

Xanthine Oxidase Inhibition in Renal Transplant Recipients

NCT01332799

07/27/17

The XART study

PI: Roberto Kalil

IRB ID #: 201010787

Project Details

I. Project Introduction

- I.1** *Project to be reviewed by:*
IRB-01
- I.2** *Project Title:*
The effects of xanthine oxidase inhibition in renal transplant patients. The XART study.
- I.3** *Short Title (optional):*
The XART study
- I.4** *Provide a short summary of the purpose and procedures of the study proposed in this IRB application.*
- *DO NOT include information on studies not proposed in this application.*
 - *Use LAY terminology only. This must be easily understandable by IRB community members and nonscientists.*
 - *DO NOT cut and paste technical abstracts from funding applications that may not be understood by a general audience.*
- Cardiovascular disease is highly prevalent in patients with chronic kidney disease and recipients of kidney transplants. Oxidant injury to the endothelium is known to be one of the mechanisms of atherosclerosis in these patients. Xanthine oxidase is an enzyme involved in the oxidant injury pathway and can be effectively inhibited by allopurinol. We intend to administer allopurinol to subjects who received a kidney transplant and study what happens to their vascular (endothelial) function, and if they have a lower rate of cardiovascular complications compared to patients who receive a placebo drug.
- I.5** *Specify your research question(s), study aims or hypotheses (do not indicate "see protocol")*
- 1-The impact of xanthine oxidase inhibition with allopurinol in endothelial function in recipients of kidney transplantation.
 - 2-The impact of xanthine oxidase inhibition with allopurinol on cardiovascular complications (fatal and non-fatal acute myocardial infarction, new onset angina, stroke, coronary revascularization, peripheral arterial revascularization) in kidney transplant recipients.

I.6 *Background and significance and/or Preliminary studies related to this project.*

(do not indicate "see protocol")

Xanthine oxidase is present in various organs: liver, kidney, heart, brain, bowels and in plasma and endothelium of coronary vessels. It catalyses the conversion of hypoxanthine to xanthine and xanthine to uric acid. These two steps also generate superoxide anions (reactive oxygen species) which can produce endothelial dysfunction. 1. Allopurinol, a xanthine-oxidase inhibitor, was discovered in the 1940s and approved by the Food and Drug Administration, in 1966 for treatment of gout. Most of its effects are via its active metabolite, oxypurinol. Both oxypurinol and higher concentrations of allopurinol are non-competitive inhibitors of xanthine oxidase. 1

In adolescents newly diagnosed with stage I hypertension, Feig et al, showed blood pressure reduction with allopurinol for 4 weeks with a lack of adverse events. 2

Allopurinol has also been shown to improve endothelial dysfunction in subjects with chronic heart failure, type II diabetes, mild hypertension, sleep apnea and heavy smokers, and more recently, subjects with chronic kidney disease 4 – 7. George et al showed that a 600 mg dose of allopurinol produced a superior endothelial function enhancement, by reducing vascular oxidative stress, as compared to a 300 mg dose or placebo. 8 Recent studies utilizing a lower dose of allopurinol in subjects with impaired renal function (Goicochea, Kao) revealed favorable results and will be discussed in the “Preliminary Studies” section.

We plan to explore the effects of allopurinol 300 mg to 600 mg in kidney transplant recipients.

I.7 *Literature cited / references (if attaching a grant or protocol enter N/A).*

1. Pacher P, Nivorozhkin A, Szabo C: Therapeutic Effects of Xanthine Oxidase Inhibitors: Renaissance Half a Century after the Discovery of allopurinol. *Pharmacol Rev* 2006; 58 (1): 87-114
2. Feig DI, Soletsky B, Johnson RJ: Effect of allopurinol on Blood pressure of Adolescents with Newly diagnosed Essential Hypertension: A randomized trial. *JAMA* 2008; 300(8): 924-932
3. Ogden CL, Carrol MD, McDowell MA, Flegal KM: Obesity among adults in the United States – no change since 2003-2004: NCHS Data Brief 2007
4. Farquharson CAJ, Butler R, Hill A, Belch JJ, Struthers AD: Allopurinol improves endothelial dysfunction in chronic heart failure. *Circulation*. 2002;106:221-226
5. Butler R, Morris AD., Belch JJ, Hill A, Struthers AD. Allopurinol Normalizes Endothelial Dysfunction in Type 2 Diabetes with Mild Hypertension. *Hypertension* 2000; 35(3);746-751
6. El Solh AA, Saliba R, Bosinski T, Grant BJ, Barbary E, Miller N: Allopurinol improves endothelial function in sleep apnea: a randomised controlled study *Eur Respir J* 2006; 27(5):997-1002
7. Guthikonda S, Sinkey C, Barenz T, Haynes WG: Xanthine oxidase inhibition reverses Endothelial Dysfunction in Heavy Smokers *Circulation* 2003; 107(3);416-421

8. George J, Carr E, Davies J, Belch JJ, Struthers A: High Dose allopurinol Improves Endothelial Function by Profoundly Reducing Vascular Oxidative Stress and Not by Lowering Uric Acid Circulation 2006; 114; 2508-2516;
9. Granger DN, Rutili G, McCord JM: Superoxide radicals in feline intestinal ischemia. *Gastroenterology* 1981; 81(1): 22-29
10. Granger DN, McCord JM, Parks DA, Hollwarth ME: Xanthine oxidase inhibitors attenuate ischemia-induced vascular permeability changes in the cat intestine. *Gastroenterology* 1986; 90 (1): 80-84,
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13. Tripatara P, Patel NS, Webb A, et al: Nitrite-Derived Nitric Oxide Protects the Rat Kidney against Ischemia/Reperfusion Injury In Vivo: Role for Xanthine Oxidoreductase *J. Am Soc Nephrol* 2007; 18: 570-580
14. Friedl HP, Smith DJ, Till GO, Thomson PD, Louis DS, Ward PA: Ischemia-reperfusion in humans: appearance of xanthine oxidase activity. *Am J Pathol* 1990; 136(3): 491-495
15. Celermajer DS, Sorensen KE, Gooch VM, et al: Non invasive detection of endothelial dysfunction in children and in adults at risk of atherosclerosis. *Lancet* 1992; 340(8828): 1111-1115
16. Steinberg HO, Chaker H, Leaming R, Johnson A, Brechtel G, Baron AD: Obesity /insulin resistance is associated with endothelial dysfunction. Implications for the syndrome of insulin resistance. *J Clin Invest* 1996; 97 (11): 2601-2610
17. Arcaro G, Zamboni M, Rossi L. et al: Body fat distribution predicts the degree of endothelial dysfunction in uncomplicated obesity. *Int J Obes Relat Metab Disord* 1999; 23 (9): 936-942
18. Baudry N, Laemmel E, Vicaut E: In vivo reactive oxygen species production induced by ischemia in muscle arterioles of mice: involvement on xanthine oxidase and mitochondria *Am J Physiol Heart Circ Physiol* 2008; 294(2): H821-H828
19. Netzer NC, Stoohs RA, Netzer CM, Clark K, Strohl KP: Using the Berlin Questionnaire to identify patients at risk for the sleep apnea syndrome. *Ann Intern Med.* 1999; 131(7):485-491
20. Pea F: Pharmacology of drugs for hyperuricemia: mechanisms, kinetics and interactions. *Contrib Nephrol* 2005; 147: 35-46
21. Agabiti-Rosei E, Mancia G, O'Rourke MF et al: Central blood pressure measurements and antihypertensive therapy: A consensus document. *Hypertension* 2007; 50(1):154-160
22. Roman MJ, Devereux RB, Kizer JR et al: Central pressure more strongly relates to vascular disease than does brachial artery pressure. The Strong Heart Study. *Hypertension* 2007; 50 (1):197-203
23. Heistad, D.D. and Armstrong, M.L: Sick vessel syndrome. *Can*

