101]

X-V-2	N,N'-(乙烷-1,2-二基)双(3-(N乙烯基甲酰胺)丙酰胺)		310.36
X-V-3	N,N'-(丙烷-1,3-二基)二乙烯磺胺		254.33
X-V-4	N,N'-双(乙烯基磺酰基乙酰基)乙二胺		324.38
X-V-5	1,3-双(乙烯基磺酰基) 2-丙醇		240.3
X-V-6	乙烯基砜		118.15
X-V-7	N,N'-亚甲基双丙烯酰胺		154.17
ECH	表氯醇		92.52
DVB	二乙烯基苯		130.2
ODE	1,7-辛二烯		110.2
HDE	1,5-己二烯		82.15

[0102] 可由本领域的技术人员根据聚合物颗粒的所需物理性质选择重复单元与交联剂的比率。例如，根据本领域中技术人员的一般性理解，当交联增加时，溶胀比通常降低，溶胀比可用于测定交联的量。

[0103] 按添加到聚合反应中的单体和交联剂的总重量计，聚合反应混合物中交联剂的量可在 3 重量% -15 重量%的范围内，更具体地在 5 重量% -15 重量%的范围内并且甚至更具体地在 8 重量% -12 重量%的范围内。交联剂可包括表 2 中交联剂的一种或其混合物。

[0104] 交联阳离子交换聚合物还可包括 pKa 降低基团，优选位于酸基附近，优选在酸基的 α 或 β 位置的吸电子取代基。吸电子基团的优选位置与酸基的 α 碳原子相连。通常，吸电子取代基为羟基、醚基、酯基、酸基或卤原子。更优选地，吸电子取代基为卤原子。最优选地，吸电子基团为氟并且与酸基的 α 碳原子相连。酸基为羧酸、膦酸、磷酸或其组合。

[0105] 其它特别优选的聚合物由 α - 氟代丙烯酸、二氟马来酸或其酸酐聚合产生。用于本文的单体包括 α - 氟代丙烯酸酯和二氟马来酸，最优选 α - 氟代丙烯酸酯。这种单

体可由多种途径制备，见例如，Gassen 等，J.Fluorine Chemistry,55，(1991)149-162，KF Pittman，C.U.，M.Ueda 等 (1980)Macromolecules 13(5)：1031-1036。通过氧化含氟芳香族化合物 (Bogachev 等,Zhurnal Organisheskoi Khimii,1986,22(12),2578-83 或氟化呋喃衍生物（见美国专利 5,112,993) 制备二氟马来酸。EP 415214 中给出了 α-氟代丙烯酸酯的合成模式。

[0106] 另外，钾结合聚合物可以是呈盐或酸形式的交联的 2- 氟代丙烯酸酯 - 二乙烯基苯 -1,7- 辛二烯共聚物。特别地，呈盐或酸形式的交联的 2- 氟代丙烯酸酯 - 二乙烯基苯 -1,7- 辛二烯共聚物呈盐形式。盐形式包含钠、钙、镁、铵或其组合；优选地，盐形式包含钙盐形式。

[0107] 另外，可用直链多元醇来稳定呈盐形式的交联的 2- 氟代丙烯酸酯 - 二乙烯基苯 -1,7- 辛二烯共聚物。特别地，按组合物的总重量计，可用 10 重量％至约 40 重量％的直链多元醇稳定呈盐形式的交联的 2- 氟代丙烯酸酯 - 二乙烯基苯 -1,7- 辛二烯共聚物。

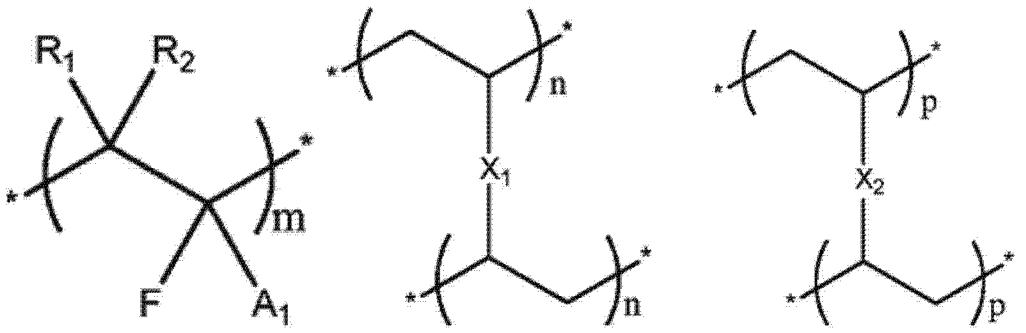
[0108] 按有效稳定聚合物盐的量，向含钾结合聚合物（例如，呈盐形式的交联的 2- 氟代丙烯酸酯 - 二乙烯基苯 -1,7- 辛二烯共聚物）的组合物中添加直链多元醇，并且通常按组合物的总重量计，约 10 重量％至约 40 重量％的直链多元醇。

[0109] 直链多元醇优选为直链糖（即，直链糖醇）。直链糖醇优选地选自 D-(+) 拉伯糖醇、赤藻糖醇、甘油、麦芽糖醇、D- 甘露糖醇、核醣醇、D- 山梨糖醇、木糖醇、苏糖醇、半乳糖醇、益寿糖、艾杜糖醇、乳糖醇及其组合，更优选地选自 D-(+) 拉伯糖醇、赤藻糖醇、甘油、麦芽糖醇、D- 甘露糖醇、核醣醇、D- 山梨糖醇、木糖醇及其组合，并且最优选地选自木糖醇、山梨糖醇及其组合。

[0110] 优选地，按组合物的总重量计，所述药物组合物包含约 15 重量％至约 35 重量％的稳定多元醇。在相同温度和储存时间下，与不含稳定多元醇的其它相同组合物相比，该直链多元醇浓度可足以减少储存时氟离子从阳离子交换聚合物的释放。

[0111] 另外，钾结合聚合物可为包含具有如以下结构表示的式 1、2 和 3 的单元的交联阳离子交换聚合物：

[0112]



式 1 式 2 式 3

[0113] 其中 R_1 和 R_2 独立地选自氢、烷基、环烷基或芳基；A_1 为呈其盐或酸形式的羧酸基、膦酸基或磷酸基；X_1 为亚芳基；X_2 为亚烷基、醚部分或酰胺部分，根据添加到聚合混合物中的单体和交联剂的比率计算，m 在约 85 至约 93 摩尔％的范围内，n 在约 1 至约 10 摩尔％的范围内，并且 p 在约 1 至约 10 摩尔％的范围内。

[0114] 当 X_2 为醚部分时，醚部分可为 $-(CH_2)_d-O-(CH_2)_e-$ 或 $-(CH_2)_d-O-(CH_2)_e-O-(CH_2)_d-$，其中 d 和 e 独立地为 1 至 5 的整数。

[0115] 优选地，d 为 1 至 2 的整数，e 为 1-3 的整数。

[0116] 当 X_2 为酰胺部分时，酰胺部分可为 $-C(O)-NH-(CH_2)_p-NH-C(O)-$，其中 p 为 1 至 8 的整数。优选地，p 为 4-6 的整数。

[0117] 与式 2 相对应的单元可源自具有式 $CH_2=CH-X_1-CH=CH_2$ 的双官能交联单体，其中 X_1 与关于式 2 定义的相同。

[0118] 与式 3 相对应的单元可源自具有式 $CH_2=CH-X_2-CH=CH_2$ 的双官能交联单体，其中 X_2 与关于式 3 定义的相同。

[0119] 关于式 1，R_1 和 R_2 为氢而 A_1 为羧酸。

[0120] 关于式 2，X_1 为任选经取代的亚苯基，并且优选为亚苯基。

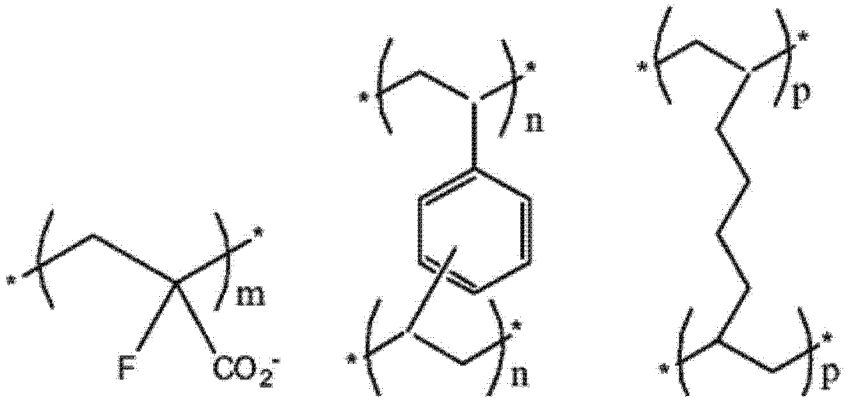
[0121] 关于式 3，X_2 为任选经取代的亚乙基、亚丙基、亚丁基、亚戊基或亚己基；更具体地，X_2 为亚乙基、亚丙基、亚丁基、亚戊基或亚己基；并且优选地，X_2 为亚丁基。具体地，R_1 和 R_2 为氢，A_1 为羧酸，X_1 为亚苯基并且 X_2 为亚丁基。

[0122] 通常，三元共聚物的式 1、2 和 3 结构单元具有特定比率，例如，其中按聚合物中式 1、2 和 3 结构单元的总重量计，根据聚合反应中所用式 11、22 和 33 的单体计算，与式 1 相对应的结构单元构成至少约 80 重量%，特别地至少约 85 重量%，并且更特别地至少约 90 重量%或约 80 重量%至约 95 重量%，约 85 重量%至约 95 重量%，约 85 重量%至约 93 重量%，或约 88 重量%至约 92 重量%，并且与式 2 相对应的结构单元和与式 3 相对应的结构单元的重量比为约 4 ： 1 至约 1 ： 4，或为约 1 ： 1。

[0123] 另外，按式 1、2 和 3 结构单元的总数量计，结构单元的比率在表示为聚合物中式 1 结构单元的摩尔分数时，为至少约 0.87 或为约 0.87 至约 0.94，或为约 0.9 至约 0.92，并且式 2 结构单元与式 3 结构单元的摩尔比为约 0.2 ： 1 至约 7 ： 1，为约 0.2 ： 1 至约 3.5 ： 1，为约 0.5 ： 1 至约 1.3 ： 1，为约 0.8 至约 0.9，或为约 0.85 ： 1；同样使用聚合反应中所用式 11、22 和 33 的单体的量进行这些计算。无需计算转化率。

[0124] 在一些方面，交联阳离子交换聚合物包含与式 1A、2A 和 3A 相对应的单元，其中式 1A、2A 和 3A 与以下结构相对应。

[0125]



式 1A 式 2A 式 3A

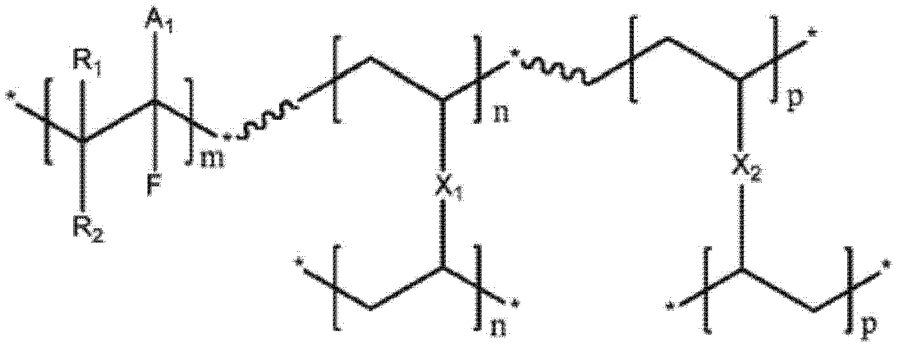
[0126] 式 1 或 1A 中，羧酸可呈酸形式（即，被氢平衡），呈盐形式（即，被抗衡离子平衡，例如 Ca^{2+}、Mg^{2+}、Na^{+}、NH_4^{+}等）或呈酯形式（即，被烷基例如甲基平衡）。优选地，羧酸呈盐形式并且与 Ca^{2+}抗衡离子平衡。

[0127] 当交联阳离子交换形式的羧酸与二价抗衡离子平衡时，两个羧酸基可与一个二价阳离子缔合。

[0128] 本文所述的聚合物通常为无规聚合物，其中未预定式 1、2 或 3（衍生自式 11、22 或 33 的单体）或 1A、2A 或 3A（衍生自式 11A、22A 或 33A 的单体）的结构单元的确切顺序。

[0129] 水解后衍生自式 11、22 或 33 的单体的阳离子交换聚合物可具有如下结构：

[0130]

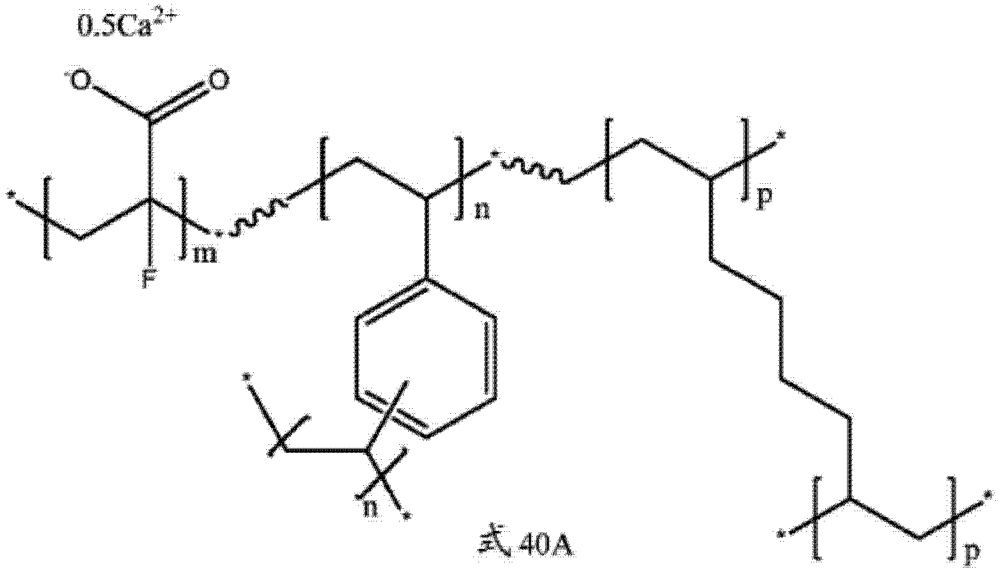


式 40

[0131] 其中 R_1、R_2、A_1、X_1和 X_2与关于式 1、2 和 3 所定义的相同并且根据添加到聚合混合物中的单体和交联剂的比率计算，m 在约 85 至约 93 摩尔％的范围内，n 在约 1 至约 10 摩尔％的范围内，并且 p 在约 1 至约 10 摩尔％的范围内。包括式 40 的聚合物结构中的波浪键以表示结构单元相互的无规连接，其中式 1 结构单元可与另一式 1 结构单元、式 2 结构单元或式 3 结构单元连接；式 2 和式 3 结构单元具有相同范围的连接可能性。

[0132] 使用本文所述的聚合工艺，用式 11A、22A 和 33A 的单体，在水解和钙离子交换后，得到具有下面所示总体结构的聚合物：

[0133]

