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Short Title: A STUDY OF FERRIC CITRATE TO IMPROVE INFLAMMATION AND LIPID LEVELS

Full Title: THE EFFECT OF FERRIC CITRATE ON INFLAMMATION AND LIPID LEVELS IN PATIENTS ON HEMODIALYSIS

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Site: The Winthrop Dialysis Center, Mineola, NY
Winthrop Dialysis at Bethpage, Bethpage, NY

SUMMARY

Short Title:	A STUDY OF FERRIC CITRATE TO IMPROVE INFLAMMATION AND LIPID LEVELS
Summary of Rationale:	The risk of cardiovascular mortality in patients with end stage renal disease on hemodialysis is 10-100 times higher than the normal population. This is due in part to high levels of inflammation and vascular calcification found in these patients. Phosphate binders, particularly non-calcium based phosphate binders, may decrease cardiovascular risk by decreasing inflammation and vascular calcification. Ferric citrate a non-calcium based phosphate binder with approximately 210 mg of ferric iron has recently been approved for patients on hemodialysis. The effect of this phosphate binder on inflammation and lipid levels is unknown but we hypothesize that ferric citrate has the potential to improve inflammation and lipid levels in patients on hemodialysis by decreasing intravenous iron requirements and by improving lipid metabolism.
Therapeutic Agent:	Ferric citrate is a salt that contains approximately 210 mg of ferric iron. Ferric citrate has been used as a phosphate binder in patients with pre-dialysis chronic kidney disease and in patients with end stage renal disease on hemodialysis. This medication is currently approved as a phosphate binder for patients on hemodialysis and peritoneal dialysis.
Objective:	To determine the effect of ferric citrate on inflammatory markers and lipid levels in patients with end stage renal disease on hemodialysis.
Hypothesis : markers and lipid levels.	Oral ferric citrate will decrease levels of inflammatory

Study Design:	This study will be designed as a single arm, prospective, experimental trial of 45 hemodialysis patients. Patients on hemodialysis at least 6 months and receiving a phosphate binder with serum phosphorus levels between 2.5 and 8.0 mg/dL, normal serum calcium levels, and on maintenance iron therapy are potentially eligible. Participants will receive ferric citrate after at least a 2 week washout period from previous phosphate binders if phosphorus is ≥ 5.5 mg/dl, calcium is within the normal range and ferritin ≥ 200 and < 600 ng/ml. Ferric citrate will be titrated to maintain serum phosphorus and calcium within acceptable levels. Inflammatory markers and lipid levels will be tested at 0, 3, and 6 months.
Sample Size:	45 enrolled with a target of 30 patients that complete the treatment
Eligibility Criteria:	Patients on hemodialysis at least 6 months and receiving a phosphate binder with serum phosphorus levels between 2.5 and 8.0, normal serum calcium levels, and on maintenance iron therapy are potentially eligible
Intervention and Dosage:	Study participants will receive ferric citrate at a starting dose of 2 tablets with each meal if serum phosphorus levels are ≥ 5.5 mg/dL calcium levels are in the normal range and ferritin ≥ 200 and < 600 ng/ml after a minimum 2 week wash out period.
Study Duration:	12 Months
Procedures:	At screening a medical history will be completed and a screening data set recorded for patients that meet study eligibility. A unique ID number will be assigned and participants will enter a minimum 2-week washout period from other phosphorus binders. At Day 0, for study participants with serum phosphorus levels ≥ 5.5 mg/dl, calcium within the normal range and ferritin ≥ 200 and < 600 ng/ml baseline levels of inflammatory markers and lipid levels will be drawn. These participants will enter the treatment phase of the study.