- atherosclerotic arteries recover? *Circulation*. 1994; 89(5): 2447-2450.
24. Rossi R, Nuzzo A, Origliani G, Modena MG: Prognostic role of flow-mediated dilation and cardiac risk factors in post-menopausal women. *J Am Coll Cardiol*, 2008; 51(10): 997-1002
25. Avolio A, Grassi G: Flow-mediated dilatation as a biomarker for cardiovascular risk in hypertension. *J. Hypertens*. 2008; 26(8): 1546-1547.
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27. Grassi G, Facchini A, Trevano FQ, et al. Obstructive sleep apnea - dependent and -independent adrenergic activation in obesity. *Hypertension* 2005; 46:321-325.
28. The Practical Guide: Identification, Evaluation, and Treatment of Overweight and Obesity in Adults. Public Health Service, National Institutes of Health, National Heart, Lung, and Blood Institute. NIH Publication No. 00-4084: p. 35, 2000.
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35. Akalin E, Ganeshan S, Winston J, Muntner P: Hyperuricemia is associated with the development of the composite outcomes of new cardiovascular events and chronic allograft nephropathy. *Transplantation* 86: 652-658, 2008.
36. Smetana M, Weinstein T, Matas Z, Gafter U, Laina A et al: Secondary prevention with antioxidants of cardiovascular disease in endstage renal disease (SPACE): randomized placebo-controlled trial. *Lancet* 356:1213-18, 2000.
36. Goicoechea M, de Vinuesa S, Verdalles U, Ruiz-Caro C et al: Effect of allopurinol in chronic kidney disease progression and cardiovascular risk. *Clin J Am Soc Nephrol*...2010

37. Kao M, Ang D, Gandy S, Lang C, Struthers A: Allopurinol reduces both left ventricular hypertrophy and endothelial dysfunction in patients with chronic kidney disease. *Nephrol Dial Transplantation* (S3) iii302, 2010.
38. Hande K, Noone R, Stone W: Severe allopurinol toxicity. Description and guidelines for prevention in patients with renal insufficiency. *Am J of Medicine* 76: 47-56, 1984.
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41. Dalbeth N, Stamp L: Allopurinol dosing in renal impairment: Walking the tightrope between adequate urate lowering and adverse events. *Seminars in Dialysis* 20: 391-395, 2007.
42. Panomvana D, Sripradit S, Angthararak S: Higher therapeutic plasma oxypurinol concentrations might be required for gouty patients with chronic kidney disease. *J Clin Rheum* 14: 6-11, 2008.

II. Research Team

II.1 *Principal Investigator*

Name	E-mail	College
Roberto Kalil	roberto-kalil@uiowa.edu	Carver College of Medicine

II.2 *Team Members* UI Team Members

Name	E-mail	College	Contact	Key Prsn	UI COI	VAMC COI
Roberto Kalil, MD	roberto-kalil@uiowa.edu	Carver College of Medicine	Yes	Yes	No	
Graziela Kalil, PharmD	graziela-kalil@uiowa.edu	Carver College of Medicine	Yes	Yes	No	
Tamara Lowe, RA	tamara-low@uiowa.edu	Carver College of Medicine	Yes	No	No	
Denice Wells, RA	denice-wells@uiowa.edu	Carver College of	No	No	No	

Medicine

Non-UI Team Members

Name	Institution	Location	FWA	Role	DHHS	Contact	Key Prsn	UI COI	VAMC COI	COI PI	Inv
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Nothing found to display.

II.3 *The Principal Investigator of this study is:*
Faculty

II.6 *Identify the key personnel. The system will automatically designate the PI and all faculty members on the project as “key personnel.” For information about other team members who should be designated as “key personnel” please click on the help information.*

Name	Is Key Personnel
Roberto Kalil, MD	Yes
Graziela Kalil, PharmD	Yes
Tamara Lowe, RA	No
Denice Wells, RA	No

III. Funding/Other Support

III.1 *Funding Sources*
Type





Source







Federal Agency US Department of Health & Human Services, National Institute

* new source name

III.2 *What type of funding agreement would be completed?*
Federal/State/Local Agency/Non-Profit Funded/Other

III.3 *Does any member of the research team have a financial conflict of interest related to this project according to the [Conflict of Interest in Research](#) policy? If yes, please indicate which members below.*

Name	Has Conflict of Interest	SFI FCOI	Management Plan
Roberto Kalil, MD	No		
Graziela Kalil, PharmD	No		

Tamara Lowe, RA	No		
Denice Wells, RA	No		
Institutional Conflict of Interest (ICOI): 			
ICOI Management Plan Status: 			

III.5 *What is the current status of this funding source?*

Source	Status	Other Status Description
US Department of Health & Human Services, National Institutes of Health	Awarded	

IV. Project Type

IV.1 *Do you want the IRB to give this project Regular (expedited or full board) review*

IV.2 *Enter the date you will be ready to begin screening subjects/collecting data for this project. (If you do not have a specified date, add "upon IRB approval")*
11/01/2010

IV.3 *Are you requesting a [waiver of informed consent/authorization](#) (subjects will not be given any oral or written information about the study)?*
No

V. Other Committee Review

V.1 *Does this project involve any substance ingested, injected, or applied to the body?*

- *Do not answer yes, if the involvement includes a device, wire, or instrument*

Yes

V.1.a *What is/are the substance(s):*
allopurinol or placebo

V.1.b *Are any of these substances defined as a [Schedule I - V Controlled Substance](#)?*
No

V.2 *Are any contrast agents used for any purpose in this study?*
No

V.4 *Are all drugs or substances in this study being used within the FDA approved population (i.e., children, adults)?*
Yes

V.5 *Are all drugs or substances in this study being used within the FDA approved indication (i.e., disease, condition)?*
No

V.6 *Are all drugs or substances in this study being used within the FDA approved dose?*
Yes

V.7 *Are all drugs or substances in this study being used within the FDA approved route of administration?*
Yes

V.8 *Drugs used in study that are not FDA approved for the population, indication, dose, or route of administration*

allopurinol (allopurinol)

Name of Sponsor

Investigator's Brochure
Version

Investigator's Brochure
Date

Planned Use in this Study

Condition/Disease Atherosclerosis
Indication(s)

Subject Population Kidney transplant recipients

Dose(s) up to 600 mg daily

Administration Oral

Dosing Regimen Daily single dose

FDA Approved Use

Approved hyperurecemia
Condition/Disease
Indication(s)

Approved Patient adult
Population

Approved Dose(s) Up to 800 mg daily

Approved Administration Oral

Approved Dosing Daily single dose
Regimen

Is this study intended to No

be reported to the FDA as a well-controlled study in support of a new indication or a significant change in the labeling for this product?