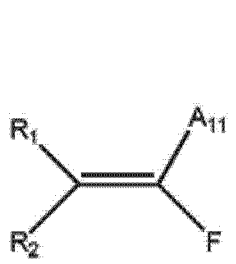


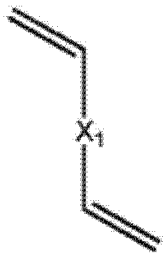
式 40A

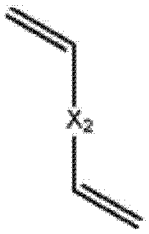
[0134] 其中根据添加到聚合混合物中的单体和交联剂的比率计算，m 在约 85 至约 93 摩尔％的范围内，n 在约 1 至约 10 摩尔％的范围内，并且 p 在约 1 至约 10 摩尔％的范围内。包括式 40A 的聚合物结构中的波浪键以表示结构单元相互的无规连接，其中式 1A 结构单元可与另一式 1A 结构单元、式 2A 结构单元或式 3A 结构单元连接；式 2A 和式 3A 结构单元具有相同范围的连接可能性。

[0135] 交联阳离子交换聚合物通常为经受聚合条件的聚合混合物的反应产物。聚合混合物还含有未化学并入聚合物的组分。交联阳离子交换聚合物通常包含氟基和为 3 种不同单体单元的聚合产物的酸基，其中一个单体包含氟基和酸基，另一单体为双官能亚芳基单体而第三个单体为双官能亚烷基、含醚或酰胺的单体。更具体地，交联阳离子交换聚合物可为包含式 11、22、33 单体的聚合混合物的反应产物。式 11 的单体、式 22 的单体和式 33 的单体具有通式：

[0136]







式 11 式 22 式 33

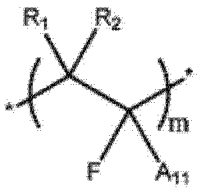
[0137] R_1和 R_2与关于式 1 定义的相同，X_1与关于式 2 定义的相同，X_2与关于式 3 定义的相同，并且 A_{11}为任选受保护的羧酸基、膦酸基或磷酸基。

[0138] 优选地，A_{11}为受保护的羧酸基、膦酸基或磷酸基。

[0139] 聚合混合物通常还包含聚合引发剂。

[0140] 包含式 11、22、33 的聚合混合物的反应产物包含具有受保护的酸基并且包含与式 10 相对应的单元和与式 2 和 3 相对应的单元的聚合物。具有受保护的酸基的聚合物产物可水解形成具有未受保护的酸基并且包含与式 1、2 和 3 相对应的单元的聚合物。与式 10 相对应的结构单元具有结构：

[0141]



式 10

[0142] R_1、R_2和 A_{11}与关于式 11 定义的相同并且 m 与关于式 1 定义的相同。

[0143] 在本发明的任何方法中，其中所述交联阳离子交换聚合物为单体聚合混合物的反应产物，A_{11}可为受保护的羧酸基、膦酸基或磷酸基。聚合反应中形成的聚合物含受保护的羧酸基、膦酸基或磷酸基。可向聚合反应中形成的聚合物添加水解剂以水解这些受保护的基

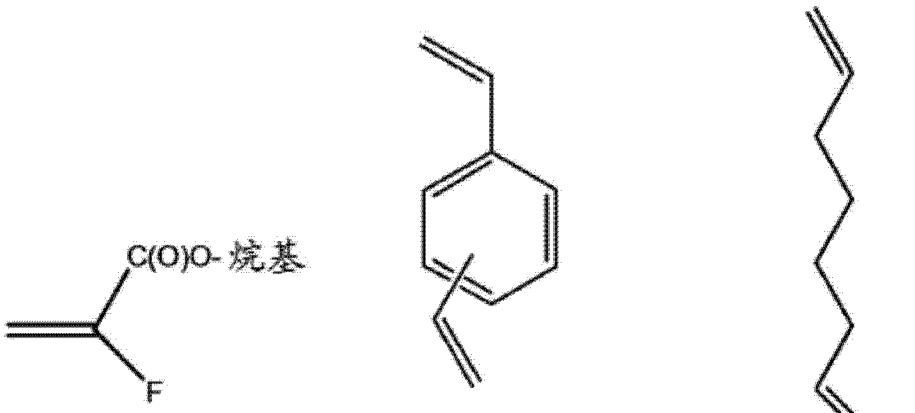
团，将其转化为羧酸基、膦酸基或磷酸基，或可使用本领域众所周知的其它去保护方法。优选使水解聚合物进行离子交换以获得供治疗用的优选聚合物盐。

[0144] 通常，按与式 11、22 和 33 相对应的单体的总重量计，聚合反应混合物包含至少约 85 重量％或约 80 重量％至约 95 重量％与式 11 相对应的单体；并且混合物的与式 22 相对应的单体和与式 33 相对应的单体的重量比为约 4 ： 1 至约 1 ： 4、约 2 ： 1 至 1 ： 2，或约 1 ： 1。

[0145] 按与式 11、22 和 33 相对应的单体的摩尔数计，聚合反应混合物可包含摩尔分数至少约 0.87 或约 0.87 至约 0.94 的与式 11 相对应的单体，并且混合物的与式 22 相对应的单体和与式 33 相对应的单体的摩尔比为约 0.2 ： 1 至约 7 ： 1、约 0.2 ： 1 至约 3.5 ： 1、约 0.5 ： 1 至约 1.3 ： 1、约 0.8 至约 0.9，或约 0.85 ： 1。

[0146] 特定交联阳离子交换聚合物为与式 11A 相对应的单体、与式 22A 相对应的单体、与式 33A 相对应的单体和聚合引发剂的反应产物。与式 11A、22A 和 33A 相对应的单体具有结构：

[0147]



式 11A 式 22A 式 33A

[0148] 其中烷基优选地选自甲基、乙基、丙基、异丙基、丁基、异丁基、仲丁基、叔丁基、戊基、异戊基、仲戊基或叔戊基。最优选地，烷基为甲基或叔丁基。-O- 烷基部分保护羧基部分免于在聚合反应期间与其它反应性部分反应并且可通过水解或下面更加详细地描述的其它去保护方法去除。

[0149] 另外，按式 11A、22A 和 33A 的单体的总重量计，反应混合物含有至少约 80 重量％，特别地至少约 85 重量％并且更特别地至少约 90 重量％或约 80 重量％至约 95 重量％、约 85 重量％至约 95 重量％、约 85 重量％至约 93 重量％或约 88 重量％至约 92 重量％的与式 11A 相对应的单体，并且与式 22A 相对应的单体和与式 33A 相对应的单体的重量比为约 4 ： 1 至约 1 ： 4 或约 1 ： 1。另外，按式 11A、22A 和 33A 的单体的总摩尔数计，反应混合物可具有摩尔分数为至少约 0.87 或约 0.87 至约 0.94 的式 11A 单体并且混合物的式 22A 单体与式 33A 单体的摩尔比为约 0.2 ： 1 至约 7 ： 1、约 0.2 ： 1 至约 3.5 ： 1、约 0.5 ： 1 至约 1.3 ： 1、约 0.8 至约 0.9，或约 0.85 ： 1。

[0150] 通常，按与式 11A、22A 和 33A 相对应的单体的总重量计，反应混合物含有约 80 重量％至约 95 重量％的与式 11A 相对应的单体。另外，与式 22A 相对应的单体和与式 33A 相

对应的单体的重量比为约 4 ： 1 至约 1 ： 4 或约 1 ： 1。另外，按式 11A、22A 和 33A 的单体的总摩尔数计，反应混合物可具有摩尔分数为约 0.9 至约 0.92 的式 11A 单体。同样，混合物的式 22A 单体与式 33A 单体的摩尔比为约 0.2 ： 1 至约 7 ： 1、约 0.2 ： 1 至约 3.5 ： 1、约 0.5 ： 1 至约 1.3 ： 1、约 0.8 至约 0.9，或约 0.85 ： 1。

[0151] 采用被引发的聚合反应，其中在聚合反应混合物中使用聚合引发剂以帮助引发聚合反应。在悬浮聚合反应中制备聚（氟代丙烯酸甲酯）或（聚 MeFA）或本发明的任何其它交联阳离子交换聚合物时，就聚合物颗粒稳定性、聚合物颗粒收率和聚合物颗粒形状而言，自由基引发剂的性质对悬浮液的质量起作用。使用水不溶性自由基引发剂，例如过氧化月桂酰，可产生高收率的聚合物颗粒。不受任何特定理论约束，据信水不溶性自由基引发剂主要在含式 11、22 和 33 的单体的分散相中引发聚合。此类反应方案提供了聚合物颗粒，而不是本体聚合物凝胶。因此，所述工艺使用水溶性低于 0.1g/L，特别是低于 0.01g/L 的自由基引发剂。聚氟代丙烯酸甲酯颗粒可用低水溶性自由基引发剂在水相中存在盐如氯化钠的情况下产生。

[0152] 聚合引发剂可选自多种类别的引发剂。例如，热暴露时生成聚合物引发基团的引发剂包括过氧化物、过硫酸盐或偶氮类引发剂（例如，2,2′ - 偶氮双 (2- 甲基丙腈）、过氧化月桂酰 (LPO)、叔丁基过氧化氢、2,2′ - 偶氮双 (2- 甲基丙酸二甲酯）、2,2′ - 偶氮双 [2- 甲基 -N-(2- 羟乙基丙酰胺]、2,2′ - 偶氮双 [2-(2- 咪唑啉 -2- 基）丙烷]、(2,2″ - 偶氮双 (2,4- 二甲基戊腈）、偶氮双异丁腈 (AIBN) 或其组合。另一类聚合物引发基团是由氧化还原反应生成的基团，例如过硫酸盐和胺。基团也可通过将某些引发剂暴露于紫外光或暴露于空气中生成。

[0153] 对于在聚合混合物中含有并非有意并入聚合物的附加组分的聚合反应而言，此类附加组分通常包含表面活性剂、溶剂、盐、缓冲液、水相聚合引发剂和 / 或本领域中技术人员已知的其它组分。

[0154] 以悬浮模式进行聚合时，在水相中可能含附加组分，而在有机相中可能含单体和引发剂。存在水相时，水相可能由水、表面活性剂、稳定剂、缓冲液、盐和聚合引发剂组成。

[0155] 表面活性剂可选自阴离子表面活性剂、阳离子表面活性剂、非离子表面活性剂、两性表面活性剂、两性离子表面活性剂或其组合。阴离子表面活性剂通常基于硫酸盐、磺酸盐或羧酸盐阴离子。这些表面活性剂包括十二烷基硫酸钠 (SDS)、十二烷基硫酸铵、其它烷基硫酸盐、月桂醇醚硫酸钠（或月桂基乙醚硫酸钠 (SLES)）、N- 十二烷基肌氨酸钠盐、月桂基二甲基氧化胺 (LDAO)、乙基三甲基溴化铵 (CTAB)、二 (2- 乙基己基）磺基琥珀酸钠盐、烷基苯磺酸盐、肥皂、脂肪酸盐或其组合。

[0156] 例如，阳离子表面活性剂含有季铵盐阳离子。这些表面活性剂为十六烷基三甲基溴化铵 (CTAB 或十六烷基三甲基溴化铵）、氯化十六烷吡啶 (CPC)、聚乙氧基化牛脂胺 (POEA)、杀藻胺 (BAC)、苄索氯铵 (BZT) 或其组合。

[0157] 两性离子或两性表面活性剂包括十二烷基甜菜碱、月桂基二甲基氧化胺、椰油酰胺丙基甜菜碱、可可两性甘氨酸盐或其组合。

[0158] 非离子表面活性剂包括烷基聚（氧化乙烯）、聚（氧化乙烯）和聚（氧化丙烯）的共聚物（商业上称为聚羟亚烃或泊洛沙胺）、烷基多葡萄糖苷（包括辛基葡糖苷、癸基麦芽糖苷）脂肪醇、鲸蜡醇、油醇、椰子酰胺 MEA、椰子酰胺 DEA 或其组合。其它药学上可接

受的表面活性剂在本领域众所周知并且在 McCutcheon 的 Emulsifiers and Detergents, N.American Edition(2007) 中有描述。

[0159] 聚合反应稳定剂可选自有机聚合物和无机微粒稳定剂。实例包括聚乙烯醇 - 共 - 乙酸乙烯酯及其一系列水解产物、聚乙酸乙烯酯、聚乙烯吡咯烷酮、聚丙烯酸盐、纤维素醚、天然树胶或其组合。

[0160] 缓冲液可选自例如,4-2- 羟乙基 -1- 哌嗪乙烷磺酸、2-{[三 (羟甲基) 甲基] 氨基 } 乙烷磺酸、3-(N- 吗啉) 丙磺酸、哌嗪 -N, N′ - 二 (2- 乙烷磺酸)、磷酸氢二钠七水合物、磷酸二氢钠一水合物或其组合。

[0161] 聚合反应盐可选自氯化钾、氯化钙、溴化钾、溴化钠、碳酸氢钠、过硫酸铵或其组合。

[0162] 正如本领域所知可使用聚合抑制剂并且选自 1,1,3- 三 (2- 甲基 -4- 羟基 -5- 叔丁基苯基) 丁烷、1,3,5- 三甲基 -2,4,6- 三 (3,5- 二 - 叔丁基 -4- 羟苄基) 苯、1- 氮杂 -3,7- 二氧杂双环 [3.3.0] 辛烷 -5- 甲醇、2,2′ - 亚乙基 - 双 (4,6- 二 - 叔丁基苯酚)、2,2′ - 亚乙基双 (4,6- 二 - 叔丁基苯基) 氟亚磷酸酯、2,2′ - 亚甲基双 (6- 叔丁基 -4- 乙基苯酚)、2,2′ - 亚甲基双 (6- 叔丁基 -4- 甲基苯酚)、2,5- 二 - 叔丁基 -4- 甲氧基苯酚、2,6- 二 - 叔丁基 -4-(二甲氨基甲基) 苯酚、2- 庚酮肟、3,3′ ,5,5′ - 四甲基联苯基 -4,4′ - 二醇、3,9- 二 (2,4- 二异丙苯苯氧基)-2,4,8,10- 四氧杂 -3,9- 二磷杂螺 [5.5] 十一烷、4,4- 二甲基噁唑烷、4- 甲基 -2- 戊酮肟、5- 乙基 -1- 氮杂 -3,7- 二氧杂双环 [3.3.0] 辛烷辛烷、6,6′ - 二羟基 -5,5′ - 二甲氧基 -[1,1′ - 二苯基]-3,3′ - 二甲醛、3,3′ - 硫代二丙酸双十八醇酯、3,3′ - 硫代二丙酸二 (十四烷醇) 酯、3,3′ - 硫代二丙酸二 (十三烷基) 酯、3-(3,5- 二 - 叔丁基 -4- 羟苯基) 丙酸十八烷基酯、四 (3,5- 二 - 叔丁基 -4- 羟基苯基) 丙酸] 羟基氢化肉桂酸季戊四醇酯、聚 (1,2- 二氢 -2,2,4- 三甲基喹啉)、D- 异抗坏血酸钠一水合物、四 (2,4- 二 - 叔丁基苯基)-4,4′ - 联苯基二亚磷酸酯、三 (3,5- 二 - 叔丁基 -4- 羟苄基) 异氰脲酸酯、三 (4- 叔丁基 -3- 羟基 -2,6- 二甲基苄基) 异氰脲酸酯、亚硝酸钠或其组合。