	For the first 2 months, calcium and phosphorus levels will be checked every 2 weeks and then monthly. At each visit Ferric citrate doses will be adjusted accordingly (see Appendix 1). Ferric citrate pill counts will be performed for each participant. Study outcomes will be collected at Day 0, 3 months and 6 months
Outcomes:	Inflammatory Markers: Percent Change in ferritin, cRP, homocysteine, TNF-alpha, IL-6, IL-8 Cholesterol Markers: Percent Change in TC, LDL, HDL Other: Intravenous iron use, Percent Change in Ca, Phos, PTH, Hemoglobin A1c levels

PURPOSE OF THE STUDY AND BACKGROUND

1 Objective

To determine the effect of oral ferric citrate on inflammatory markers and lipid levels.

1.1 Hypothesis:

Oral ferric citrate will reduce levels of inflammatory markers and lipid levels in patients on hemodialysis.

2 Background and Rationale –

In patients with end stage renal disease (ESRD) receiving dialysis, the risk of cardiovascular death has been estimated to be 10-100 times higher than age, sex and race matched controls from the general population without renal disease [(1)]. This exorbitant risk has been attributed not only to traditional cardiovascular risk factors, but also risk factors more specific to ESRD including chronic inflammation and vascular calcification [(2)]. Chronic inflammation is particularly prevalent in patients with ESRD [(3)]. Increases in oxidative stress causing increased free radical production and low antioxidant levels are common [(4)]. Parenteral iron therapy, which is common in patients on dialysis, may contribute to this increase in oxidative stress [(5)] leading to increased inflammation [(6)] and a higher cardiovascular risk [(7)]. Vascular calcification is highly prevalent and often severe in patients with ESRD [(8)]. This vascular calcification contributes to the high rates of cardiovascular death seen in patients with ESRD. Risk factors for calcification include hyperphosphatemia, high calcium intake and high calcium X phosphorus product [(9)].

In a prospective cohort study of 10,044 incident hemodialysis patients, treatment with a phosphate binder was independently associated with improved survival [(10)]. Non-calcium based binders may further decrease cardiovascular risk [(11)]. Sevelamer, a non-calcium-containing phosphate binder, has been shown to have anti-inflammatory properties and to lower serum lipid levels and calcium phosphate product in patients on hemodialysis [(11-14)]. Ferric citrate is a novel phosphorus binder that has been shown to improve serum phosphorus levels and decrease intravenous iron requirements for patients on hemodialysis [(15)]. Ferric citrate has the potential to decrease cardiovascular risk through multiple mechanisms: 1) acting as a non-calcium based binder to decrease serum phosphorus levels and vascular calcification, 2) decreasing intravenous iron requirements which in turn may decrease oxidative stress and inflammation, 3) binding endotoxin in the gut [(14)], and 4) improving lipid metabolism. The purpose of this study is to examine the effect of ferric citrate on inflammatory markers and lipid levels.

CHARACTERISTICS OF THE RESEARCH POPULATION

3 Experimental Plan

3.1 Number of Patients

45 hemodialysis patients

3.2 Estimated Study Duration/Timeline:

12 months: 3 months for participant recruitment, 2-week wash-out period, a 6 month treatment period, and 3 months for data analysis and manuscript preparation.

3.3 Patient Eligibility

Adult patients with ESRD on three times per week hemodialysis at least 6 months prior to screening and receiving therapy with a phosphate binder and maintenance iron for at least 1 month prior to screening are potentially eligible.

3.3.1 Inclusion Criteria

1- Hemodialysis treatment for ≥ 6 months
2- Phosphate binder treatment for ≥ 1 month
3- Maintenance iron therapy with no more than 125mg IV iron weekly for ≥ 1 month
4- Serum phosphorus levels between 2.5 and 8.0 at screening and phosphorus ≥ 5.5 mg/dL after the washout period
5- Serum ferritin ≥ 200 and < 600 ng/ml after the washout period
6- Serum calcium levels within normal range
7- Predicted survival greater than 6 months

3.3.2 Exclusion criteria

1- Age < 18 years
2- Failure to provide informed consent
3- Intact PTH < 70 pg/ml or > 1,000 pg/ml
4- URR < 65%
5- Niacin and nicotinamide use
6- Oral iron use
7- Vitamin C supplement use
8- Parathyroidectomy within 6 months before the screening visit
9- Active malignancy
10- Patients undergoing hemodialysis via a catheter or AV graft
11- Received any amount more than 250mg of IV iron over the two weeks prior to screening