Is this study intended to support a significant change in the advertising for this product? No

Does this planned use of the product in this study, taking into consideration the route of administration, the dosage level, and the subject population, significantly increase the risk (or decrease the acceptability of the risk) associated with the use of this product? No

Rationale:

Allopurinol is routinely used in kidney transplant recipients who develop gout and/or hyperuricemia for many years. In this study, the goal is to examine the anti-oxidant effects of this drug that are believed to be beneficial in cardiovascular diseases. The maximum dose to be used (600 mg) will be below the maximum FDA approved dose (800 mg)

V.9 *Will any subject be asked to undergo a diagnostic radiation procedure (including radiographic, nuclear medicine, DEXA)?*
No

V.14 *Will any subject be asked to undergo a radiation therapy procedure (including external beam therapy, brachytherapy, or nuclear medicine therapy)?*
No

V.20 *Does this project involve the deliberate transfer of recombinant or synthetic nucleic acid molecules, or DNA or RNA derived from recombinant or synthetic nucleic acid molecules, into one or more human research participant?*
No

V.21 *Will any portion of this project be conducted in the CRU, or does it use any CRU resources?*

Yes

V.22 *Will this project use any resource/patients of the HCCC?*

No

V.25.a *Will the study involve any of the following activity at UI Health Care, even if subjects or their insurance will not be billed for the item or service, and regardless of the study funding source (including studies with departmental or no funding)?*

- *Procedures, tests, examinations, hospitalizations, use of Pathology services, use of clinic facilities or clinical equipment, or any patient care services, including services conducted in the Clinical Research Unit; or*
- *Physician services or services provided by non-physicians who are credentialed to bill (ARNPs, Physician Assistants, etc.)*

Yes

V.26 *The study involves nursing, nursing resources or evaluates nursing practices.*

No

VI. Subjects

VI.1 *How many adult subjects do you expect to consent or enroll for this project?*
120

VI.2 *What is the age of the youngest adult subject?*
18.0

VI.3 *What is the age of the oldest adult subject?*
90.0

VI.4 *What is the percentage of adult male subjects?*
50

VI.5 *What is the percentage of adult female subjects?*
50

VI.6 *How many minor subjects do you expect to consent or enroll for this project?*
0

VI.13 *Describe EACH of your subject populations*

- *Include description of any control group(s)*
- *Specify the Inclusion/Exclusion criteria for EACH group*
- *Studies under IRB-03 enrolling non veterans as part of the subject population must present a compelling argument to the IRB for the*

inclusion of non-Veterans (e.g., insufficient number of Veterans; survey of VA employees; study of active duty military; study involving Veterans' family members), and the research is relevant to the care of Veterans or active duty military personnel.

Subject selection procedures

1. Age: 18 years of age or older
2. Sex: Both male and female population
3. Recipients of kidney transplantation and with stable kidney function
4. Ethnic background: subjects of all ethnicities

Exclusion Criteria:

- * Current use of allopurinol
- * History of Gout
- * History of non-adherence with routine clinic and laboratory visits.
- * Recent diagnosis of acute rejection (3 months)
- * Baseline estimated glomerular filtration rate of < 30 ml/min
- * Difficult to control hypertension (subjects requiring 4 or more anti-hypertensive medications)
- * Pregnancy and/or lactation
- * History of allergy/adverse reaction to allopurinol
- * History of allergy/adverse reaction to adhesive.
- * EKG showing atrial fibrillation.
- * Clinically significant hepatic insufficiency
- * History of positive stress test in the past 6 months
- * Current use of amoxicillin, ampicillin, aluminium hydroxide, phenprocoumon, coumadin, vidarabine, azathioprine, cyclophosphamide, didanosine, theophylline, mercaptopurine or warfarin.
- * Medical conditions requiring continuous use of phosphodiesterase inhibitors and/or the inability to withhold phosphodiesterase inhibitors for 48 hours prior to Nitroglycerin administration.

VI.14 ***Provide an estimate of the total number of subjects that would be eligible for inclusion in each of your study populations (include your control population if applicable)***

We follow approximately over 1200 patients with kidney transplants in the organ transplant center. This will be a placebo controlled study.

VI.15 ***Describe how you will have access to each of your study populations in sufficient number to meet your recruitment goals.***

List of active clinic patients seen on a regular basis in the outpatient transplant clinic.

VI.16 ***Do you plan to recruit/enroll non-English speaking people?***

No

VI.18 ***Do you propose to enroll any of the following in this study as subjects?***

- ***Employee of the PI or employee of a research team member***
- ***Individual supervised by PI or supervised by member of research team***
- ***Individual subordinate to the PI or subordinate to any member of the***

research team

- *Student or trainee under the direction of the PI or under the direction of a member of the research team*

No

VI.20 *Will subjects provide any information about their relatives?*

No

VI.23 *Will anyone (other than the subject) provide you with information about the subject (e.g. proxy interviews)?*

No

VI.26 *Is this project about pregnant women?*

No

VI.27 *Will this project involve fetuses?*

No

VI.28 *Does this project involve adult subjects who may be incompetent or have limited decision-making capacity on initial enrollment into the study?*

No

VI.32 *Does this project involve subjects whose capacity to consent may change over the course of the study?*

No

VI.37 *Does this project involve prisoners as subjects?*

No

VII.A. Project Description (A)

VII.A.1 *Where will project procedures take place (check all that apply)?*

- CRU

VII.A.2 *Is this project also being conducted by other researchers at their own sites (e.g. a multi-site collaborative project)?*

No

VII.B. Project Description (B)

VII.B.1 *Does this project involve any of the following (Check all that apply):*

- ☐

Registry – The collection and maintenance of data (not including biologic samples) in which: (1) the individuals in the registry have a common or related condition(s), and/or (2) the individuals

in the registry are interested in being contacted for future studies by investigators other than those listed in Section II of this project. ([UI Guide](#))

- ☐ **Repository** – The collection, storage, and distribution of human biologic samples and/or data materials for research purposes. Repository activities involve three components: (i) the collection of data and/or specimens such as blood, tissue, saliva, etc.; (ii) the storage of data or specimens, and data management function; and (iii) the sharing of data/specimens with recipient investigators other than the original investigators. (paraphrased from [OHRP](#))
- ☐ **Expanded Access** – A process regulated by the Food and Drug Administration (FDA) that allows manufacturers to provide investigational new drugs to patients with serious diseases or conditions who cannot participate in a clinical trial. Examples of expanded access include non-protocol access to experimental treatments, including protocol exception, single-patient IND, treatment IND, compassionate use, emergency use, continued access to investigational drug, and parallel track ([ClinicalTrials.gov](#) & [FDA](#)).
- ☒ **Clinical (or Treatment) trial** – A prospective biomedical or behavioral research study of new treatments, new drug or combinations of drugs, new devices, or new approaches to surgery or radiation therapy. (NIH and [ClinicalTrials.gov](#) & [FDA](#))
- ☐ **Physiology intervention/study** – A pharmacologic or measurement study aimed at understanding basic mechanisms of disease and/or of normal human physiology, often without any therapeutic intent (though a clinical trial could include such components, often labeled as “translational” or “basic science” aims.) Measurements in such studies could include, but are not limited to, a blood draw, EKG, EEG, MRI, auditory or sensory testing, checking vital signs, DEXA scans, eye tracking, specimen collection, exercise, fasting, special diets, etc.
- ☐ **Behavioral intervention/study** – May be used to refer to studies of individual or group behavior. This option does not include drugs, biologics, or devices but could include psychotherapy, lifestyle counseling, behavior modification, etc.
- ☐ **Diagnostic trial** – Protocol designed to evaluate one or more interventions aimed at identifying a disease or health condition ([ClinicalTrials.gov](#) & [FDA](#))