[0163] 通常,使聚合混合物经受聚合条件。正如本文已经讨论那样,虽然优选悬浮聚合,但是也可在本体、溶液或乳液聚合工艺中制备本发明的聚合物。根据本发明的公开内容,此类工艺的详情在本领域中普通技术人员的技术范围内。聚合条件通常包括聚合反应温度、压力、混合和反应器几何形状、聚合混合物的添加顺序和速率等。

[0164] 聚合温度通常在约 50 至 100℃范围内。聚合压力通常在大气压力下运行,但是可在高压 (例如 130PSI 氮气) 下运行。聚合取决于聚合规模和所用设备,并且在本领域中普通技术人员的技术范围内。在以引用的方式并入本文的美国申请公布第 2005/0220752 号中描述了各种 α - 氟代丙烯酸酯聚合物和这些聚合物的合成。

[0165] 如本文连同实例更加详细描述那样,可在聚合悬浮聚合反应中,通过制备有机相和水相合成交联阳离子交换聚合物。有机相通常含有式 11 的单体、式 22 的单体、式 33 的单体和聚合引发剂。水相含有悬浮稳定剂、水溶性盐、水和任选缓冲液。然后合并有机相和水相并且在氮气下搅拌。通常加热混合物约 2.5 至约 3.5h 到约 60℃至约 80℃,在引发聚合后使其上升到 95℃,然后冷却至室温。冷却之后,去除水相。向混合物中加水,搅拌混合物,并过滤所生成的固体。用水、醇或醇 / 水混合物洗涤固体。

[0166] 如上所述，聚合悬浮稳定剂，例如聚乙烯醇，用于防止聚合过程中颗粒聚结。另外，已经观察到在水相中加氯化钠减少了聚结和颗粒聚集。适合该目的的其它盐包括在水相中可溶的盐。按约 0.1 重量％至约 10 重量％，特别地约 2 重量％至约 5 重量％并且甚至更特别地约 3 重量％至约 4 重量％的浓度添加水溶性盐。

[0167] 优选地，制备 2- 氟代丙烯酸甲酯 (90 重量％）、1,7- 辛二烯 (5 重量％）和二乙烯基苯 (5 重量％）的有机相并且添加 0.5 重量％的过氧化月桂酰以引发聚合反应。另外，制备水、聚乙烯醇、磷酸盐、氯化钠和亚硝酸钠的水相。在氮气下并且在保持温度低于约 30℃的同时，将水相和有机相混合在一起。一经完全混合，就边不断搅拌边逐渐加热反应混合物。引发聚合反应之后，使反应混合物的温度上升到约 95℃。一旦聚合反应完全，就将反应混合物冷却至室温并去除水相。在向混合物中加水后，可通过过滤分离固体。所生成的产物为交联 (2- 氟代丙烯酸甲酯）- 二乙烯基苯 -1,7- 辛二烯三元共聚物。

[0168] 如本文所讨论，聚合后，产物可水解或另外用本领域中已知的方法去保护。为了水解具有酯基的聚合物以形成具有羧酸基的聚合物，优选地，用强碱（例如，NaOH、KOH、$Mg(OH)_2$或 $Ca(OH)_2$）水解聚合物以去除烷基（例如，甲基）并形成羧酸盐。根据水解混合物的 pH，形成 (2- 氟代丙烯酸）- 二乙烯基苯 -1,7- 辛二烯三元共聚物的质子形式。可选地，可用强酸（例如，HCl）水解聚合物以形成羧酸盐。优选地，在约 30℃至约 100℃的温度下用过量氢氧化钠水溶液水解 (2- 氟代丙烯酸）- 二乙烯基苯 -1,7- 辛二烯三元共聚物以产生 (2- 氟代丙烯酸钠）- 二乙烯基苯 -1,7- 辛二烯三元共聚物。通常，水解反应进行约 15-25h。水解后，过滤固体并用水和 / 或醇洗涤。

[0169] 水解反应或其它去保护步骤中形成的聚合物盐的阳离子取决于该步骤中所用的碱。例如，用氢氧化钠作为碱时，形成聚合物的钠盐。通过使钠盐与过量的含水金属盐接触可使这种钠离子与另一种阳离子交换以产生所需聚合物盐的不溶性固体。所需离子交换后，用醇和 / 或水洗涤产物并且直接干燥或在用变性醇脱水处理后干燥；优选地，用水洗涤产物并直接干燥。例如，通过用将钠替换为钙的溶液洗涤，例如使用氯化钙、醋酸钙、乳酸葡萄糖酸钙或其组合洗涤，将阳离子交换聚合物的钠盐转化为钙盐。并且，更具体地，为将钠离子交换为钙离子，使 (2- 氟代丙烯酸钠）- 二乙烯基苯 -1,7- 辛二烯三元共聚物与过量氯化钙水溶液接触以产生交联 (2- 氟代丙烯酸钙）- 二乙烯基苯 -1,7- 辛二烯三元共聚物的不溶性固体。如果水解混合物的 pH 足够低，则形成 (2- 氟代丙烯酸）- 二乙烯基苯 -1,7- 辛二烯三元共聚物的质子形式。

[0170] 使用这种悬浮聚合工艺，以高收率分离出交联聚 MeFA 聚合物，通常高于约 85％，更特别地高于约 90％。并且甚至更特别地高于约 93％。第二步（即，水解）的收率优选地以 100％存在，从而提供水解后高于约 85％，更特别地高于约 90％。并且甚至更特别地高于约 93％的总体收率。

[0171] 为了向组合物中添加直链多元醇，则用多元醇（例如，山梨糖醇）水溶液将聚合物的盐调成浆料，通常按聚合物重量计，浆料含过量的多元醇。进行该步骤可减少组合物中的无机氟化物。将浆料维持在本领域中技术人员已知的条件下，例如至少 3h 并且维持在环境温度和压力下。然后过滤出固体并干燥至所需水分含量。

[0172] 高血压、高血钾症和慢性肾病的治疗方法可使用多个治疗期，包括 1、2、4、6、8、12、16、20、24、28、32、36、40、44、48、52 周或更多周数的治疗期。治疗期也可为 2 年、3 年、4 年、

5 年或更长。

[0173] 使用本发明的方法为患者治疗高血钾症或慢性肾病时，患者的估计肾小球滤过率 (eGFR) 可为约 15mL/min/1.73m^{2}至约 44mL/min/1.73m^2。

[0174] 治疗高血钾症的方法、在有慢性肾病、2 型糖尿病、心力衰竭或其组合的患者中治疗高血压的方法及本发明的治疗慢性肾病的方法可产生几种改善，例如与用钾结合剂治疗之前的患者的血清钾水平相比，治疗 48h 或更长时间后患者的血清钾水平降低；与用钾结合剂治疗之前的患者的 eGFR 相比，治疗 2、3、4、5、6 个月或更长时间后患者的 eGFR 增大；与用钾结合剂治疗之前的患者的尿 ACR 相比，治疗 2、3、4、5、6 个月或更长时间后患者的尿白蛋白：肌酐比 (ACR) 降低；与用钾结合剂治疗之前的患者的收缩压和舒张压相比，治疗 1、2、3、4、5、6、7 天或更长时间后患者的收缩压和舒张压降低；与用钾结合剂治疗之前的患者的血清醛固酮水平相比，治疗 6、12、24、48、72h 或更长时间后患者的血清醛固酮水平降低，或其组合。

[0175] 对于血清钾水平、eGFR、血压和 ACR 的变化，应理解即使在描述所述方法，涉及施用呈盐或酸形式的 2- 氟代丙烯酸酯 - 二乙烯基苯 -1,7- 辛二烯共聚物时，钾结合剂也可为本文所述的任一种试剂。

[0176] 在正任选用有效量的肾素 - 血管紧张素 - 醛固酮系统 (RAAS) 试剂治疗的有需要的慢性肾病患者中治疗高血钾症的方法包括向患者施用有效量的钾结合剂并观察到 (i) 与用钾结合剂治疗之前的患者的血清肌酐水平相比，患者的血清肌酐水平降低，(ii) 与任选用 RAAS 剂治疗但未用钾结合剂治疗的慢性肾病患者相比，终末期肾病的进展时间增加，(iii) 与任选用 RAAS 剂治疗但未用钾结合剂治疗的慢性肾病患者相比，存活率增加，或 (iv) 与用钾结合剂治疗之前的患者的 eGFR 相比，估计肾小球滤过率 (eGFR) 增大或稳定，所有这些表明所述患者的肾功能增强或稳定。

[0177] 钾结合剂可为呈盐或酸形式的交联的 2- 氟代丙烯酸酯 - 二乙烯基苯 -1,7- 辛二烯共聚物。

[0178] 治疗高血钾症的方法、在有慢性肾病、2 型糖尿病、心力衰竭或其组合的患者中治疗高血压的方法及治疗慢性肾病的方法可导致与用钾结合剂治疗之前的患者的 eGFR 相比，在用钾结合剂治疗后患者的 eGFR 增大至少 4、5、6mL/min/1.73m^{2}或更多。

[0179] 在有需要的患者治疗高血压、高血钾症或慢性肾病时，钾结合剂的有效量包含高达 60g 的最大日剂量。钾结合剂的有效量可为约 3g 至约 60g、约 5g 至约 60g、约 7g 至约 60g、约 10g 至约 60g、约 12g 至约 60g 或约 15g 至约 60g 的日剂量。

[0180] 钾结合剂的有效量可为约 3g 至约 40g、约 5g 至约 40g、约 10g 至约 40g 或约 15g 至约 40g 的日剂量。

[0181] 特别地，钾结合剂的有效量可为约 18g 至约 60g 或约 18g 至约 40g 的日剂量。

[0182] 当钾结合剂为呈盐或酸形式的交联的 2- 氟代丙烯酸酯 - 二乙烯基苯 -1,7- 辛二烯共聚物时，通过测定交联 2- 氟代丙烯酸酯 - 二乙烯基苯 -1,7- 辛二烯共聚物的盐形式加上钙抗衡离子的量，计算按克数计的剂量。因此，该剂量不包括施用给患者的粉末中可能含有的水和山梨糖醇。

[0183] 给药可每日一次、每日两次或每日三次，然而，优选每日一次或每日两次，最优选每日一次。

[0184] 本发明的治疗高血压、高血钾症或慢性肾病的方法还可包括向患者施用有效量的肾素－血管紧张素－醛固酮系统 (RAAS) 试剂；测定患者体内的血清钾水平；并且根据血清钾水平，如果高于或等于 5.1mEq/L，则增大随后向患者施用的钾结合剂的量。治疗高血压、高血钾症或慢性肾病的方法还可包括其中钾结合剂的量每天增加 5g 或 10g 的步骤。

[0185] 本发明的治疗高血压、高血钾症或慢性肾病的方法还可包括向患者施用有效量的肾素－血管紧张素－醛固酮系统 (RAAS) 试剂；测定患者体内的血清钾水平；并且根据血清钾水平，如果低于 4.0mEq/L，则减少随后向患者施用的钾结合剂的量。治疗高血压、高血钾症或慢性肾病的方法还可包括其中钾结合剂的量每天减少 5g 或 10g 的步骤。

[0186] 本发明的治疗高血压、高血钾症或慢性肾病的方法还可包括治疗蛋白尿症。

[0187] 另外，治疗高血压、高血钾症、蛋白尿症或慢性肾病的方法可包括用有效量的 RAAS 试剂治疗患者，RAAS 试剂为血管紧张素转化酶 (ACE) 抑制剂、血管紧张素受体阻断剂 (ARB)、醛固酮拮抗剂 (AA)、醛固酮合酶抑制剂或其组合。特别地，可用有效量的 RAAS 试剂治疗患者，RAAS 试剂为 ACE 抑制剂、ARB 或其组合。

[0188] 对于用有效量的 RAAS 试剂治疗患者的方法，RAAS 试剂的有效量包含最大日耐受剂量。

[0189] RAAS 试剂包含福辛普利 (fosinopril)、雷米普利 (ramipril)、卡托普利 (captopril)、赖诺普利 (lisinopril)、群多普利 (trandolapril)、莫西普利 (moexipril)、喹那普利 (quinapril)、依那普利 (enalapril)、贝那普利 (benazepril)、培哚普利 (perindopril)、依普沙坦 (eprosartan)、奥美沙坦 (olmesartan)、氯沙坦 (losartan)、替米沙坦 (telmisartan)、缬沙坦 (valsartan)、坎地沙坦 (candesartan)、厄贝沙坦 (irbesartan)、阿齐沙坦酯 (azilsartan medoxomil)、安体舒通 (spironolactone)、依普利酮 (eplerenone) 或其组合。

[0190] 特定 RAAS 试剂的最大日耐受剂量为 4mg/ 日（群多普利）、8mg/ 日（培哚普利）、20mg/ 日（雷米普利）、30mg/ 日（莫西普利）、32mg/ 日（坎地沙坦）、40mg/ 日（福辛普利、赖诺普利、依那普利、贝那普利、奥美沙坦）、80mg/ 日（喹那普利、替米沙坦、阿齐沙坦酯）、100mg/ 日（氯沙坦）、300mg/ 日（卡托普利、厄贝沙坦）、320mg/ 日（缬沙坦）、or 800mg/ 日（依普沙坦）。

[0191] 当 RAAS 试剂包含安体舒通时，最大日耐受剂量为 200mg/ 日。

[0192] 当 RAAS 试剂包含依普利酮时，最大日耐受剂量为 50mg/ 日。

[0193] 用本发明的治疗高血压、高血钾症或慢性肾病的方法治疗的患者可进一步用有效量的 β－肾上腺素能阻断剂治疗。β－肾上腺素能阻断剂可包含倍他索洛尔 (betaxolol)、比索洛尔 (bisoprolol)、阿替洛尔 (atenolol)、美托洛尔 (metoprolol)、奈比洛尔 (nebivolol)、美托洛尔 (metoprolol)、艾司洛尔 (esmolol)、醋丁洛尔 (acebutolol)、普萘洛尔 (propranolol)、纳多洛尔 (nadolol)、卡维地洛 (carvedilol)、拉贝洛尔 (labetalol)、索他洛尔 (sotalol)、噻吗洛尔 (timolol)、卡替洛尔 (carteolol)、喷布洛尔 (penbutolol)、吲哚洛尔 (pindolol) 或其组合。

[0194] 在上述所有方法中，钾结合剂可为呈盐或酸形式的交联的 2- 氟代丙烯酸酯－二乙烯基苯 -1,7- 辛二烯共聚物。

[0195] 如本文所使用的术语“治疗”包括实现治疗效益。用治疗效益意指根除、改善或预

防治疗的潜在病症。例如，在高血钾症患者中，治疗效益包括根除或改善潜在高血钾症。同样，以根除、改善或预防与潜在病症相关的一种或多种生理症状实现治疗效益，以致尽管患者仍患有潜在病症，但在患者中观察到好转。例如，向经历高血钾症的患者施用钾结合聚合物不但在患者的血清钾水平降低时，而且在相对于伴随高血钾症的其它病症例如肾衰竭，在患者中观察到好转时提供了治疗效益。在一些治疗方案中，即使可能尚未作出高血钾症的诊断，也可向处于发展高血钾症风险的患者或向报告出高血钾症的一种或多种生理症状的患者施用本发明的交联阳离子交换聚合物或组合物。