12- Whole blood transfusion within 3 months prior to screening
13- Active bleeding from any site other than the dialysis access within 1 month prior to screening
14- Hospitalization within 1 month prior to screening
15- Current febrile illness or active chronic infection
16- Ongoing or uncontrolled inflammatory disorder
17- Liver cirrhosis
18- Likelihood of imminent renal transplantation

3.4 Patient Enrollment

All hemodialysis patients at Winthrop University Hospital Dialysis centers will be potentially eligible. It is estimated that approximately 300 hemodialysis patients are dialyzed at these centers

METHODS AND PROCEDURES

4 Study Procedures

4.1 Study Design

This study will be designed as an experimental trial in which 45 hemodialysis patients will be given ferric-citrate after a 2-week wash period from phosphate binders.

4.2 Screening

After providing informed consent, screening procedures will be initiated. The baseline data set will be recorded as below. Participants will be assigned a unique ID number. Participants that meet all inclusion and exclusion criteria will be entered into the study.

4.3 Wash-out

Wash-out will begin immediately after screening for participants that meet study eligibility. All previous phosphate binders will be discontinued for a minimum of 2 weeks. At the end of 2 weeks, calcium, phosphorus, Tsat and ferritin levels will be measured and all participants with phosphorus levels ≥ 5.5 mg/dL, calcium within the normal range and ferritin ≥ 200 and < 600 ng/mL will have blood drawn for levels of inflammatory markers and lipids and will enter the treatment phase of the study. For participants who do not meet this criteria at the end of the initial two week washout period, calcium, phosphorus, Tsat and ferritin levels will be checked for entry criteria each week thereafter. If the participant remains ineligible to enter the treatment phase after 4 weeks, he/she will be withdrawn from the study.

4.4 Treatment

Ferric citrate will be initiated in 1gm capsules containing approximately 210mg of ferric iron at a dose of 6 capsules per day (2 with each meal). Ferric citrate will be titrated every 2 weeks throughout the trial by the primary investigator using serum calcium and phosphorus values and a previously defined titration schedule (Appendix 1). Patients will be on study Ferric Citrate for a 6 month study treatment period.

4.5 Concomitant Medications

Only study investigators will adjust intravenous iron therapy throughout the duration of the trial. Participants with a serum ferritin of < 200 ng/ml will be given a 1 gm load of ferric gluconate delivered over 8 hemodialysis sessions. For participant with a ferritin > 600 ng/ml, all intravenous iron therapy will be

discontinued. All other medications except prohibited medications (see below) will be dosed based on the discretion of the treating physicians

4.6 Prohibited Therapy

Any phosphate binder other than ferric citrate
Any other investigational medication
Niacin and nicotinamide
Oral iron therapy
Vitamin C supplements

4.7 Treatment Failure

Subjects will be considered treatment failures if they are ≥80% compliant with 12 doses/d of ferric citrate and have two consecutive serum phosphorus values >8.0 mg/dl (serum phosphorus will be checked at next HD session if >8.0). These subjects will be discontinued from the study drug and will resume their previous phosphate binder, but will be encouraged to complete all study visits.

4.8 Study Drug With-holding

Subjects will be stopped on study drug if: 1) they have an adverse event necessitating study drug discontinuation, 2) Serum phosphorus < 2.5 3) Investigator's discretion

4.9 Laboratory Considerations

All study outcomes will be drawn at the onset of hemodialysis. All labs will be non-fasting. Attempts will be made to draw labs at approximately the same time of the day at time 0, 3 months and 6 months.

4.10 Safety Considerations

Adverse event information will be collected from the time a consented subject is screened until the end of the study. All adverse and serious adverse events will be recorded according to standard definitions.