- ☐ **Non-clinical** – any college/department that would regularly submit to [IRB-02](#)
- ☐ **Other**

VII.B.1.a *Does this project involve any of the following (Check all that apply):*

- ☐ **Phase I trials** – include initial studies to determine the metabolism and pharmacologic actions of drugs in humans, the side effects associated with increasing doses, and to gain early evidence of effectiveness; may include healthy participants and/or patients ([ClinicalTrials.gov](#) & [FDA](#))
- ☐ **Phase II trials** – include controlled clinical studies conducted to evaluate the effectiveness of the drug for a particular indication or indications in patients with the disease or condition under study and to determine the common short-term side effects and risks ([ClinicalTrials.gov](#) & [FDA](#))
- ☐ **Phase III trials** – include expanded controlled and uncontrolled trials after preliminary evidence suggesting effectiveness of the drug has been obtained, and are intended to gather additional information to evaluate the overall benefit-risk relationship of the drug and provide an adequate basis for physician labeling([ClinicalTrials.gov](#) & [FDA](#))
- ☒ **Phase IV trials** – studies of FDA-approved drugs to delineate additional information including the drug's risks, benefits, and optimal use([ClinicalTrials.gov](#) & [FDA](#))

VII.B.1.b *Provide the [NCT](#) (National ClinicalTrials.gov Identifier) number*
NCT01332799

VII.B.2 *Does this project involve a [drug washout](#) (asking subject to stop taking any drugs s/he is currently taking)?*
No

VII.B.6 *Will any subjects receive a [placebo](#) in this study when, if they were not participating, they could be receiving an FDA-approved treatment for their condition?*
No

VII.B.11 *Is there a separate, written protocol that will be submitted in addition to this IRB New Project form? (Note: a grant application is not considered to be a*

protocol)

No

VII.B.18 *Does this project involve testing the safety and/or efficacy of a medical device?*

No

VII.C. Project Description (C)

VII.C.1 *Does this project involve any research on genes or genetic testing/research?*

No

VII.D. Project Description (D)

VII.D.1 *Check all materials/methods that will be used in recruiting subjects (you will need to attach copies of all materials at the end of the application):*

- Letter -
- Use of any information available to the researchers or their colleagues because this person is a patient OR use of any information considered to be Protected Health Information (PHI) OR review of patient/clinic records - EPIC

VII.D.2 *List the individual data elements you will need to access/use from the patient or clinic records to identify potential subjects for recruitment*
Age, date of transplant, creatinine levels (to estimate glomerular filtration rate GFR), history of hyperucemia, medications list (to check for current use of allopurinol or potential interactions), allergy history, and history of non-compliance with medical or laboratory visits.

VII.D.3 *Describe why you could not practicably recruit subjects without access to and use of the information described above*

It is not reasonable to approach subjects that easily meet exclusion criteria. It would be very time consuming for the research team and for the subjects to be answering questions that they do not need to spend their time if they are not eligible.

VII.D.4 *Describe why you could not practicably obtain authorization from potential subjects to review their patient or clinic records for recruitment purposes.*

The large number of potential subjects to be screened by sending letters or calling would make this study extremely difficult to conduct, impractical. Furthermore, the amount of information needed to screen is minimal (see VIID.2).

VII.D.5 *Describe plans to protect the identifiers from improper use or disclosure*

Subjects will be de-identified with a coding system that does not use any

information related to their identifiers. Only the research team will have access to the code.

VII.D.6 ***Describe plans to destroy identifiers at the earliest opportunity consistent with conduct of the research***

All identifiers will be destroyed and use of de-identifiers will be immediately applied after enrollment in participating in the study. Database will contain only the de-identified research code. We will keep identifiers to avoid re-approaching an individual that has previously declined participation in the study or was determined to be ineligible. This list will be kept confidential in a separate file.

VII.D.7 ***Does the research team agree that the requested information will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the study, or for other research for which the use or disclosure of the requested information would be permitted by the HIPAA Privacy Rule***

Yes

VII.D.8 ***Will a member of the research team discuss the study with the subject in person prior to the subject agreeing to participate?***

Yes

VII.D.9 ***Describe the physical location where the consent process will take place:***
Kidney transplant clinic in person, or over the Clinical Research Unit also in person.

VII.D.10 ***Will a member of the research team discuss the study with the subject by phone prior to the subject agreeing to participate?***

Yes

VII.D.11 ***Describe:***

Potential study subjects will receive a letter by mail with the consent form to review before discussion with the research team. They will have a number available in the consent form to call my office and/or the office of the research assistant. Alternatively, we plan to call after 2 weeks if we don't hear from the potential study subjects by letter or phone.

VII.D.12 ***Who will be involved in the consent process (including review of consent document, answering subjects' questions)?***

Name	Consent Process Involvement
Roberto Kalil, MD	Yes
Graziela Kalil, PharmD	No
Tamara Lowe, RA	Yes
Denice Wells, RA	Yes

VII.D.15 ***Check all materials that will be used to obtain/document informed consent:***

- Consent Document

- VII.D.16** *Are you requesting a waiver of documentation of consent (either no subject signature or no written document)?*
No
- VII.D.19** *Before the subject gives consent to participate are there any screening questions that you need to directly ask the potential subject to determine eligibility for the study?*
Yes
- VII.D.20** *List any screening questions you will directly ask the potential subject to determine eligibility.*
History of allergy to allopurinol. History of gout. In the event that the electronic medical records are incomplete or inaccurate it is important to make sure that the information on allergy to the study drug is reliable reason why we plan to ask these questions.
All other questions will be answered using information from the electronic medical records detailed in section VII D.2
- VII.D.21** *Will you keep a screening log or other record that would include information on people who do not enroll in the study?*
Yes
- VII.D.22** *Describe the information being collected and the purpose for keeping this information.*
Only basic demographic information such as name and date of the documentation. No need to store clinical information.
- VII.D.23** *Will this information be shared with anyone outside the UI research team members?*
No
- VII.D.25** *After the subject agrees to participate (signs consent), are there any screening procedures, tests, or studies that need to be done to determine if the subject is eligible to continue participating?*
Yes
- VII.D.26** *List and describe screening*
Female subjects of childbearing potential will be tested for pregnancy before starting the study. If positive, they can not participate in the study.
- VII.D.27** *Discuss how much time a potential subject will have to agree to consider participation and whether or not they will be able to discuss the study with family/friends before deciding on participation.*
2 weeks
- VII.D.28** *How long after the subject agrees to participate do study procedures begin?*
It can start immediately or at patient convenience.

VII.D.29 *Provide a description of the enrollment and consent process for adult subjects*

- *Describe each study population separately including control population*
- *Include when recruitment and consent materials are used*
- *Use 3rd person active voice “The Principal Investigator will identify subjects. For example, the principal investigator will identify potential subjects, the study coordinator will discuss the study with subjects over the telephone and schedule the first study visit, etc...”*
- *Describe the steps that will be taken by the research team to minimize the possibility of coercion or undue influence during the consent process*

Recruitment will occur from potential participants from the Kidney Transplant Clinic at the University of Iowa Hospitals and Clinics meeting inclusion criteria.