[0196] 终末期肾病特征在于患者正在透析或经肾移植。

[0197] 蛋白尿症，也称为蛋白尿或尿白蛋白，是其中尿含有异常量的蛋白质的一种病状。白蛋白是血液中的主要蛋白质。蛋白质是所有身体部位，包括肌肉、骨、毛发和指甲的组成部件。血液中的蛋白质还执行许多重要功能。其保护身体免于感染，帮助血液凝集，并保持适量的流体在整个身体循环。

[0198] 当血液通过健康的肾脏时，其过滤出废产物并留下身体需要的物质，如白蛋白和其它蛋白质。大多数蛋白质太大而不能通过肾脏的过滤器进入尿液。然而，当称为肾小球的肾脏过滤器损坏时，来自血液的蛋白质可以渗入尿液中。

[0199] 蛋白尿症是慢性肾病 (CKD) 的病征，其可由糖尿病、高血压和在肾脏中引起炎症的疾病产生。为此，测试尿液中的白蛋白是每个人常规医疗评估的一部分。肾脏疾病病有时称为肾病。如果 CKD 进展，则当肾脏完全衰竭时，可导致终末期肾病 (ESRD)。有 ESRD 的患者必须接受肾移植或称为透析的定期血液清洗治疗。

[0200] 用于本发明方法中的钾结合聚合物可作为含有效量，即有效实现治疗或预防效益的量的钾结合聚合物和药学上可接受的载体的药物组合物施用。对特定应用有效的实际量将取决于患者（例如，年龄、体重等）、受治病状和施用途径。尤其根据本文的公开内容，有效量的测定完全在本领域中技术人员的能力范围之内。用于人的有效量将由动物模型测定。例如，可配制用于人的剂量以达到已经在动物中发现有效的胃肠浓度。

[0201] 本文所述的聚合物和组合物可用作食品和 / 或食品添加剂。可在食用前或在包装的同时将其加入食品中。

[0202] 可使用各种施用途径或方式向患者递送本文所述的聚合物或其药学上可接受的盐或组合物。最优选的施用途径为口服、肠内或直肠。直肠施用途径为本领域的技术人员已知。肠内施用途径通常指直接施用到胃肠道一段，例如通过胃肠管或通过吻合口。最优选的施用途径为口服。

[0203] 聚合物（或其药学上可接受的盐）本身可施用或呈药物组合物的形式施用，其中活性化合物与一种或多种药学上可接受的赋形剂掺和或混合。根据本发明使用的药物组合物可按常规方式使用一种或多种药学上可接受的赋形剂配制成生理学上可使用的制剂，所述赋形剂包括载体、稀释剂和有利于处理活性化合物的助剂。适当的组合物将取决于所选施用途径。

[0204] 对于口服施用，可通过将聚合物或组合物与本领域众所周知的药学上可接受的赋形剂合并，容易地配制本发明的聚合物和组合物。此类赋形剂使得本发明的组合物能够配制成片剂、丸剂、糖衣丸、胶囊、液体、凝胶、糖浆、膏剂、混悬剂、糯米纸囊剂等，供要治疗的患者口服摄入。

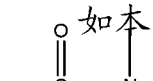
[0205] 口服组合物不可有肠溶衣。

[0206] 口服用药物制剂可作为固体赋形剂获得，任选研磨所得混合物并且若需要，在添加适合助剂之后加工颗粒混合物，以获得片剂或糖衣丸核。具体而言，适合的赋形剂为填料例如糖，包括乳糖或蔗糖；纤维素制剂例如玉米淀粉、小麦淀粉、米淀粉、马铃薯淀粉、白明胶、黄蓍胶、甲基纤维素、羟丙基甲基纤维素、羧甲基纤维素钠和 / 或聚乙烯吡咯烷酮 (PVP)；和本领域已知的各种调味剂。若需要，可添加崩解剂，例如交联聚乙烯吡咯烷酮、琼脂或海藻酸或其盐例如海藻酸钠。

[0207] 活性成分（例如，聚合物）按重量计构成口服剂型的约 20％以上，更特别地约 40％以上，甚至更特别地约 50％以上，并且最特别地约 60％以上，其余部分包含适合的赋形剂。在含水和直链多元醇的组合物中，聚合物按重量计构成口服剂型的优选约 20％以上，更特别地约 40％以上，并且甚至更特别地约 50％以上。

[0208] 本发明的聚合物可作为呈液体组合物形式的药物组合物提供。药物组合物可含分散于适合液体赋形剂中的聚合物。适合的液体赋形剂在本领域中已知；见，例如，Remington’s Pharmaceutical Sciences。

[0209] 除非另外指出，如本文单独地或作为另一基团的一部分描述的烷基是含 1-20 个碳原子且优选 1-8 个碳原子的任选经取代的直链饱和单价烃基，或含 3-20 个碳原子且优选 3-8 个碳原子的任选经取代的支链饱和单价烃基。未取代烷基的实例包括甲基、乙基、正丙基、异丙基、正丁基、异丁基、仲丁基、叔丁基、正戊基、异戊基、仲戊基、叔戊基等。

[0210] 如本文所使用的术语“酰胺部分”表示包括至少一个酰胺键(即， )的二价(即，双官能)基团，例如-C(O)-NR_A-R_C-NR_B-C(O)-，其中 R_A和 R_B独立地为氢或烷基并且 R_C为亚烷基。例如，酰胺部分可为 -C(O)-NH-$(CH_2)_p$-NH-C(O)-，其中 p 为 1 至 8 的整数。

[0211] 如本文单独地或作为另一基团的一部分使用的术语“芳基”指任选经取代的单价芳香族烃基，优选在环部分中含 6-12 个碳的单价单环或双环基团，例如苯基、联苯基、萘基、经取代的苯基、经取代的联苯基或经取代的萘基。苯基和经取代的苯基是最优选的芳基。术语“芳基”还包括杂芳基。

[0212] 术语“羧酸基”、“羧酸”或“羧基”指单价基团 -C(O)OH。根据 pH 条件，所述单价基团可呈 -C(O)O^-Q^+形式，其中 Q^+为阳离子（例如，钠），或非常靠近的两个单价基团可与二价阳离子 Q^{2+}（例如，钙、镁）键合，或存在这些二价基团与 -C(O)OH 的组合。

[0213] 如本文所使用的术语“环烷基”任选地指一个环中含 3-8 个碳原子而在多环基团中含多达 20 个碳原子的任选经取代的环状饱和单价桥接或非桥接烃基。示例性的未取代环烷基包括环丙基、环丁基、环戊基、环己基、环庚基、环辛基、金刚烷基、降冰片基等。

[0214] 用作前缀，作为另一基团的一部分的术语“亚”指其中从基团的两个末端碳的每一个，或如果所述基团为环状，则从环中两个不同碳原子的每一个去除一个氢的二价基团。例如，亚烷基指二价烷基例如亚甲基 ($-CH_2-$) 或乙烯基 ($-CH_2CH_2-$)，并且亚芳基指二价芳基例如邻亚苯基、间亚苯基或对亚苯基。

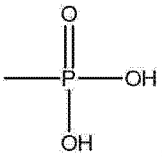
[0215] 如本文所使用的术语“醚部分”指包括至少一个醚键（即，-O-）的二价（即，双官能）基团。例如，如本文所定义的式 3 或 33 中，醚部分可为 $-R_AOR_B-$ 或 $-R_AOR_COR_B$，其中 R_A、R_B

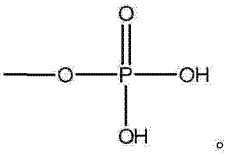
和 R_C独立地为亚烷基。

[0216] 如本文单独地或作为另一基团的一部分使用的术语“杂芳基”指 5-10 个环原子的任选经取代的单价单环或双环芳族基团，其中一个或多个，优选 1、2 或 3 个环原子为独立选自 N、O 和 S 的杂原子，而其余环原子为碳。示例性杂芳基部分包括苯并呋喃基、苯并 [d] 噻唑基、异喹啉基、喹啉基、噻唑基、咪唑基、噁唑基、喹啉基、呋喃基、噻唑基、吡啶基、呋喃基、噻吩基、吡啶基、噁唑基、吡咯基、吲哚基、喹啉基、异喹啉基等。

[0217] 如本文单独地或作为另一基团的一部分使用的术语“杂环”指 4-8 个环原子的饱和或不饱和单价单环基团，其中一个或两个原子为独立选自 N、O 和 S 的杂原子，而其余环原子为碳原子。另外，杂环可与苯基或杂芳基环稠合，条件是整个杂环不完全为芳香族。示例性杂环基团包括上述杂芳基、吡咯烷基、哌啶基、吗啉基、哌嗪基等。

[0218] 如本文所述的术语“烃”描述只由碳和氢元素组成的化合物或基团。

[0219] 术语“膦酸基”或“膦酰基”指单价基团  。

[0220] 术语“磷酸基”或“磷酰基”指单价基团  。

[0221] 如本文单独地或作为另一基团的一部分使用的术语“受保护”指阻断在化合物受保护部分的反应，而在足够温和以免扰乱化合物的其它取代基的条件下易于去除的基团。例如，受保护的羧酸基 $-C(O)OP_g$或受保护的磷酸基 $OP(O)(OH)OP_g$或受保护的膦酸基 $-P(O)(OH)OP_g$各有一个与酸基的氧缔合的保护基 P_g，其中 P_g可为烷基（例如，甲基、乙基、正丙基、异丙基、正丁基、异丁基、仲丁基、叔丁基、正戊基、异戊基、仲戊基、叔戊基等）、苄基、硅烷基（例如，三甲基硅烷基 (TMS)、三乙基硅烷基 (TES)、三异丙基硅烷基 (TIPS)、三苯基硅烷基 (TPS)、叔丁基二甲基硅烷基 (TBDMS)、叔丁基二苯基硅烷基 (TBDPS) 等）。在“Protective Groups in Organic Synthesis”，T.W.Greene 和 P.G.M.Wuts，John Wiley&Sons，1999 中可找到各种保护基及其合成。当术语“受保护”介绍一系列可能受保护的基团时，意图是术语适用于该组的每个成员。即，短语“受保护的羧酸基、膦酸基或磷酸基”应解释为“受保护的羧酸基、受保护的膦酸基或受保护的磷酸基”。同样，短语“任选受保护的羧酸基、膦酸基或磷酸基”应解释为“任选受保护的羧酸基、任选受保护的膦酸基或任选受保护的磷酸基”。

[0222] 如“经取代的芳基”、“经取代的烷基”等中的术语“经取代”意指在所讨论的基团（即，该术语后的烷基、芳基或其它基团）中，至少一个与碳原子结合的氢原子经一个或多个取代基取代，所述取代基为例如羟基 (-OH)、烷基硫代、膦基、酰胺基 ($-CON(R_A)(R_B)$ 其中 R_A和 R_B独立地为氢、烷基或芳基）、氨基 ($-N(R_A)(R_B)$ 其中 R_A和 R_B独立地为氢、烷基或芳基）、卤代基（氟代、氯代、溴代或碘代）、甲硅烷基、硝基 ($-NO_2$)、醚基 ($-OR_A$其中 R_A为烷基或芳基）、酯基 ($-OC(O)R_A$其中 R_A为烷基或芳基）、酮基 ($-C(O)R_A$其中 R_A为烷基或芳基）、杂环基等。当术语“经取代”引出一系列可能的经取代的基团时，意味着该术语适用于该组的每个成员。即，短语“任选经取代的烷基或芳基”应解释为“任选经取代的烷基或任选经取代的芳基”。

[0223] 已对本发明进行了详细描述，显然修改和变化在在不背离所附权利要求中所定义的本发明的范围的情况下可进行修改和改。

实施例

[0224] 提供下列非限制性实施例是为了进一步说明本发明。

[0225] 实施例 1：载山梨糖醇的交联 (2- 氟代丙烯酸钙)- 二乙烯基苯 -1,7- 辛二烯共聚物

[0226] 购买 2- 氟代丙烯酸甲酯 (MeFA) 并在使用之前真空蒸馏。从 Aldrich 购得二乙烯基苯 (DVB)(工业级，80％，异构体混合物)，并且按收到的原样使用。从商业来源购得 1,7- 辛二烯 (ODE)、过氧化月桂酰 (LPO)、聚乙烯醇 (PVA)(通常分子量为 85,000-146,000，87-89％水解)、氯化钠 (NaCl)、磷酸氢二钠七水合物 ($Na_2HPO_4 \cdot 7H_2O$) 和磷酸二氢钠一水合物 ($NaH_2PO_4 \cdot H_2O$) 并按收到的原样使用。

[0227] 在带适当搅拌和其它设备的适当大小的反应器中，通过混合 2- 氟代丙烯酸甲酯、1,7- 辛二烯和二乙烯基苯来制备单体有机相的 90 ： 5 ： 5 重量比混合物。添加一半份数的过氧化月桂酰作为聚合反应的引发剂。由水、聚乙烯醇、磷酸盐、氯化钠和亚硝酸钠制备稳定水相。在大气压力下于氮气下，在保持温度低于 30℃的同时将水相和单体相混合在一起。在不断搅拌的同时逐渐加热反应混合物。聚合反应一旦开始，就使反应混合物的温度上升到最高 95℃。

[0228] 聚合反应完成之后，冷却反应混合物并去除水相。加水，搅拌混合物，并通过过滤分离固体物质。然后用水洗涤固体以得到交联 (2- 氟代丙烯酸甲酯)- 二乙烯基苯 -1,7- 辛二烯共聚物。在 90℃下用过量氢氧化钠水溶液水解 (2- 氟代丙烯酸甲酯)- 二乙烯基苯 -1,7- 辛二烯共聚物 24h 得到 (2- 氟代丙烯酸钠)- 二乙烯基苯 -1,7- 辛二烯共聚物。水解后，过滤固体并用水洗涤。将 (2- 氟代丙烯酸钠)- 二乙烯基苯 -1,7- 辛二烯共聚物在室温下暴露于过量氯化钙水溶液以得到不溶性交联 (2- 氟代丙烯酸钙)- 二乙烯基苯 -1,7- 辛二烯共聚物。

[0229] 钙离子交换后，在环境温度下用 25-30％ w/w 山梨糖醇水溶液将湿聚合物调成浆料以得到载山梨糖醇的聚合物。通过过滤去除过量山梨糖醇。在 20-30℃下干燥所生成的聚合物，直至达到所需水分含量 (10-25w/w/％)。这样提供了载山梨糖醇的交联 (2- 氟代丙烯酸钠)- 二乙烯基苯 -1,7- 辛二烯共聚物 (5016CaS)。

[0230] 实施例 2：II 期临床研究

[0231] 研究设计概述。研究有两个 5016CaS 治疗期 :8 周的治疗引发期，接着是另 44 周的长期维持期，这样允许用 5016CaS 治疗总计长达一年 (即 52 周)。合格的非高血钾患者在持续期间开始 1-4 周的导入期 (组群 1 和 2)。合格的高血钾患者立即开始用 5016CaS 治疗 (组群 3)。第一次出现血清钾 (K^+) ＞ 5.0- ＜ 6.0mEq/L 时，根据基线血清钾将来自全部 3 个组群的合格患者分配到两个层组之一并且按范围从 10 至 40g/ 日的随机分配起始剂量，接受 5016CaS 治疗。剂量按聚合物阴离子加上钙的量计 (例如，按水和山梨糖醇自由基计)。聚合物阴离子加上钙的 10g 剂量相当于聚合物阴离子的 8.4g 剂量。每位患者研究持续时间长达 62 周 (包括筛选和随访过程) 并且研究群体约 306 名患者。研究变量包括血清钾、血压、估计 GFR 和 ACR 的变化。