Any SAE, including death from any cause, which occurs during this trial, if related or possibly related to the study drug, must be reported to Keryx within 24 hours of becoming aware of the SAE. The site will submit the SAE Worksheet to Keryx. Please forward the SAE (available 24 hours/day, 7 days/week) to the following:

Phone: Keryx 1-212-531-5756
Email: Madlen.Malinowski@keryx.com
Fax: Keryx 1-646-417-5457

A report must be submitted within 24 hours of the initial reporting to Keryx. Withdrawal from the trial and all therapeutic measures taken will be at the discretion of the Principal Investigator (PI). All SAEs (related or of possible relationship to the study drug) will be followed until satisfactory resolution or until the PI deems the event to be chronic or the subject to be stable.
Keryx will be responsible for reporting of any SAE to the FDA if applicable. Keryx will notify the FDA of any related, unexpected, fatal or life-threatening experience (expedited report) associated with the use of the study drug. The investigator is responsible for informing the Institutional Review Board (IRB), according to the IRB's requirements.

5 Dataset

5.1 Recorded at Screening (Time -2 weeks)

5.1.1 Name
5.1.2 Date of enrollment
5.1.3 Age
5.1.4 Gender
5.1.5 Race
5.1.6 Ethnicity
5.1.7 Cause of ESRD
5.1.8 Medication list including statin use and current binder use
5.1.9 ESA, vitamin D and vitamin D analog use over the 1 month prior to screening
5.1.10 Comorbid condition list including CAD/CVD status
5.1.11 Dialysis Vintage
5.1.12 KT/V
5.1.13 URR
5.1.14 Hemoglobin
5.1.15 Serum Albumin
5.1.16 intact-PTH

5.2 Drawn at -2 days

5.2.1 Serum Calcium, Phosphorus
5.2.2 Serum Iron, TIBC, Ferritin

5.3 Recorded prior HD # 1 (Time 0)

5.3.1 Serum Albumin
5.3.2 Intravenous iron use over the 6 months prior to study entry

5.4 Drawn prior to HD # 1 (Time 0)

5.4.1 Fasting serum Total Cholesterol, LDL, HDL, Triglycerides
5.4.2 Inflammatory markers (ferritin, cRP, homocysteine, TNF-alpha, IL-6, IL-8)

5.4.3 Hemoglobin A1c

5.5 Recorded monthly

5.5.1 Calcium and phosphorus levels (and every two week for the first 2 months)
5.5.2 Ferric citrate pill counts

5.6 Drawn at 3 months

5.6.1 Serum Calcium, Phosphorus
5.6.2 Fasting serum Total Cholesterol, LDL, HDL, Triglycerides
5.6.3 Inflammatory markers (ferritin, cRP, homocysteine, TNF-alpha, IL-6, IL-8)
5.6.4 Serum Iron, TIBC, Ferritin
5.6.5 Hemoglobin A1c

5.7 Recorded at 3 months

5.7.1 Serum Albumin
5.7.2 Intact-PTH
5.7.3 Intravenous iron use over the prior 3 months
5.7.4 Ferric citrate pill count

5.8 Drawn at end of study (Time 6 months)

5.8.1 Serum Calcium, Phosphorus
5.8.2 Serum Iron, TIBC, Ferritin
5.8.3 Fasting serum Total Cholesterol, LDL, HDL, Triglycerides
5.8.4 Inflammatory markers (ferritin, cRP, homocysteine, TNF-alpha, IL-6, IL-8)
5.8.5 Hemoglobin A1c

5.9 Recorded at end of study (Time 6 months)

5.9.1 Serum Albumin
5.9.2 intact-PTH
5.9.3 Intravenous iron use over the prior 3 months
5.9.4 Ferric citrate pill count

6 Removal and Replacement of Patients

6.1 Removal of Patients (early termination)

In accordance with the current version of the Declaration of Helsinki and other applicable regulations, a patient has the right to withdraw from the study at any time and for any reason without prejudice to his or her medical care and treatment.

The investigator will withdraw any patient who is unable to complete the full 6 months of study due to hospitalization or other unexpected event.