1-A list of potential study participants will be identified by the research team, obtained from our routine outpatient schedule.

2-Consent document will be obtained at the transplant clinic, or the Clinical Research Unit, or by mail. By mail, potential participants will receive a consent form and a cover letter summarizing the protocol to facilitate understanding of the study. The consents may be mailed or distributed during a clinic visit to the Transplant Organ Center at UIHC. A telephone number will be listed in the consent document for further information if needed by potential participants. A return card with the option to participate or not in the study, in a self addressed, stamped envelope will be included in the same letter containing the consent document.

There will be plenty of time (2 weeks) for the potential participant to decide to enroll or not in the study. They will be given a number to call to ask any question they have about the study.

Potential study subjects will receive a call in 2 weeks if we don't receive the card with an answer accepting or declining participation in the study. We will offer to answer and clarify any questions about the study, the study visits, duration of each visit, and what happens in each study visit.

If patient is not decided about the study, we will be available to answer further questions should this be necessary for the patient to make a decision. We will again make clear that the participation in the study does not interfere with routine transplant care, and the participation it is totally voluntary.

3-If we don't receive the consent document or a call from the potential subjects in 2 weeks after sending the letter, we will contact them by phone to know if they are interested in the study or not. If potential study subjects request more time to consider participating in the study, we will allow as much time possible at the study subject convenience to decide.

4-After agreeing in being in the study, we will schedule the first (randomization) study visit in the Clinical Research Unit over the phone with the study subject or in person at the transplant clinic.

VII.D.37 *Does the study include any form of deception (e.g., providing participants with false information, misleading information, or withholding information about*

certain study procedures)?

Examples:

- *Procedure includes a cover story that provides a plausible but inaccurate account of the purposes of the research.*
- *Participants will be provided with false information regarding the particular behaviors of interest in the research.*
- *Procedures include a confederate pretending to be another participant in the study.*
- *Participants will be told that the research includes completion of a particular task, when in fact, that task will not be administered.*
- *Study is designed to introduce a new procedure (or task) that participants are not initially told about.*
- *If yes, a waiver of informed consent must be requested under question IV.3.*

No

VII.E. Project Description (E)

VII.E.1 *Will subjects be randomized?*
Yes

VII.E.1.a *Will any subjects be blinded to which study arm they have been assigned?*
Yes

VII.E.1.b *Does the protocol permit telling subjects their treatment assignment at the end of the entire study?*
Yes

VII.E.1.c *Describe the circumstances under which subjects will be told what study arm they have been assigned.*
In case of adverse reaction to the study drug, besides discontinuing the drug, it will be very important to inform the patient immediately about his/her allergy to the drug to protect them from being exposed again to this drug and prevent serious adverse reactions.
In the end of the study, we will notify the patient about what arm of the study ne/she was on, and if ther was a benefit from the active drug to the participants.

VII.E.2 *Describe randomization scheme/assignment including ratio such as 1:1, 2:1 etc.*
Randomization will be performed using a software to a ratio of 1:1 with 1 arm for active drug (allopurinol) and 1 arm for placebo.

VII.E.3 *Will any questionnaires, surveys, or written assessments be used to obtain data*

directly from subjects in this study?

No

VII.E.5 *Does this project involve creating any audiotapes, videotapes, or photographs?*

No

VII.E.6 *Provide a detailed description in sequential order of the study procedures following the consent process - DO NOT cut and paste from the Consent Document.*

Describe study populations separately if they will be participating in different procedures - include CONTROL population if applicable.

DESCRIBE:

- *What subjects will be asked to do/what happens in the study (in sequential order)*
- *The time period over which procedures will occur*
- *The time commitment for the subject for individual visits/procedures*
- *Long-term followup and how it occurs*

Each visit will last approximately 2 hours. There is a total of 5 visits as follows: baseline (0 week), 2 months, 12 months, 24 months, and 36 months post randomization.

After the last visit at 36 months, no long-term follow-up is planned.

Below is a detailed explanation of the initial randomization procedure, and each test performed in each visit.

Administration: Study drug or placebo administration will occur at the time of randomization after completion of pre-assessment. The specific agent will be coded with an identification number label. Assignments will be made in a sequential order as subjects are randomized. Accountability will be maintained with a hardcopy log. The log will contain the date dispensed, date returned, subject name, code, pill count, drug lot number and expiration date, and information for a perpetual inventory.

Pulse Wave Velocity and Estimated Aortic Pressure

We will assess two markers of vascular stiffness, namely pulse wave velocity (PWV) and estimated aortic pressure by reflected pulse waves. These techniques provide an assessment of subclinical vascular damage, and are impaired by both endothelial dysfunction and vascular structural abnormalities. In particular, hypertension can increase vascular stiffness through reduced endothelial production of mediators such as nitric oxide (which would usually reduce vascular stiffness), hypertrophy and fibrosis of the medial layer, and (eventually) sub-intimal atherosclerotic plaques. As vascular stiffness increases, the speed at which the pulse wave travels increases, and this can be measured using EKG-tonometric techniques. 21 Increased PWV leads to a more rapid return to the central aorta of the peripherally reflected wave during diastole. Ultimately, the reflected wave can return so fast it superimposes itself on the aortic systolic wave, and can significantly augment aortic pressure. Such augmentation cannot be detected in usual brachial pressure measurements. However, the contour

(though not the amplitude) of the radial pulse wave can be used to analyze the position of the reflected wave in the cardiac cycle, and a derived aortic systolic pressure can be calculated from radial pulse tonometry using an algorithm (validated versus directly measured aortic pressure). Such non-invasive estimates of central aortic pressure have been shown to be better predictors of cardiovascular events than usual brachial pressure in epidemiological studies. 22 In addition, and importantly for our study, estimated aortic pressure has been shown to be predictive of the effects of anti-hypertensive drugs to reduce cardiovascular events. 21 The European Society of Hypertension Consensus Statement on central blood pressure recommends combining pulse wave analysis derived estimates of central aortic pressure with measures of pulse wave velocity for a more comprehensive assessment of vascular function. 21

Technique: We measure estimated aortic pressure and PWV using arterial applanation tonometry and EKG (SphygmoCor SCOR PVX system). This uses a noninvasive, pen-like probe (a tonometer) applied to three superficial artery sites: the radial, carotid, and femoral arteries. The total testing time is under one hour. Initially, radial artery tonometry is performed to obtain central blood pressure by pulse wave analysis. The system uses mathematical transforms to derive the central aortic pressure pulse waveform and then calculates a range of central indices of ventricular-vascular interaction, which are displayed both graphically and numerically. The pulse wave analysis method provides a quality score based on the standard deviation of individual pulse analyses obtained over 10 seconds. The measurements will be repeated multiple times, and only accept recordings that have a quality score above 90, and when two consecutive augmentation pressure measurements are within 10% of each other. The quality score is also recorded for each subject so it can be used if necessary to help identify outliers (and perhaps for endpoint weighting in future analyses). The primary endpoint for this test is augmentation pressure (corrected for heart rate), which is the pressure added to aortic systolic pressure by the reflected wave. A secondary endpoint will be aortic systolic pressure.