[0232] 将合格患者分配到两个5016CaS治疗层组之一，其中层组1包括血清K^+＞5.0-5.5mEq/L的患者，在每个组群中这些患者按1：1：1比率随机接受10g/日、20g/日或30g/日5016CaS起始剂量。层组2包括血清K^+＞5.5-＜6.0mEq/L的患者，在每个组群中这些患者按1：1：1比率随机接受20g/日、30g/日或40g/日5016CaS起始剂量。

[0233] 患者在第1天的晚上按其指定剂量水平开始5016CaS治疗。他们继续服用氯沙坦100mg/d(有或无安体舒通25-50mg/d)或预先研究ACEI和/或ARB与安体舒通25-50mg/d(按照其组群1或2分配)，以及任何其它方案允许的抗高血压疗法。组群3中的患者继续其预先研究ACEI和/或ARB。

[0234] 5016CaS施用剂量和途径。从第1天开始按等分剂量口服5016CaS每日两次，52周(仅晚上用药)。患者服用5016CaS每日两次，饮食规律(早餐和晚餐)。从第3天开始根据适当的滴度算法(治疗开始或长期保养)按需调节5016CaS剂量并且到51周就诊。最低允许剂量为0g/d(5016CaS未分散)并且最大剂量为60g/d。

[0235] 图1-5，通过下列患者亚型检查钾减少、血液控制、eGFR变化和蛋白尿变化：(1)尿液中有任意量的蛋白质的患者，(2)有微量蛋白尿的患者，(3)有大量蛋白尿的患者和(4)有4期慢性肾病(CKD)的患者。图1显示，这些患者类型全部经历血清钾减少。图2和3显示血压降低并且5016CaS在所有患者类型中降低血液同样有效。图4显示在任何患者类型中蛋白尿水平未明显升高，所以5016CaS有效地稳定了患者的蛋白质排泄量。图5显示在所有患者中肾功能似乎稳定，在有4期CKD的患者中肾功能有改善可能。

[0236] 182名患者完成研究方案，按照该实施例2进行分析。在基线时统计显著量的这些患者的白蛋白肌酐比率(ACR)≥30mg/g而其它患者的ACR＞300mg/g并且估计肾小球滤过率(eGFR)为15-44mL/min/1.73m^2。对于所有这些患者而言，患者的血清钾浓度在24周时从基线的平均5.27mEq/L降到平均4.57mEq/L。对于ACR≥30mg/g的患者而言，在24周时患者的血清钾浓度从基线的平均5.28mEq/L降到平均4.60mEq/L。对于ACR＞300mg/g的患者而言，在24周时患者的血清钾浓度从基线的平均5.35mEq/L降到平均4.65mEq/L。对于eGFR为15-44mL/min/1.73m^2的患者而言，在24周时患者的血清钾浓度从基线的平均5.33mEq/L降到平均4.59mEq/L。

[0237] 对于eGFR为15-44mL/min/1.73m^2的患者而言，在24周时患者的eGFR从基线的平均32mL/min/1.73m^2增加到平均38mL/min/1.73m^2。对于这些患者而言eGFR的这种增加具有统计显著性。

[0238] 分别对于所有组和每个组的患者而言(例如，ACR≥30mg/g，ACR＞300mg/g，eGFR为15-44mL/min/1.73m^2)，在24周治疗期后ACR未显著变化。

[0239] 对于所有这些患者而言，在24周时患者的收缩压从基线的平均154降到平均137并且在24周时患者的舒张压从基线的平均83降到平均74。对于ACR≥30mg/g的患者而言，在24周时患者的收缩压从基线的平均154降到平均138并且在24周时患者的舒张压从基线的平均84降到平均74。对于ACR＞300mg/g的患者而言，在24周时患者的收缩压从基线的平均154降到平均137并且在24周时患者的舒张压从基线的平均86降到平均73。对于eGFR为15-44mL/min/1.73m^2的患者而言，在24周时患者的收缩压从基线的平均152降到平均135并且在24周时患者的舒张压从基线的平均82降到平均73。

[0240] 图6-9呈现了来自具有预先存在的高血钾症，服用稳定剂量的RAAS抑制剂，未经

导入期进行试验的某一组 90 名患者的一年数据。这些图显示肾功能（图 6）和尿蛋白排泄量（图 8）似乎稳定，血清钾（图 7）和血压（图 9）降低。分析这些患者 12 个月的数据时，平均 eGFR 在基线 (BL) 时为 46mL/min/1.73m^2，在 1 个月 (M1) 时为 49mL/min/1.73m^2，在 2 个月 (M2) 时为 51mL/min/1.73m^2，在 6 个月 (M6) 时为 49mL/min/1.73m^{2}并且在 12 个月 (M12) 时为 48mL/min/1.73m^2（图 6）。在 12 个月治疗期间这些患者的 eGFR 无显著变化。这些患者还经历了血清钾水平显著降低。（图 7）例如，平均血清钾水平在基线 (BL) 时为 5.3mEq/L，在 1 个月 (M1) 时为 4.5mEq/L，在 2 个月 (M2) 时为 4.5mEq/L，在 6 个月 (M6) 时为 4.6mEq/L 并且在 12 个月 (M12) 时为 4.6mEq/L。同样这些患者的平均尿 ACR 在基线 (BL) 时为 853mg/g，在 1 个月 (M1) 时为 900mg/g，在 2 个月 (M2) 时为 971mg/g，在 6 个月 (M6) 时为 930mg/g 并且在 12 个月 (M12) 时为 802mg/g。这些患者的平均收缩压在基线 (BL) 时为 157mmHg，在 1 个月 (M1) 时为 138mmHg，在 2 个月 (M2) 时为 139mmHg，在 6 个月 (M6) 时为 138mmHg 并且在 12 个月 (M12) 时为 134mmHg。平均舒张压在基线 (BL) 时为 85mmHg，在 1 个月 (M1) 时为 74mmHg，在 2 个月 (M2) 时为 73mmHg，在 6 个月 (M6) 时为 73mmHg 并且在 12 个月 (M12) 时为 77mmHg。

[0241] 表 1 中按层组给出了血清钾从基线到第 4 周或首次剂量滴定的平均变化，以先到者为准。为了与研究方案一致，对 4 周就诊之前未滴定的患者使用最新的血清钾非缺失测量（末次观测值结转法，即 LOCF）。在两个层组的所有剂量组中 5016CaS 降低血清钾 ;p 值表明减少量在统计上明显不等于零。两个层组的参考组是为 III 期研究选择的随机起始剂量。

[0242]

表 1. 在层组内通过随机起始剂量估计的中央血清 K^+从基线到第 4 周或首次剂量滴定时的平均变化

第 4 周或首次滴定时	*层组 1 局部血清 K^+>5.0-5.5mEq/L*				*层组 2 局部血清 K^+>5.5-<6.0mEq/L*			
	10 g/d N=74	*20 g/d N=73*	*30 g/d N=73*	*总量 N=220*	*20 g/d N=26*	*30 g/d N=28*	*40 g/d N=30*	*总量 N=84*
从基线开始血清 K^+(mEq/L)的变化								
n[a]	73	73	72	218	26	27	30	83
最小二乘均数±标准误差	-0.35 ± 0.066	-0.51 ± 0.066	-0.54 ± 0.066	-0.47 ± 0.038	-0.85 ± 0.136	-0.95 ± 0.132	-0.90 ± 0.127	-0.90 ± 0.076
95%置信区间	-0.48, -0.22	-0.64, -0.38	-0.67, -0.41	-0.54, -0.39	-1.12, -0.58	-1.21, -0.68	-1.15, -0.65	-1.05, -0.75
p 值[b]	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
与参考比较								
平均差	参考	0.17	0.19		参考	0.097	0.050	
95%置信区间		-0.018, 0.35	0.006, 0.37			-0.28, 0.48	-0.32, 0.42	
p 值[c]		0.076	0.043			0.61	0.79	

表头计数包括层组内按每个随机起始剂量接受 RLY5016 的所有随机患者(意向治疗人群)。使用平行线协方差分析(ANCOVA)模型单独分析每个层组，其中结果是从基线开始血清 K^+的变化。每个模型含对随机起始剂量、组群和连续基线血清 K^+的固定效应。使用对协变量观测值的线性对比生成给定的每个随机起始剂量的估计值和置信区间。

a 意向治疗人群中在基线时有非缺失基线血清 K^+的患者数量。

b p 值检验血清 K^+从基线开始的平均变化为 0 的假设。

c p 值检验剂量组间血清 K^+从基线开始的变化的两两差异。正值表示与参考组相比，从基线开始具有较大的减少。

[0243] 在两个层组的所有剂量组中 5016CaS 降低了血清钾，与剂量滴定早在第 3 天开始并且大致在第 2 周后稳定无关。在两个层组的所有剂量组中大多数患者能够在剂量滴定前

后将血清钾维持在 4.0mEq/L-5.0mEq/L 的范围内。

[0244] 主要结果，使用平行线 ANCOVA 模型分析的血清钾在第 4 周或首次 5016CaS 剂量滴定时从基线的平均变化，在 S1 中为 0.47±0.038(p ＜ 0.001) 并且在 S2 中为 -0.90±0.076(p ＜ 0.001)。治疗中值 2 天后平均 K 减少量为 -0.29±0.03(S1) 和 -0.55±0.05mEq/L(S2)。表 2 总结了平均值和从基线的变化，允许滴定。

[0245] 表 2.

[0246]

	层组 1((S1)，BL K>5.0-5.5mEq/L)			层组 2((S2)，BL K>5.5-<6.0mEq/L)		
	基线 (n=217)	第 4 周 (n=197)	第 8 周 (n=185)	基线 (N=84)	第 4 周 (n=70)	第 8 周 (n=70)
平均 K (SE) (mEq/L)	5.15 (0.02)	4.54 (0.03)	4.59 (0.03)	5.64 (0.04)	4.65 (0.06)	4.52 (0.06)
LS 平均变化 (SE)(mEq/L)	_	-0.61 (0.03)	-0.55 (0.03)	_	-0.97 (0.06)	-1.10 (0.06)

[0247] 在治疗起始天数内 5016CaS 降低了血清 K，作用持续 12 个月，无明显副作用。

[0248] 实施例 3：对来自 II 期临床研究的收缩压的分析

[0249] 以下部分含有对实施例 2 公开的 II 期临床研究的 8 周治疗起始期间平均收缩压的重复测量分析结果。表 3 至表 6 给出了从基线的平均变化的分析。表 3 和 4 给出了所有患者的结果；表 5 和 6 给出了根据筛选时的高血钾症状态分析的亚组（组群 3)。一般而言，层组 2 中的患者（血清 K^+ ＞ 5.5- ＜ 6.0mEq/L 的患者）比层组 1 中的患者（血清 K^+ ＞ 5.0-5.5mEq/L 的患者）经历更小的血压平均变化。组群 3 中参加高血钾研究而未参与导入期的患者造成平均收缩压降低（表 5 和 6)。

[0250] 对于表 3-6，表头计数包括层组内按每个随机起始剂量接受 RLY5016 的所有随机患者（意向治疗人群）。从用于重复测量的混合模型得到数据，其中结果变量为收缩压 (SBP) 从基线开始的变化。单独分析每个层组。每个模型含有就诊相互作用对组群、随机起始剂量、时间（就诊）、连续基线 SBP 和随机起始剂量的固定效应。使用非均质 Toeplitz 结构为患者自身相关性建模。使用对协变量观测值的线性对比生成每个随机起始剂量的估计值、标准误差 (SE) 和置信区间。随机用药组的总体估计值、标准误差 (SE) 和置信区间在用药组间呈平均分配。由接受 RLY5016，有基线测量值并且对该分析贡献至少一个基线后测量值的随机患者的数量确定分析的患者总数 N。并非全部患者在每次就诊时都贡献了测量值。

[0251] 表 3. 通过随机起始剂量估计的层组 1 所有患者收缩压从基线开始的平均变化

[0252]

	层组 1-局部血清 K+ >5.0-5.5mEq/L			
SBP 从基线开始的变化 (mmHg)	*10g/d N=74*	*20g/d N=73*	*30g/d N=73*	*总量 N=220*
分析的患者，N	74	73	73	220
第 3 天，n	70	70	72	212
最小二乘均数±SE	-9.3 ± 1.8	-4.9 ± 1.8	-10.3 ± 1.8	-8.2 ± 1.0
95%置信区间	-12.8, -5.7	-8.5, -1.4	-13.9, -6.8	-10.2, -6.1
第 1 周，n	72	71	72	215
最小二乘均数±SE	-11.1 ± 1.9	-8.8 ± 2.0	-12.0 ± 1.9	-10.6 ± 1.1
95%置信区间	-14.9, -7.3	-12.6, -4.9	-15.8, -8.2	-12.8, -8.4
第 2 周，n	70	70	71	211
最小二乘均数±SE	-12.4 ± 2.0	-5.7 ± 2.0	-13.8 ± 2.0	-10.6 ± 1.1
95%置信区间	-16.3, -8.5	-9.6, -1.8	-17.7, -9.9	-12.9, -8.4
第 3 周，n	64	69	71	204
最小二乘均数±SE	-11.5 ± 2.1	-7.5 ± 2.0	-12.5 ± 2.0	-10.5 ± 1.2
95%置信区间	-15.6, -7.4	-11.5, -3.5	-16.4, -8.6	-12.8, -8.2
第 4 周，n	65	67	69	201
最小二乘均数± SE	-13.3 ± 2.0	-8.0 ± 2.0	-12.4 ± 2.0	-11.2 ± 1.1
95%置信区间	-17.2, -9.3	-11.9, -4.1	-16.2, -8.5	-13.5, -9.0
第 5 周，n	65	66	67	198
最小二乘均数±SE	-12.0 ± 2.0	-9.6 ± 2.0	-13.7 ± 2.0	-11.8 ± 1.2
95%置信区间	-15.9, -8.0	-13.5, -5.7	-17.7, -9.8	-14.0, -9.5
第 6 周，n	65	66	64	195
最小二乘均数±SE	-13.3 ± 2.1	-6.9 ± 2.0	-12.8 ± 2.1	-11.0 ± 1.2
95%置信区间	-17.3, -9.3	-10.9, -2.9	-16.8, -8.7	-13.3, -8.7
第 7 周，n	64	64	65	193
最小二乘均数±SE	-15.6 ± 2.0	-9.5 ± 2.0	-11.0 ± 2.0	-12.0 ± 1.2
95%置信区间	-19.5, -11.6	-13.6, -5.5	-15.0, -7.0	-14.3, -9.7
第 8 周，n	66	64	66	196
最小二乘均数±SE	-16.3 ± 2.0	-12.0 ± 2.0	-13.8 ± 2.0	-14.0 ± 1.1
95%置信区间	-20.2, -12.5	-15.9, -8.1	-17.7, -10.0	-16.3, -11.8

[0253] 表 4. 通过随机起始剂量估计的层组 2 所有患者收缩压从基线开始的平均变化

[0254]