Pulse wave velocity is estimated using the same tonometer to transcutaneously record pressure pulse waveforms in the two arteries at different distances from the heart. The pressure pulse waveform is recorded simultaneously with an electrocardiogram (EKG) signal, which provides an R-wave timing reference. We use the carotid and femoral artery sites so the pulse wave velocity can be measured in a section of artery that includes the aorta. The software processes each set of pressure pulse and EKG waveform data to calculate the mean time difference between the R-wave and the pressure wave- on a beat-by-beat basis. The PWV is then calculated using the mean time difference and the arterial path length between the two recording sites (measured on each subject at the start of the study). We use similar quality control measures to the pulse wave contour analysis, including duplicate measurements, and recording of quality scores for individual subjects. The primary endpoint for this test is pulse wave velocity (in m/sec).

Flow Mediated Dilatation of the Brachial Artery:

We will assess endothelial function by measuring flow-mediated dilatation (FMD) of the brachial artery. The vascular endothelium produces multiple factors that regulate vascular tone, platelet adhesion and aggregation, lipid transport, macrophage migration, vascular smooth muscle proliferation,

thrombosis, and fibrinolysis. Most in vivo assessments of endothelial function focus on vascular tone as an index of overall endothelial health. Endothelial dysfunction contributes both to the pathogenesis and subsequent complications of atherosclerosis, and changes in endothelial modulation of vascular tone precede development of atherosclerotic lesions in monkeys.²³ Though there are multiple techniques for measuring endothelial function in humans, we chose brachial FMD because it is non-invasive, relatively rapid and well validated. Flow-mediated vasodilatation is endothelium-dependent in animals and abolished by local inhibition of nitric oxide generation in man. Thus, brachial FMD likely reflects conduit vessel endothelial function. Brachial FMD correlates with coronary artery endothelial function, is abnormal in patients with obstructive coronary artery atherosclerosis, and predicts atherosclerotic events beyond conventional risk factor profiling (Framingham scores).²⁴ Even in patients without evidence of atherosclerosis, impaired brachial FMD is associated with hypertension, hypercholesterolemia, diabetes mellitus, cigarette smoking, increasing age, male gender, and menopause.²⁵ In hypertension, impaired brachial FMD correlates with evidence of target organ damage (heart, vascular and kidney), and is improved by chronic but not acute blood pressure lowering.²⁵ Of particular relevance to this study, subjects who exhibit improvements in brachial FMD have fewer coronary events on long-term follow-up than subjects who do not improve. As a control, nitroglycerin-mediated brachial dilatation is used to test endothelium-independent dilatation of the brachial artery.

Technique: The brachial artery is imaged with a 13 MHz linear array transducer ultrasound system (AU4, BioSound). A continuous ECG recording is obtained, and non-invasive arterial pressure measured at baseline and after each intervention. A 5 cm length of the brachial artery is imaged in longitudinal section above the antecubital fossa and the optimal probe site on the skin marked. The non-dominant arm will be used. Baseline images of brachial artery diameter and Doppler velocities from the center of the vessel are obtained and displayed on a split screen. An occluding forearm cuff placed 5 cm below the antecubital fossa is inflated to 240 mmHg for 5 min, and then deflated to induce reactive hyperemia. Brachial artery diameter and velocity are continuously measured during cuff inflation and for 2 min after cuff deflation, when brachial artery diameter has peaked. At the end of the study (after ischemia-reperfusion intervention has finished), flow mediated vasodilatation (reactive hyperemia will be repeated post ischemia-reperfusion. Once basal diameter and flow have been restored, nitroglycerin (400 µg) is administered sublingually, and brachial artery diameter and Doppler velocity recorded for 6 min. Our ultrasound operator has to demonstrate the ability to obtain reproducible images of the brachial artery with a coefficient of variation of <2% for brachial artery diameter and <10% for brachial artery flow. This assessment is based on the results from one subject studied on five different days and is repeated in a manner every 3 months. In our hands we have shown using this protocol that experimental hyperhomocysteinemia and cigarette smoking blunt brachial FMD, and xanthine oxidase inhibition improves it.

Analysis: Brachial artery diameter and blood velocity measurements are analyzed by a dedicated research sonographer, blinded to the identity of the subject, diagnosis, and study intervention. Video tapes of brachial artery images

are digitized and transferred to a workstation. B mode images of the longitudinal section of the brachial artery at baseline are digitized in a gated manner using the onset of the QRS complex to trigger frame capture at end- diastole. An automated neural network based method for complete near and far wall border detection is used to measure arterial diameter in each frame (Brachial Analysis Tool, Medical Imaging Applications, Iowa City, USA). Peak Doppler flow velocity is calculated and averaged over 5 consecutive cardiac cycles. Percentage change in diameter and velocity is calculated for the interventions of reactive hyperemia and sublingual nitroglycerin. The maximal flow-mediated change in vessel diameter occurs at 1 minute post-hyperemia, and this is the primary endpoint. Changes in diameter induced by nitroglycerin (maximal response at 6 min) are used as an index of vascular smooth muscle sensitivity to nitric oxide, and will be a secondary endpoint.

Nitroglycerin Mediated Vasodilatation of the Brachial Artery:

Once basal diameter and flow have been restored, brachial artery diameter and velocity are continuously measured at base and 6 minutes post administration of sublingual nitroglycerin (400 mcg).

Blood Pressure and Pulse Rate Variability

The measurement of indirect arterial pressure with a beat-to-beat finger systolic and diastolic blood pressure recording (Finapres 2350; Ohmeda) during ultrasound and Doppler procedures described in the previous paragraph ("Flow-mediated dilatation of the brachial artery). Rationale: Data from this measurement will allow us to assess blood pressure variability.

24 hour ambulatory blood pressure monitoring: Subjects will be instructed to refrain from bathing or showering within that 24 hour time frame. The blood pressure cuff will be worn on the arm with the higher SBP (if applicable). The monitor measures blood pressure every 30 minutes during the day and hourly at night. The mean day and night-time ambulatory blood pressure will be used for analysis.

Laboratory (blood and urine) assays during each study visit:

- i) Blood work for creatinine, uric acid, random urine for protein-to-creatinine, and a CBC will be performed in UIHC Pathology Laboratory. IL-6 and hsCR-P will be performed at the Analytical Laboratory of the CRU in the Institute for Clinical and Translational Science (ICTS). Measurements of allopurinol metabolite (Oxypurinol) will be conducted at a outside commercial laboratory designated by the UIHC
- ii) Urine test for urine beta-hCG to evaluate for pregnancy will be performed using a commercially available kit in the CRU.
- iii) Voluntary blood sample collection at each visit for storage and use in potential future research studies.

Visit 1 (week 0)

A research team member will discuss the study details described in this informed

consent document. A physician or nurse practitioner will review the medical history and perform a physical examination.

Heart rate, respirations (breathing), temperature, blood pressure, weight and height will be obtained.

After sitting for 5 minutes, blood pressure will be obtained twice in each arm.

The arm with the highest blood pressures will be used for all further measurements during this study.

The weight and height will be used to determine the body mass index (BMI). The BMI is one way to indicate weight status (i.e., lean or over weight).

An electrocardiogram (EKG - a tracing of the heart's electrical activity) will be obtained.

Waist circumference will be obtained with a measuring tape.

About 1 ounce of blood will be drawn from a vein in the arm. These samples will test your blood for substances that are potentially harmful to your blood vessels.

Study subjects will be instructed to present to the Clinical Research Unit in the morning. The visit will take approximately 1 and 1/2 hour. Measurement of Flow-Mediated Dilatation (FMD) will be obtained as described in the previous section. Laboratory tests will be collected (blood and urine), and randomization will take place. Blood pressure and pulse rate variability will be obtained using the Finapres digital device simultaneously with the FMD measurement. The final procedure during this visit is to place the 24h BP monitor and provide the appropriate instructions as described above.