	层组 2-局部血清 K+ >5.5-<6.0mEq/L			
SBP 从基线开始的变化(mmHg)	*20 g/d N=26*	*30g/d N=28*	*40g/d N=30*	*总量 N=84*
分析的患者，N	26	28	29	83
第 3 天，n	26	27	29	82
最小二乘均数±SE	-7.3 ± 3.5	-9.6 ± 3.4	-6.6 ± 3.3	-7.8 ± 2.0
95%置信区间	-14.2, -0.4	-16.3, -2.9	-13.1, -0.08	-11.7, -4.0
第 1 周，n	24	28	28	80
最小二乘均数±SE	-6.2 ± 4.2	-11.5 ± 3.9	-4.8 ± 3.9	-7.5 ± 2.3
95%置信区间	-14.4, 1.9	-19.2, -3.9	-12.5, 2.8	-12.1, -3.0
第 2 周，n	24	27	26	77
最小二乘均数±SE	-5.8 ± 4.2	-7.7 ± 4.0	-3.3 ± 4.0	-5.6 ± 2.4
95%置信区间	-14.2, 2.5	-15.6, 0.2	-11.3, 4.6	-10.3, -1.0
第 3 周，n	24	25	25	74
最小二乘均数±SE	-12.0 ± 3.8	-10.0 ± 3.6	-8.3 ± 3.6	-10.1 ± 2.1
95%置信区间	-19.4, -4.6	-17.2, -2.9	-15.5, -1.2	-14.3, -5.9
第 4 周，n	24	25	24	73
最小二乘均数± SE	-9.6 ± 3.1	-10.7 ± 3.0	-3.8 ± 3.0	-8.1 ± 1.7
95%置信区间	-15.7, -3.5	-16.6, -4.9	-9.7, 2.1	-11.5, -4.6
第 5 周，n	24	25	23	72
最小二乘均数±SE	-8.3 ± 3.6	-9.4 ± 3.5	-6.0 ± 3.5	-7.9 ± 2.0
95%置信区间	-15.3, -1.2	-16.2, -2.7	-13.0, 0.9	-11.9, -3.9
第 6 周，n	24	25	22	71
最小二乘均数±SE	-7.5 ± 3.6	-11.4 ± 3.4	-5.4 ± 3.6	-8.1 ± 2.0
95%置信区间	-14.5, -0.5	-18.1, -4.6	-12.4, 1.6	-12.1, -4.1
第 7 周，n	24	25	22	71
最小二乘均数±SE	-10.4 ± 3.4	-8.4 ± 3.3	-1.3 ± 3.4	-6.7 ± 1.9
95%置信区间	-17.1, -3.7	-14.8, -1.9	-8.0, 5.4	-10.5, -2.9
第 8 周，n	24	26	24	74
最小二乘均数±SE	-7.8 ± 3.5	-11.0 ± 3.4	-1.7 ± 3.5	-6.9 ± 2.0
95%置信区间	-14.8, -0.9	-17.6, -4.4	-8.5, 5.1	-10.8, -3.0

[0255] 表 5. 通过随机起始剂量估计的层组 1 筛选时有高血钾的患者收缩压从基线开始的平均变化

[0256]

SBP 从基线开始的变化(mmHg)	*层组 1-局部血清 K+ >5.0-5.5mEq/L*			
	10 g/dN=57	*20 g/dN=57*	*30 g/dN=56*	*总量 N=170*
分析的患者，N	57	57	56	170
第 3 天，n	56	56	56	168
最小二乘均数±SE	-9.8 ± 2.0	-5.6 ± 2.0	-12.5 ± 2.0	-9.3 ± 1.2
95%置信区间	-13.8, -5.8	-9.6, -1.6	-16.5, -8.5	-11.6, -7.0
第 1 周，n	55	55	55	165
最小二乘均数±SE	-11.4 ± 2.2	-9.9 ± 2.2	-12.7 ± 2.2	-11.3 ± 1.3
95%置信区间	-15.7, -7.1	-14.2, -5.6	-16.9, -8.4	-13.8, -8.9
第 2 周，n	54	54	54	162
最小二乘均数±SE	-12.3 ± 2.3	-5.8 ± 2.3	-15.2 ± 2.3	-11.1 ± 1.3
95%置信区间	-16.8, -7.8	-10.3, -1.3	-19.8, -10.7	-13.7, -8.5
第 3 周，n	49	53	54	156
最小二乘均数±SE	-11.6 ± 2.5	-10.2 ± 2.4	-13.8 ± 2.4	-11.9 ± 1.4
95%置信区间	-16.4, -6.7	-14.9, -5.5	-18.5, -9.1	-14.6, -9.1
第 4 周，n	51	52	53	156
最小二乘均数±SE	-13.4 ± 2.3	-10.8 ± 2.3	-14.2 ± 2.3	-12.8 ± 1.3
95%置信区间	-18.0, -8.8	-15.4, -6.3	-18.7, -9.7	-15.4, -10.2
第 5 周，n	50	51	53	154
最小二乘均数± SE	-11.4 ± 2.3	-10.5 ± 2.3	-15.0 ± 2.3	-12.3 ± 1.3
95%置信区间	-16.0, -6.8	-15.1, -5.9	-19.5, -10.5	-14.9, -9.7
第 6 周，n	50	51	52	153
最小二乘均数±SE	-12.3 ± 2.2	-6.8 ± 2.2	-15.0 ± 2.2	-11.4 ± 1.3
95%置信区间	-16.6, -7.9	-11.1, -2.5	-19.3, -10.7	-13.8, -8.9
第 7 周，n	50	49	52	151
最小二乘均数±SE	-14.5 ± 2.1	-9.0 ± 2.1	-13.2 ± 2.1	-12.2 ± 1.2
95%置信区间	-18.6, -10.3	-13.2, -4.8	-17.3, -9.1	-14.6, -9.8
第 8 周，n	51	49	52	152
最小二乘均数±SE	-16.6 ± 2.2	-13.0 ± 2.3	-14.9 ± 2.2	-14.8 ± 1.3
95%置信区间	-21.0, -12.3	-17.4, -8.6	-19.2, -10.5	-17.3, -12.3

[0257] 表 6. 通过随机起始剂量估计的层组 2 筛选时有高血钾的患者收缩压从基线开始的平均变化

[0258]

	层组 2-局部血清 K^+>5.5-<6.0 mEq/L			
SBP 从基线开始的变化(mmHg)	20 g/d N=24	30 g/d N=24	40g/d N=25	总量 N=73
分析的患者，N	24	24	24	72
第 3 天，n	24	23	24	71
最小二乘均数±SE	-10.2 ± 3.6	-11.2 ± 3.7	-6.5 ± 3.7	-9.3 ± 2.1
95%置信区间	-17.3, -3.0	-18.5, -3.9	-13.6, 0.7	-13.4, -5.1
第 1 周，n	22	24	23	69
最小二乘均数±SE	-8.4 ± 4.4	-13.8 ± 4.3	-2.1 ± 4.3	-8.1 ± 2.5
95%置信区间	-17.0, 0.3	-22.2, -5.4	-10.7, 6.4	-13.0, -3.2
第 2 周，n	22	23	21	66
最小二乘均数±SE	-8.0 ± 4.3	-10.4 ± 4.2	-0.3 ± 4.3	-6.2 ± 2.5
95%置信区间	-16.4, 0.4	-18.6, -2.1	-8.8, 8.2	-11.1, -1.4
第 3 周，n	22	21	20	63
最小二乘均数±SE	-14.1 ± 3.9	-12.8 ± 3.9	-6.7 ± 4.0	-11.2 ± 2.3
95%置信区间	-21.7, -6.4	-20.5, -5.1	-14.5, 1.2	-15.6, -6.7
第 4 周，n	22	21	19	62
最小二乘均数±SE	-12.0 ± 3.2	-13.6 ± 3.2	-4.0 ± 3.3	-9.9 ± 1.9
95%置信区间	-18.3, -5.8	-19.9, -7.3	-10.6, 2.5	-13.5, -6.2
第 5 周，n	22	21	18	61
最小二乘均数± SE	-10.1 ± 3.7	-12.9 ± 3.8	-4.1 ± 4.0	-9.1 ± 2.2
95%置信区间	-17.5, -2.8	-20.3, -5.5	-11.9, 3.7	-13.4, -4.7
第 6 周，n	22	21	17	60
最小二乘均数±SE	-9.9 ± 3.5	-14.2 ± 3.6	-2.1 ± 3.8	-8.7 ± 2.1
95%置信区间	-16.8, -3.0	-21.2, -7.2	-9.6, 5.5	-12.9, -4.6
第 7 周，n	22	21	17	60
最小二乘均数±SE	-12.7 ± 3.5	-11.9 ± 3.5	1.9 ± 3.8	-7.6 ± 2.1
95%置信区间	-19.5, -5.9	-18.8, -5.0	-5.5, 9.4	-11.6, -3.5
第 8 周，n	22	22	19	63
最小二乘均数±SE	-11.4 ± 3.6	-14.4 ± 3.5	-0.3 ± 3.8	-8.7 ± 2.1
95%置信区间	-18.4, -4.4	-21.3, -7.4	-7.7, 7.1	-12.8, -4.6

[0259] 实施例 4:对来自 II 期临床研究的舒张压的分析

[0260] 该部分含有对实施例 2 公开的 II 期临床研究的 8 周治疗起始期间平均舒张压的重复测量分析结果。表 7 至表 10 给出了舒张压从基线开始的平均变化的分析。表 7 和 8 给出了所有患者的结果；表 9 和 10 给出了根据筛选时的高血钾症状态分析的亚组（组群 3）。组群和层组中的患者都经历了舒张压平均适度降低。

[0261] 对于表 7-10，表头计数包括层组内按每个随机起始剂量接受 RLY5016 的所有随机患者（意向治疗人群）。从用于重复测量的混合模型得到数据，其中结果变量为舒张压 (DBP) 从基线开始的变化。单独分析每个层组。每个模型含有就诊相互作用对组群、随机起始剂量、时间（就诊）、连续基线 DBP 和随机起始剂量的固定效应。使用非均质 Toeplitz 结构为患者自身相关性建模。使用对协变量观测值的线性对比生成每个随机起始剂量的估计值、标准误差 (SE) 和置信区间。随机用药组的总体估计值、标准误差 (SE) 和置信区间在

用药组间呈平均分配。由接受RLY5016，有基线测量值并且对该分析贡献至少一个基线后测量值的随机患者的数量确定分析的患者总数N。并非全部患者在每次就诊时都贡献了测量值。

[0262] 表7. 通过随机起始剂量估计的层组1所有患者舒张压从基线开始的平均变化

[0263]

	层组1-局部血清 K^+>5.0-5.5mEq/L			
DBP从基线开始的变化(mmHg)	*10 g/d N=74*	*20g/d N=73*	*30 g/d N=73*	*总量 N=220*
分析的患者N	74	73	73	220
第3天，n	70	70	72	212
最小二乘均数±SE	-3.8 ± 1.1	-3.1 ± 1.1	-5.8 ± 1.1	-4.2 ± 0.6
95%置信区间	-6.0, -1.7	-5.2, -1.0	-7.9, -3.7	-5.5, -3.0
第1周n	72	71	72	215
最小二乘均数±SE	-6.0 ± 1.2	-5.4 ± 1.2	-7.0 ± 1.2	-6.1 ± 0.7
95%置信区间	-8.3, -3.7	-7.7, -3.1	-9.3, -4.7	-7.4, -4.8
第2周，n	70	70	71	211
最小二乘均数±SE	-6.6 ± 1.3	-6.1 ± 1.3	-6.1 ± 1.3	-6.3 ± 0.7
95%置信区间	-9.0, -4.1	-8.6, -3.6	-8.6, -3.7	-7.7, -4.8
第3周，n	64	69	71	204
最小二乘均数±SE	-5.0 ± 1.2	-6.0 ± 1.2	-8.0 ± 1.2	-6.3 ± 0.7
95%置信区间	-7.4, -2.5	-8.4, -3.6	-10.4, -5.7	-7.7, -4.9
第4周，n	65	67	69	201
最小二乘均数±SE	-5.8 ± 1.2	-6.5 ± 1.2	-8.0 ± 1.2	-6.7 ± 0.7
95%置信区间	-8.1, -3.4	-8.8, -4.1	-10.3, -5.7	-8.1, -5.4
第5周，n	65	66	67	198
最小二乘均数±SE	-6.0 ± 1.3	-5.9 ± 1.3	-8.4 ± 1.3	-6.8 ± 0.7
95%置信区间	-8.6, -3.5	-8.5, -3.4	-10.9, -5.9	-8.2, -5.3
第6周，n	65	66	64	195
最小二乘均数± SE	-5.7 ± 1.3	-6.4 ± 1.3	-6.6 ± 1.3	-6.2 ± 0.8
95%置信区间	-8.3, -3.1	-9.0, -3.8	-9.2, -4.0	-7.7, -4.8
第7周，n	64	64	65	193
最小二乘均数±SE	-6.3 ± 1.4	-6.0 ± 1.4	-6.5 ± 1.3	-6.3 ± 0.8
95%置信区间	-8.9, -3.6	-8.7, -3.4	-9.2, -3.9	-7.8, -4.8
第8周，n	66	64	66	196
最小二乘均数±SE	-7.6 ± 1.4	-7.3 ± 1.4	-6.8 ± 1.4	-7.2 ± 0.8
95%置信区间	-10.3, -4.9	-10.1, -4.6	-9.5, -4.1	-8.8, -5.7

[0264] 表8. 通过随机起始剂量估计的层组2所有患者舒张压从基线开始的平均变化

[0265]

	层组 2-局部血清 K^+>5.5-<6.0mEq/L			
DBP 从基线开始的变化(mmHg)	20g/d N=26	30 g/d N=28	40g/d N=30	总量 N=84
分析的患者 N	26	28	29	83
第 3 天，n	26	27	29	82
最小二乘均数±SE	-1.7 ± 2.0	-3.9 ± 2.0	-5.4 ± 1.9	-3.7 ± 1.1
95%置信区间	-5.6, 2.3	-7.8, -0.08	-9.1, -1.7	-5.9, -1.5
第 1 周，n	24	28	28	80
最小二乘均数±SE	-1.4 ± 2.5	-5.3 ± 2.4	-4.4 ± 2.3	-3.7 ± 1.4
95%置信区间	-6.4, 3.5	-9.9, -0.7	-9.0, 0.2	-6.4, -1.0
第 2 周，n	24	27	26	77
最小二乘均数±SE	-7.2 ± 2.0	-3.0 ± 1.9	-5.5 ± 1.9	-5.3 ± 1.1
95%置信区间	-11.2, -3.3	-6.8, 0.8	-9.4, -1.7	-7.5, -3.0
第 3 周，n	24	25	25	74
最小二乘均数±SE	-7.0 ± 2.1	-7.1 ± 2.0	-5.9 ± 2.0	-6.7 ± 1.2
95%置信区间	-11.1, -2.8	-11.1, -3.1	-9.9, -1.9	-9.0, -4.3
第 4 周，n	24	25	24	73
最小二乘均数± SE	-7.7 ± 2.2	-6.3 ± 2.2	-1.9 ± 2.2	-5.3 ± 1.3
95%置信区间	-12.1, -3.3	-10.6, -2.0	-6.2, 2.4	-7.8, -2.8
第 5 周，n	24	25	23	72
最小二乘均数± SE	-8.2 ± 1.8	-6.8 ± 1.8	-4.4 ± 1.8	-6.5 ± 1.0
95%置信区间	-11.8, -4.7	-10.3, -3.4	-8.0, -0.9	-8.5, -4.5
第 6 周，n	24	25	22	71
最小二乘均数±SE	-7.1 ± 2.0	-8.9 ± 2.0	-4.3 ± 2.0	-6.8 ± 1.2
95%置信区间	-11.1, -3.1	-12.8, -5.1	-8.4, -0.3	-9.1, -4.5
第 7 周，n	24	25	22	71
最小二乘均数±SE	-7.3 ± 1.9	-9.0 ± 1.8	-3.4 ± 1.9	-6.6 ± 1.1
95%置信区间	-10.9, -3.6	-12.6, -5.4	-7.1, 0.3	-8.7, -4.5
第 8 周，n	24	26	24	74
最小二乘均数±SE	-4.5 ± 2.1	-7.0 ± 2.0	-1.8 ± 2.0	-4.4 ± 1.2
95%置信区间	-8.5, -0.4	-10.9, -3.1	-5.8, 2.2	-6.7, -2.1