Following randomization, study subjects will be assigned to allopurinol or placebo. The starting dose of allopurinol is 300 mg daily. Patients will receive this dose for 1 week and will have an increase of 100 mg each week for 3 weeks to achieve the maximum (final) dose of 600 mg as maintenance dose for the remaining of the study (3 years). Study subjects will be contacted by phone to monitor any adverse effect of the study drug on a weekly basis for the first 4 weeks to monitor for adverse effects, and will be oriented to call for any of these signs described above at any time and immediately discontinue the study drug. If no adverse reactions and good tolerance of the study drug, we don't plan to call study subjects further for this purpose. Study subjects will have our number to call 24/7.

In case of suspected allopurinol toxicity at any point, study subjects will be advised to stop taking the study drug immediately and drink plenty of fluids, at least 10-12 glasses per day.

Visit 2 (month 2)

Procedures will be identical to visit 1. Duration of the visit is the same. Labs with this visit and all future visits will include oxypurinol levels.

Visit 3 (12 months)

Same as visit 2

Visit 4 (24 months)

Same as visit 3

Visit 5 (36 months)

Same as visit 3

Completion of the study.

ADDENDUM:

Patients will receive a letter informing the completion of treatments and discontinuation of further research visits due to lack of research funding. Detailed instructions and phone for contact if any questions provided in the letter.

VII.E.7 *Will you attempt to recontact subjects who are lost to follow-up?*

No - followup is not required in this study

VII.E.9 *Will subjects be provided any compensation for participating in this study?*

Yes

VII.E.10 *Cash*

No

VII.E.11 *Gift Card*

No

VII.E.12 *Check*

Yes

VII.E.13 *Who will be providing the research compensation check to the subject?*

Accounting Services directly via the e-Voucher system

VII.E.16 *Other*

No

VII.E.19 *Describe the compensation plan including*

- *Compensation amount and type per visit*
- *Total compensation*
- *Pro-rating for early withdrawal from study*

The total number of visits will be 5. For each visit the participant will receive \$50.00. The total compensation will therefore be \$250.00. We will pro-rate the compensation if early withdrawal from the study according to the number of visits.

Your parking expenses will be covered for the time where you are in the Clinical Research Unit for the study visits.

VIII. Risks**VIII.1 *What are the risks to subjects including***

- *emotional or psychological*
- *financial*
- *legal or social*
- *physical?*

Medications (Drugs) Used During This Study:

Nitroglycerin - Sublingual (under the tongue): Nitroglycerin may cause light-headedness, dizziness, headache, and low blood pressure. You could experience light-headedness and dizziness with change in position from lying to sitting. If so, your blood pressure will be monitored. You will be asked questions to determine if you are having any of these symptoms. These effects usually last for only a few minutes. There is a small risk of infection from the spray bottle when giving you this drug under the tongue.

Allopurinol - Oral (by mouth): The following are some of the potential side effects that may result from use of Allopurinol. Most of the side effects are rare and occur in about 1% of people on Allopurinol. We have listed potential side effects and the rate of occurrence below. The most common side effect is a skin rash. You will be monitored weekly by telephone call from the research team. If any indication of side-effects the study drug will be discontinued. You will be asked to report for follow up.

Life Threatening

- Jaundice (0-0.05%)
- Liver Damage (0-2%)
- Kidney Failure (0-0.05%)
- Severe allergic reactions (0.4%)
- Stevens-Johnson syndrome (less than 1 %)

Serious

- Anemia (0-0.05%) Bruising (0-2%)
- Fever (Drug fever: 0-3%)
- Diarrhea (0-3%)
- Vomiting (less than 1%)
- Acute gout (0-2%)

Mild

- Headache (less than 1%)
- Body aches (less than 1%)
- Stomach disorder (stomach upset less than 1%)
- Painful voiding (less than 1%)
- Nausea, (nausea +/- vomiting 0-2%)
- Pruritus (less than 1%)
- Skin rash (less than 1%)

Women Capable of Becoming Pregnant: If you are a woman who is capable of becoming pregnant, we will ask you to have a pregnancy test before beginning and while participating in this study. You must use effective birth control methods and try not to become pregnant while participating in this study. This involves using two barrier methods such as male and female condoms, diaphragms, spermicides (which are creams or gels that contain a chemical to kill sperm), or an intrauterine device (IUD). Women can use birth control pills, shots or patches during this study according to their primary care physician. If you become pregnant, there may be unknown risks to your fetus, or risks to your fetus that we did not anticipate, associated with being in the study. There may be

long-term effects of the treatment being studied that could increase the risk of harm to an unborn child. If you believe or know you have become pregnant while participating in this research study, please contact Dr. Roberto Kalil, M.D. (319) 384-7998 as soon as possible.

Pulse wave analysis and velocity: Although this test is entirely safe, some people may feel uncomfortable with the sensor placement and location of the sensor at the hip (or groin area over the artery). Minimal skin area will be exposed. You will be able to wear shorts or underwear and a sheet to cover the area will be used for your privacy.

Blood loss: About 1/2 cup of blood in total will be drawn during the 3-year study period. No significant side effects are expected with this volume of blood loss over the study period. The risk of anemia (or low blood count) with this amount of blood draw is small as the body continually makes red blood cells.

Blood sampling: Blood samples will be drawn from your arm. The risks and discomfort of drawing blood include bruising or the possibility of pain at the site of the draw, light-headed or a dizzy feeling, bruising where the needle was inserted, and rarely, infection at the site of the blood draw.

Adhesive electrode patches: The patches used for electrocardiogram (EKG) and heart monitoring during the procedures may cause minor local irritation to the skin.

Information will be kept in password protected files, and will be deidentified. Only research team members will have access to data.

VIII.2

What have you done to minimize the risks?

- *If applicable to this study ALSO include:*
 - *How you (members of your research team at Iowa) will monitor the safety of individual subjects.*
 - *Include a description of the availability of medical or psychological resources that subjects might require as a consequence of participating in this research and how referral will occur if necessary (e.g. availability of emergency medical care, psychological counseling, etc.)*

Oral allopurinol: Prior to enrollment in the study, subjects with history of adverse reaction to allopurinol will be excluded from study participation. Current FDA-approved labeling is that doses of up to 800 mg of allopurinol can be given to patients with GFR 80 ml/min. Considering the potential renal dysfunction of renal transplant recipients, we plan to start all patients with a dose of 300 mg, which is less than 50% of the maximum dose allowed by the FDA. If well tolerated, the dose will be escalated by 100 mg each week with maximum dose up to 600 mg at 4 weeks for the remaining of the study. Levels of oxypurinol and uric acid will be measured regularly although there has been some recent debate about whether side effects with allopurinol are even due to high circulating levels (versus a dose-independent idiosyncratic reaction).²⁶ In addition, once weekly telephone calls will be made to subjects to evaluate for side effects of nausea, pruritus, skin rash, weight loss, anorexia, vomiting or diarrhea. If a subject

reports skin rash, he/she will be instructed to return to the clinical research unit for evaluation and will be instructed to discontinue the study medication.

c) Monitoring and documentation and reporting of Adverse Events:

Monitoring, documentation and reporting of adverse events will be performed by the members of the research team: Roberto S. Kalil, MD, William Haynes MD, Christine Sinkey RN, Tammy Lowe RA, Rebecca Beek RA and will be reported to the Clinical Research Unit Safety Committee for review.

d) Frequency for review of summarized safety information:

Screening questions for possible side effects of allopurinol such as skin rash, pruritis, anorexia, nausea, vomiting will be also asked during weekly telephone calls during the first 4 weeks until study subjects reach the maximum study dose (600 mg daily).

All adverse events will be reported to the Clinical Research Unit Committee.

e) Stopping Rules:

Subjects will be withdrawn from the study and the study medication discontinued, if they report a skin rash while on the study medication. They will be requested to present to the nearest healthcare facility for evaluation for Stevens-Johnson syndrome. In case of suspected drug-toxicity, besides stopping the drug, subjects will be instructed to drink plenty of fluids (10 to 12 glasses of water a day).

VIII.3

Does this study have a plan to have an individual or committee review combined data from all subjects on a periodic basis (such as summary or aggregate safety and/or efficacy data)?

No

IX. Benefits

IX.1

What are the direct benefits to the subject (do not include compensation or hypothesized results)?

No direct benefits are expected.

IX.2

What are the potential benefits to society in terms of knowledge to be gained as a result of this project?

The need for improvement in cardiovascular outcomes in recipients of kidney transplantation is critical. Finding a treatment that is effective, safe and at very low-cost such as allopurinol would be highly beneficial for recipients of kidney transplantation.

X. Privacy & Confidentiality

X.1

What are you doing to protect the privacy interests of the subjects?

Obtaining the consenting and all contact with study subjects will take place in a private room in the Clinical Research Unit with one of the research team members. Information will be kept in locked cabinets, and computers with password protected access. Data will be de-identified for analysis. Presentations

and publications will follow standard norms of not using any potential identifier.

X.2 *Are you collecting the Social Security Number of any subjects for any purpose?*

Yes

X.3 *Provide the intended usage of SSN:*

- To provide compensation to subjects

X.4 *How will information/data be collected and stored for this study (check all that apply):*

- Paper/hard copy records (hard copy surveys, questionnaires, case report forms, pictures, etc.) - ANy hard copy records will be kept in a locked cabinet with access restricted to the research team only. The cabinet is located at T311-GH. We anticipate a minimum use of hard copy records as most of the information needed will be obtained from the electronic medical records.
- Electronic records (computer files, electronic databases, etc.) - Data from EPIC will be extracted in a de-identified fashion. Computers with password protected access can be used for data storage. Patient information is immediately de-identified as it is entered in the study database for statistical analysis. Patient level, clinician level, and clinic level data for this study will be stored electronically in the REDCap platform. The REDCap platform is managed by the Institute for Clinical and Translational Science at the University of Iowa. Only IRB approved research team members will have access to the REDCap data platform. Each team members will be granted access to the REDCap data system through a secure login. In the REDCap data platform, primary data is secured in HCIS Pomerantz Data Center. Data backups are secured in ITS Lindquist Data Center. Operating system security includes: secure logins, data encryption at rest, remote system logging and configuration and change management. Data backups are encrypted both in flight and at rest. Copies of data are replicated to the remote data center every 15 minutes. There are 100+ point in time copies of data available at any time. Disaster recovery has been tested.
 - Name - Lee Carmen
 - Title - BSEE
 - University Job Classification - VP of IT security at UIHC
- Biologic samples (blood draws, cheek swabs, saliva samples, tissue samples, etc.) - All labels in study specimens will have a code that de-identifies study participants information and stored in a secure freezer at the Clinical Research Unit.
 - Name - Tamara Lowe
 - Title - Research Assistant II
 - University Job Classification - UIHC staff RA

X.5 *Do the confidentiality protections indicated above allow only members of the research team to access the data/specimens?*

Yes

- X.7** *Does your study meet the NIH criteria for a [Certificate of Confidentiality](#) or will you be applying for Certificate of Confidentiality?*
No

XI. Data Analysis

- XI.1** *Describe the analysis methods you will use, including, if applicable, the variables you will analyze*
- Primary endpoints
1. Changes in endothelial function measured by flow mediated dilation of the brachial artery.
 2. Changes in 24h ambulatory blood pressure monitoring.
 3. Changes in Augmentation Index (AIx) and Pulse Wave Velocity (PWV)
 3. Rates of cardiovascular events
 4. Changes in renal function (eGFR) and proteinuria
 5. Cardiovascular variability (HR and BP) assessed by Finapres®
- Secondary endpoints
1. Changes in markers of inflammation: hs CRP and IL-6
 2. Changes in renal function (eGFR) and proteinuria
- Analysis:
- Linear mixed model analysis for repeated measures will be used to compare mean response in sAMBP, dAMBP, and FMD between allopurinol and placebo. The fixed effects in the model will include treatment (allopurinol vs. placebo), time (baseline vs. 2 month, 12, 24 and 36 months), and treatment*time interaction. The test for the treatment*time interaction effect will correspond to comparing the mean change in sAMBP, dAMBP, FMD or BP variability at 2, 12, 24 and 36 months from baseline levels between the allopurinol treated group and the placebo group. The same model will be used to compare changes in laboratory parameters over time.
- XI.2** *Provide the rationale or power analysis to support the number of subjects proposed to complete this study.*
- Based on a standard deviation of 3.06%, assuming that the absolute difference in FMD between allopurinol and placebo group will at least 1.9%, our sample size (n=60 per group) will be powered at 80% to detect a 0.05 significance level, applying the Bonferroni corrected T test to detect this difference in one or more data point. We believe this is a conservative estimate as the predicted magnitude in change in FMD was calculated using published data from trials administering 300 mg of allopurinol (Kao et al). We plan to use a higher dose of 600 mg, and it is well known that there is a dose-dependent improvement in FMD therefore we may observe a larger difference with a higher statistical power in this study.

XII. Future Research

XII.1 *Do you wish to keep any information about subjects involved with this research project so that members of the current research team may contact them in the future for your own research projects?*
Yes

XII.2 *Do you wish to keep any information about subjects involved with this research project so that other researchers may contact them for future research?*
No

XII.3 *List the data or information you will keep:*
Basic clinic and demographic data for possible participation in follow-up studies. These will include, age, gender, race, type of transplant (living donor or deceased-donor), number of transplants, history of cardiovascular disease, hypertension, diabetes mellitus, hyperlipidemia, smoking status, obesity, history of cardiovascular revascularization or peripheral vascular disease and revascularization, pre-transplant and post-transplant cardiac stress tests, coronary angiogram, echocardiograms, history of acute or chronic transplant rejection. Laboratory data will include serum creatinine, electrolytes, lipid profile, CBC, calcium, phosphorus, vitamin D levels, intact PTH levels, urine analysis, random urine tests for protein and creatinine measurement, Interleukin-6, C-reactive protein levels, uric acid, and oxypurinol levels. Flow-mediated dilatation scores, blood pressure measurements, pulse wave analysis, blood pressure and pulse monitoring will be kept with the demographic, laboratory and clinical data detailed above.

XII.4 *Does this project involve storing any data, tissues or specimens for future research?*
Yes – contribution for future use is optional

XII.5 *Describe how you will keep track of those who consent to future use and those who do not and how you will prevent future use for those who do not consent.*
Screening logs will document patient's option.