[0266] 表 9. 通过随机起始剂量估计的层组 1 筛选时有高血钾的患者舒张压从基线开始的平均变化

[0267]

	层组 -局部血清 K^+>5.0-5.5mEq/L			
DBP 从基线开始的变化(mmHg)	10g/d N=57	20 g/d N=57	30g/d N=56	总量 N=170
分析的患者 N	57	57	56	170
第 3 天，n	56	56	56	168
最小二乘均数±SE	-3.7 ± 1.3	-4.5 ± 1.3	-7.1 ± 1.3	-5.1 ± 0.7
95%置信区间	-6.1, -1.2	-7.0, -2.0	-9.6, -4.6	-6.5, -3.7
第 1 周，n	55	55	55	165
最小二乘均数±SE	-5.8 ± 1.3	-6.6 ± 1.3	-7.5 ± 1.3	-6.6 ± 0.8
95%置信区间	-8.4, -3.2	-9.2, -3.9	-10.2, -4.9	-8.1, -5.1
第 2 周，n	54	54	54	162
最小二乘均数±SE	-7.1 ± 1.5	-7.4 ± 1.5	-6.5 ± 1.5	-7.0 ± 0.9
95%置信区间	-10.0, -4.1	-10.4, -4.5	-9.5, -3.6	-8.7, -5.3
第 3 周，n	49	53	54	156
最小二乘均数±SE	-5.2 ± 1.5	-7.4 ± 1.4	-9.7 ± 1.4	-7.4 ± 0.8
95%置信区间	-8.1, -2.2	-10.2, -4.5	-12.5, -6.8	-9.0, -5.7
第 4 周，n	51	52	53	156
最小二乘均数± SE	-5.6 ± 1.4	-8.5 ± 1.4	-10.0 ± 1.3	-8.0 ± 0.8
95%置信区间	-8.2, -2.9	-11.2, -5.9	-12.6, -7.3	-9.6, -6.5
第 5 周，n	50	51	53	154
最小二乘均数±SE	-6.5 ± 1.5	-8.3 ± 1.5	-9.5 ± 1.4	-8.1 ± 0.8
95%置信区间	-9.4, -3.6	-11.1, -5.4	-12.3, -6.7	-9.7, -6.4
第 6 周，n	50	51	52	153
最小二乘均数±SE	-5.6 ± 1.5	-7.3 ± 1.5	-7.7 ± 1.5	-6.8 ± 0.9
95%置信区间	-8.6, -2.6	-10.3, -4.3	-10.7, -4.7	-8.6, -5.1
第 7 周，n	50	49	52	151
最小二乘均数±SE	-5.5 ± 1.6	-7.1 ± 1.6	-7.7 ± 1.5	-6.8 ± 0.9
95%置信区间	-8.6, -2.4	-10.2, -4.0	-10.8, -4.7	-8.5, -5.0
第 8 周，n	51	49	52	152
最小二乘均数±SE	-7.2 ± 1.6	-8.1 ± 1.6	-8.1 ± 1.6	-7.8 ± 0.9
95%置信区间	-10.4, -4.1	-11.4, -4.9	-11.3, -5.0	-9.7, -6.0

[0268] 表 10. 通过随机起始剂量估计的层组 2 筛选时有高血钾的患者舒张压从基线开始的平均变化

[0269]

	层组 2-局部血清 K^+>5.5-<6.0mEq/L			
DBP 从基线开始的变化(mmHg)	20g/d N=24	30 g/d N=24	40g/d N=25	总量 N=73
分析的患者 N	24	24	24	72
第 3 天，n	24	23	24	71
最小二乘均数±SE	-1.6 ± 2.2	-4.1 ± 2.2	-5.9 ± 2.2	-3.9 ± 1.3
95%置信区间	-5.9, 2.6	-8.5, 0.3	-10.1, -1.6	-6.4, -1.4
第 1 周 n	22	24	23	69
最小二乘均数± SE	-1.5 ± 2.7	-6.4 ± 2.7	-4.4 ± 2.7	-4.1 ± 1.6
95%置信区间	-6.9, 3.9	-11.6, -1.2	-9.7, 0.9	-7.2, -1.1
第 2 周，n	22	23	21	66
最小二乘均数±SE	-7.7 ± 2.2	-4.0 ± 2.2	-4.7 ± 2.2	-5.5 ± 1.3
95%置信区间	-12.0, -3.4	-8.3, 0.2	-9.0, -0.3	-7.9, -3.0
第 3 周，n	22	21	20	63
最小二乘均数± SE	-7.2 ± 2.3	-7.6 ± 2.3	-6.9 ± 2.3	-7.2 ± 1.3
95%置信区间	-11.7, -2.7	-12.1, -3.1	-11.5, -2.3	-9.9, -4.6
第 4 周，n	22	21	19	62
最小二乘均数±SE	-8.0 ± 2.4	-6.9 ± 2.5	-2.6 ± 2.6	-5.8 ± 1.4
95%置信区间	-12.7, -3.2	-11.7, -2.0	-7.6, 2.4	-8.6, -3.0
第 5 周，n	22	21	18	61
最小二乘均数±SE	-8.6 ± 1.9	-7.3 ± 2.0	-5.1 ± 2.1	-7.0 ± 1.1
95%置信区间	-12.4, -4.9	-11.2, -3.5	-9.1, -1.0	-9.3, -4.8
第 6 周，n	22	21	17	60
最小二乘均数± SE	-7.6 ± 2.1	-10.0 ± 2.2	-4.8 ± 2.3	-7.5 ± 1.3
95%置信区间	-11.8, -3.4	-14.2, -5.8	-9.3, -0.2	-10.0, -5.0
第 7 周，n	22	21	17	60
最小二乘均数±SE	-7.5 ± 2.0	-9.4 ± 2.1	-3.0 ± 2.2	-6.6 ± 1.2
95%置信区间	-11.5, -3.5	-13.5, -5.4	-7.4, 1.4	-9.0, -4.3
第 8 周，n	22	22	19	63
最小二乘均数±SE	-4.8 ± 2.2	-8.6 ± 2.2	-2.1 ± 2.3	-5.2 ± 1.3
95%置信区间	-9.1, -0.4	-12.9, -4.3	-6.7, 2.5	-7.7, -2.6

[0270] 实施例 5：血清钾和血清醛固酮水平间关系的研究

[0271] 在该项研究的实验组中使用雄性、单侧肾切除、自发性高血压大鼠 (SHR)(N = 32)。非操纵 SHR(N = 6) 用作对照组。使动物适应低 Ca^{2+}和 Mg^{2+}饮食 (TD04498) 两周。然后将实验组的饮食转变成补充了安体舒通 (0.4% w/w，TD120436) 的饮食并且在研究持续期间为饮用水补充阿米洛利 (amiloride)(0.05mM) 和喹那普利 (30mg/L)。

[0272] 对照组的动物在研究持续期间保持用 TD04498 饮食和未经补充的水。

[0273] 在 16 天后对所有动物进行基线抽血。根据基线血清钾水平将动物随机分成 4 个

组并接受如下表所述的钾结合剂治疗方案。

[0274]

组别	治疗	N
1	TD120436(未治疗)	8
2	TD120436+2%钾结合剂	8
3	TD120436+4%钾结合剂	8
4	TD120436+6%钾结合剂	8
5	对照	6

[0275] 治疗方案开始9天和15天后收集血液、粪便和尿液。在研究结束时收获近端和远端胃肠段。在各时间点测定血清、粪便和尿钾水平和血清醛固酮水平。

[0276] 分析在基线、第9天和第15天时对照、未治疗和实验组的血清钾水平(mmol/L)。与未治疗组相比,平均血清钾降低水平在第9天时为-9.1%(2%钾结合剂)、-18.2%(4%钾结合剂)和-20.3%(6%钾结合剂),并且在第15天时为-6.9%(2%钾结合剂)、-13.2%(4%钾结合剂)和-17.4%(6%钾结合剂)。与未治疗组相比,观察到第9天用钾结合剂和第15天以两个更高剂量治疗的所有组中血清钾水平显著降低。使用双因素ANOVA加上Bonferroni事后检验进行分析(与未处理组相比**P＜0.01;***P＜0.001)。

[0277] 还分析了在基线、第9天和第15天时对照、未治疗和实验组的血清醛固酮水平(pg/mL)。与未治疗组相比,平均血清醛固酮降低水平在第9天时为-22.7%(2%钾结合剂)、-53.0%(4%钾结合剂)和-57.6%(6%钾结合剂),并且在第15天时为-16.6%(2%钾结合剂)、-37.9%(4%钾结合剂)和-50.3%(6%钾结合剂)。与未治疗组相比,在第9天用钾结合剂和第15天以两个更高剂量治疗的所有组中观察到血清醛固酮水平显著降低。使用双因素ANOVA加上Bonferroni事后检验进行分析(与未处理组相比*P＜0.05;**P＜0.01;***P＜0.001)。

[0278] 所有治疗组间尿钾排泄水平无差异。

[0279] 研究显示,随着血清钾减少观察到血清醛固酮减少。

[0280] 在介绍本发明或其优选实施方案的要素时,冠词“一种”、“一个”、“该”和“所述”旨在意为存在一种或多种要素。术语“包含”、“包括”和“具有”旨在为包容性并且意味着除所列要素外,可能存在另外的要素。

[0281] 鉴于以上,将看出实现了本发明的若干目的并获得其它有利结果。

[0282] 由于可以在不背离本发明的范围的情况下对上述方法进行各种改变,因此意欲表明以上描述所包含的和附图中所示出的所有内容应解释为说明性的而非限制性的意义。

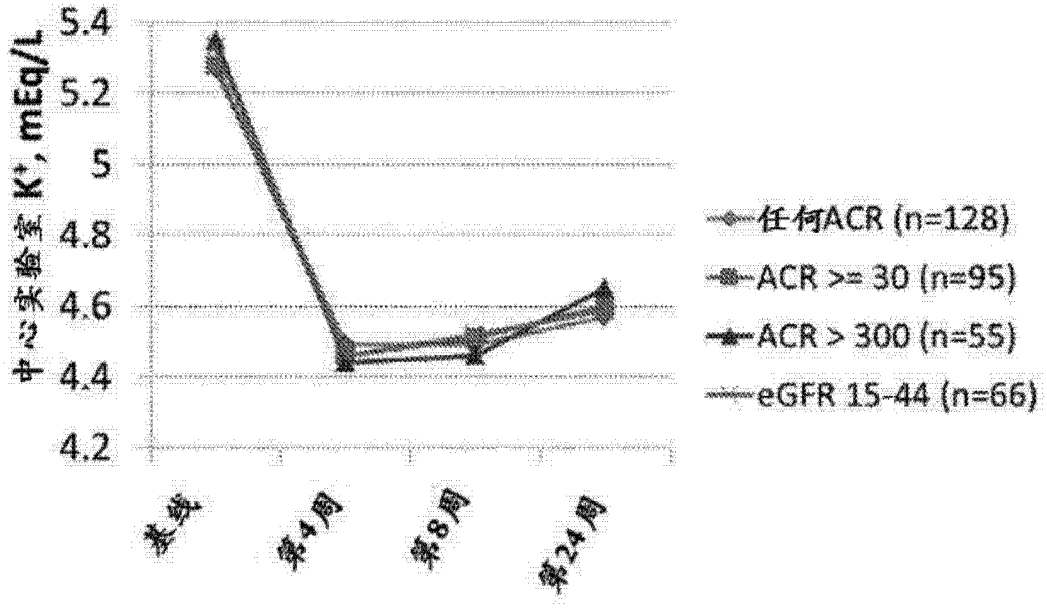

中心实验室 K+, mEq/L
5.4
5.2
5
4.8
4.6
4.4
4.2
基线
第4周
第8周
第24周
任何ACR (n=128)
ACR >= 30 (n=95)
ACR > 300 (n=55)
eGFR 15-44 (n=66)

图 1

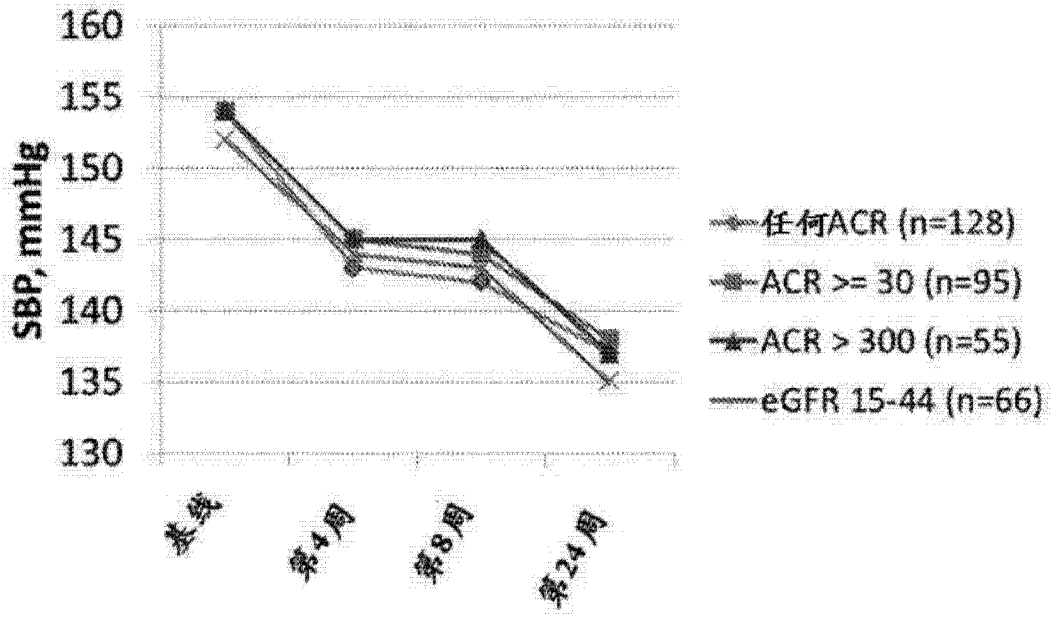

SBP, mmHg
160
155
150
145
140
135
130
基线
第4周
第8周
第24周
任何ACR (n=128)
ACR >= 30 (n=95)
ACR > 300 (n=55)
eGFR 15-44 (n=66)

图 2

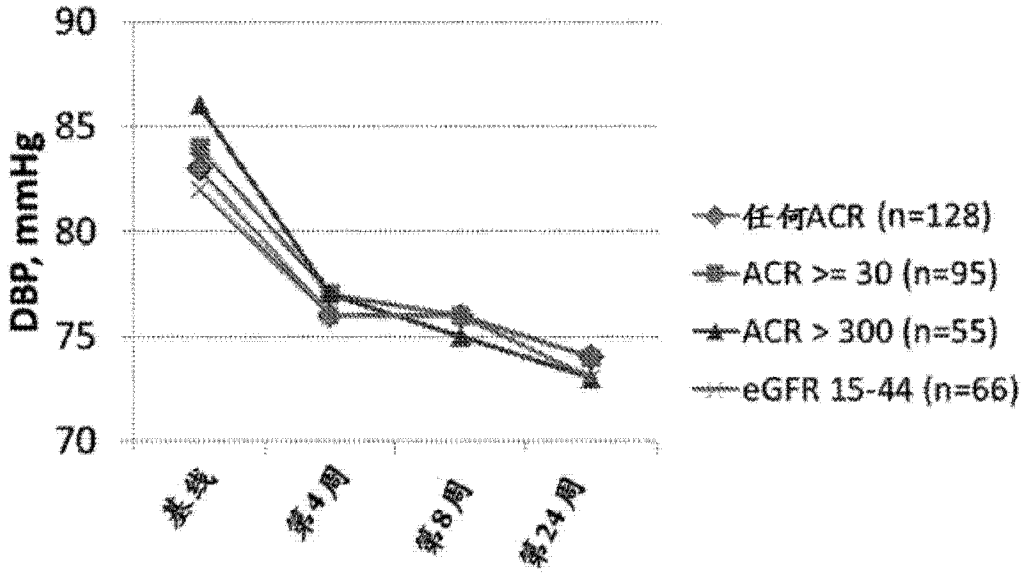

90
85
80
75
70
DBP, mmHg
基线
第4周
第8周
第24周
任何ACR (n=128)
ACR >= 30 (n=95)
ACR > 300 (n=55)
eGFR 15-44 (n=66)

图 3

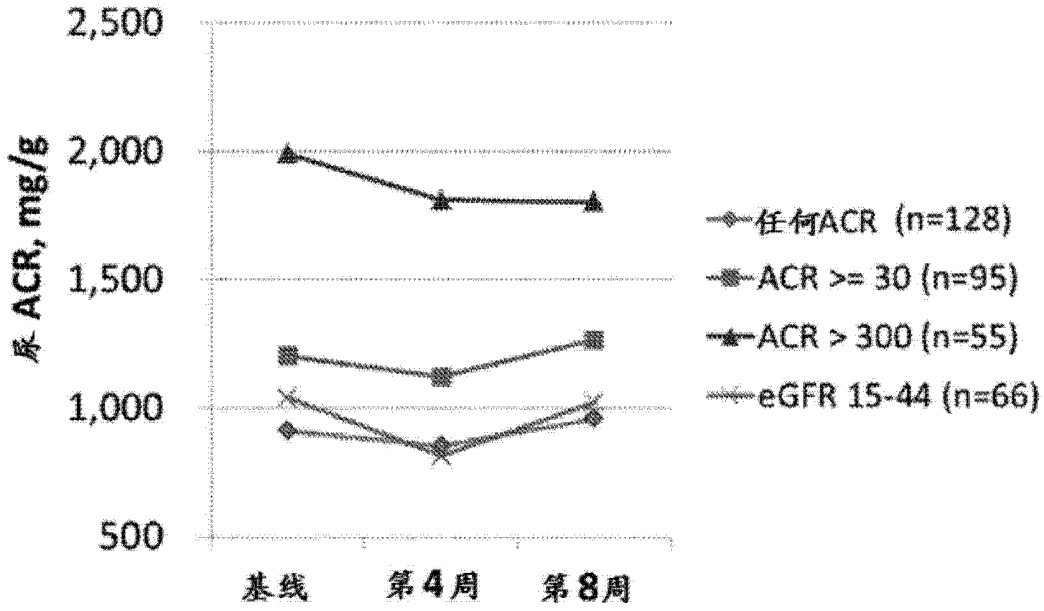

2,500
2,000
1,500
1,000
500
尿 ACR, mg/g
基线
第4周
第8周
任何ACR (n=128)
ACR >= 30 (n=95)
ACR > 300 (n=55)
eGFR 15-44 (n=66)

图 4

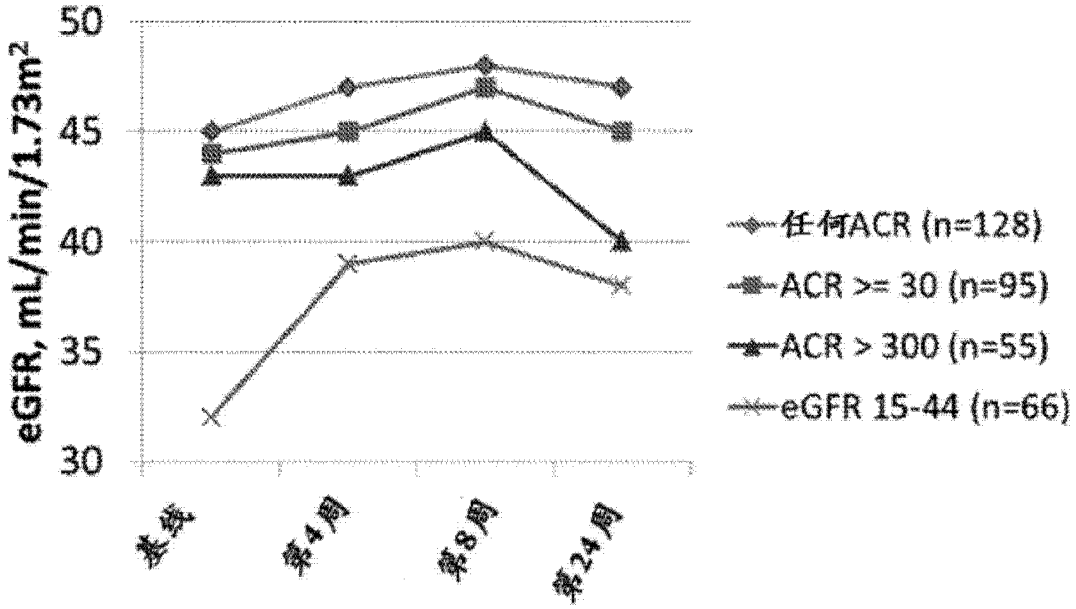

50
45
40
35
30
eGFR, mL/min/1.73m2
基线
第4周
第8周
第24周
任何ACR (n=128)
ACR >= 30 (n=95)
ACR > 300 (n=55)
eGFR 15-44 (n=66)

图 5

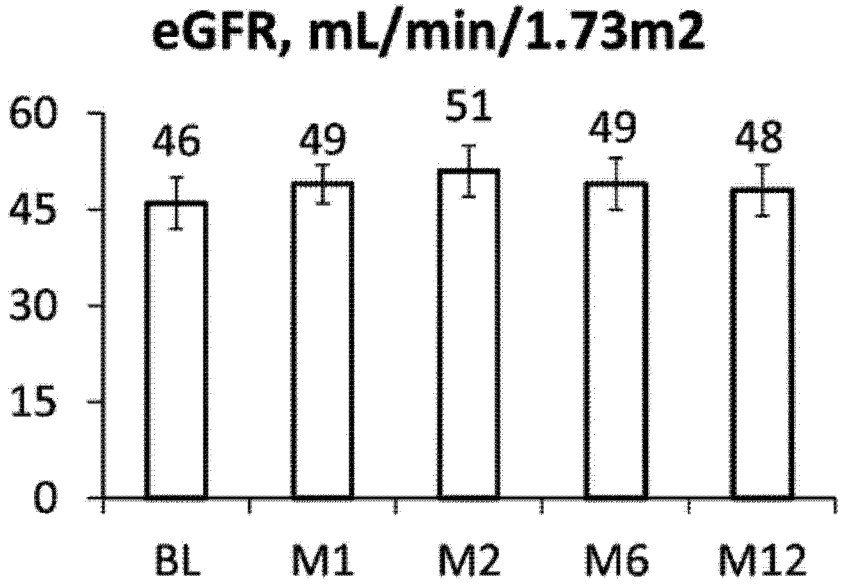

eGFR, mL/min/1.73m2
60
45
30
15
0
46
49
51
49
48
BL
M1
M2
M6
M12

图 6

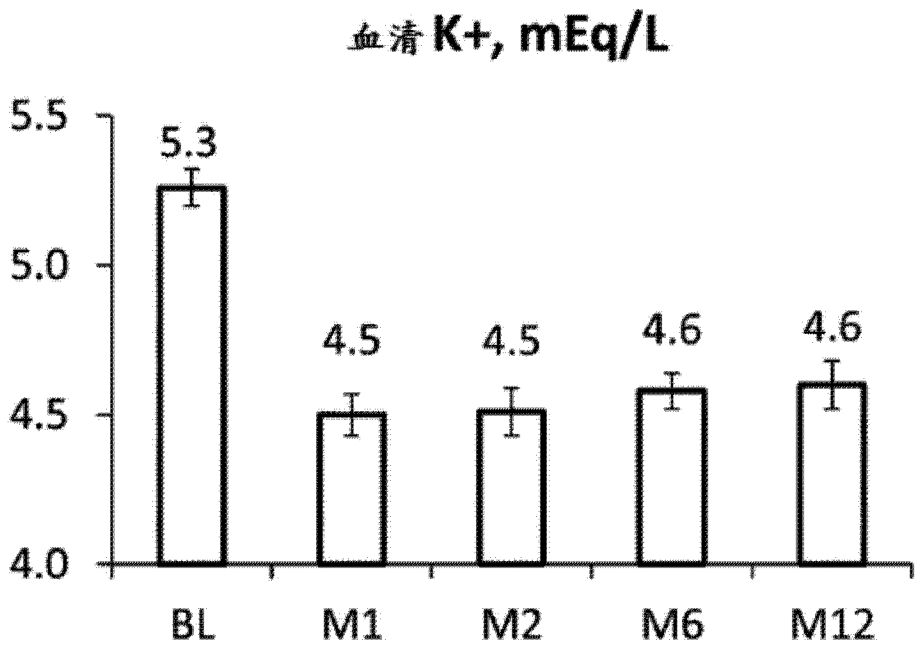

血清 K+, mEq/L
5.5
5.0
4.5
4.0
5.3
4.5
4.5
4.6
4.6
BL
M1
M2
M6
M12

图 7

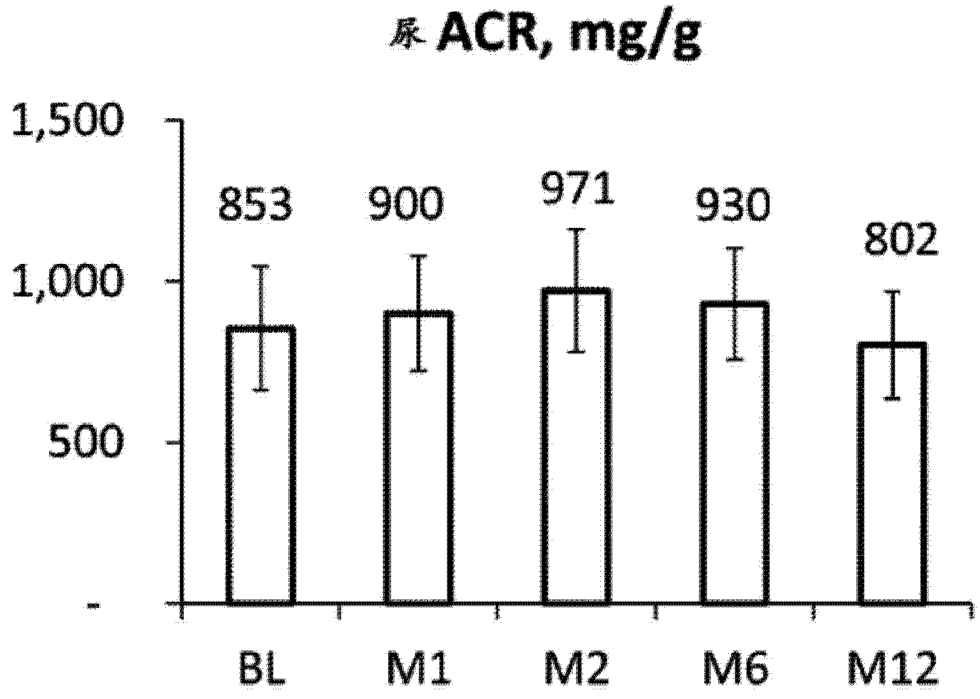

尿 ACR, mg/g
1,500
1,000
500
-
853
900
971
930
802
BL
M1
M2
M6
M12

图 8

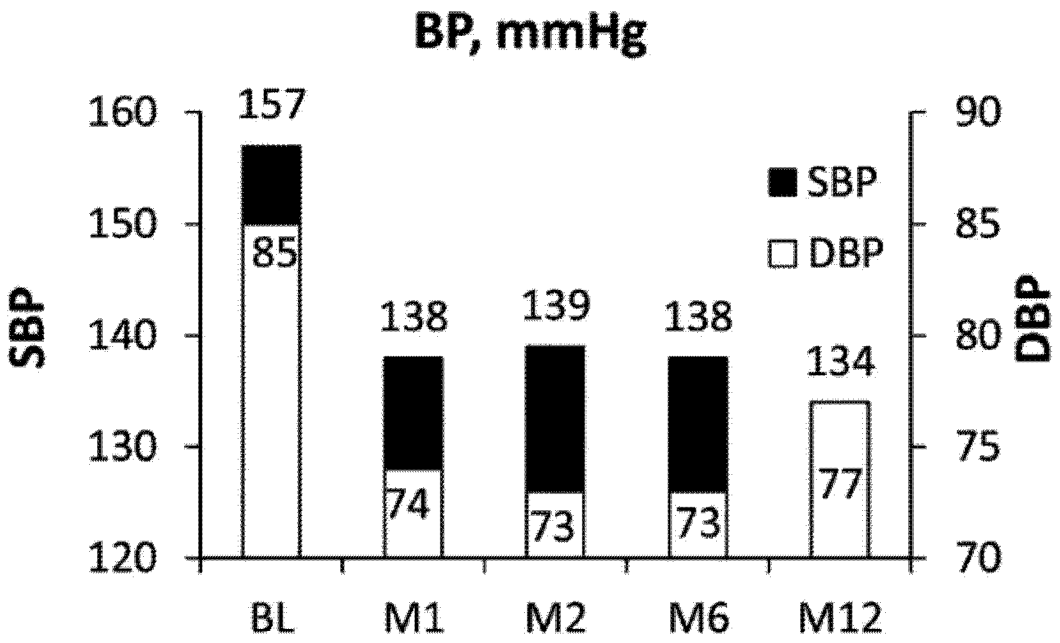

BP, mmHg
SBP
DBP
160
150
140
130
120
90
85
80
75
70
157
85
138
74
139
73
138
73
134
77
BL
M1
M2
M6
M12

图 9