Considerations for patient withdrawal include:

6.1.1 Subject request
6.1.2 Lost to follow-up
6.1.3 Pregnancy
6.1.4 Kidney Transplantation
6.1.5 Safety considerations

Data for these patients will be included in the final statistical analysis.

6.2 Replacement of Patients

In the event of withdrawal under the circumstances stated in 6.1, then the patient accrual list will be decremented by one, allowing for full enrollment of 45 patients.

7 Statistical Considerations

7.1 Outcomes

7.1.1 Cholesterol Markers: Percent Change in TC, LDL, HDL, Triglycerides
7.1.2 Inflammatory Markers: Percent Change in ferritin, cRP, homocysteine, TNF-alpha, IL-6, IL-8
7.1.3 Other: Intravenous iron use, Change in Ca, Phos, PTH, Hemoglobin A1c levels

7.2 Covariates

Name, Age, Gender, Race, Ethnicity, ESA use, IV iron use, vitamin D and vitamin D analog use, CAD/CVD status, Dialysis Vintage, KT/V/URR, Hemoglobin, Hemoglobin A1c, Serum Albumin

7.3 Analysis

All outcomes are continuous variables. Student's t test will be used to test for statistical significance. Multiple regression analysis will be used for controlling covariates and testing the interaction among covariates. Analysis of repeated outcome measures will be based on hierarchical linear model (HLM) including trajectories over time within each patient.

8 Confidentiality and storage of data

8.1 All records will be kept in a locked file cabinet. The subject's names will be kept on a password protected database and will be linked only with a study identification number for this research. There will only be one copy of the file linking a subject's name to his/her unique identifier. All data will be entered into a computer that is password protected and accessible only by study investigators.

8.2 Clinical information will not be released without written permission of the subject, except as necessary for viewing by study investigators and monitoring by IRB, the FDA and the OHRP.

8.3 Data will be stored in a locked office of the investigators and maintained for a minimum of three years after the completion of the study.

RISK/BENEFIT ASSESSMENT

9 Risk

9.1 Patients will undergo at least a 2 week washout period where their current phosphate binder will be temporarily discontinued. During this period they may run the risk of elevated blood phosphorus levels but will be monitored closely and will be restarted on their prior phosphorus binder if two consecutive phosphorus values are over 8.0 mg/dL.

9.2 The most serious possible side effect of ferric citrate is iron overload.

9.3 The most common side effects are diarrhea, nausea, vomiting, cough and dark stools.

9.4 There may be side effects and reactions which are unknown at this time and so it is not certain how each patient will respond to ferric citrate. Some patients may have an allergic reaction to the drug. If they have a very bad allergic reaction, this can be a life threatening medical condition.

10 Protection against risk

The researchers will discuss possible difficulties and the chances that they will happen. Potential risks and discomforts will be minimized to the greatest extent possible by weekly monitoring of patients and adjustment of the study drug. Patients will be withdrawn from the study upon evidence of study related difficulty or adverse events. After study withdrawal or end of study, patients will receive the necessary follow-up as detailed in the methods and procedures section above. If as a result of study participation patients experience physical injury from known or unknown risks of study, immediate medical care and treatment, including hospitalization, if necessary, will be available. No funds have been set aside for compensation; therefore patients will be responsible for the costs of their medical treatment, either, directly or through their medical insurance and/or other forms of medical coverage.

11 Potential benefits to the subjects

It is not known if the treatment received will be of benefit to the patient. There may be no direct benefit from agreeing to participate in this study. However, this study may help others in the future determine the effect of ferric citrate on inflammatory markers and lipid levels in patients with end stage renal disease on hemodialysis.

INVESTIGATOR'S QUALIFICATIONS AND EXPERIENCE

All investigators have completed the CITI tutorial and have received training in the protection of human subjects. A copy of a valid CITI certificate and recent CV/resume of each investigator will be submitted to the IRB

SUBJECT IDENTIFICATION, RECRUITMENT AND CONSENT/ASSENT

12 Method of Subject Identification and Recruitment

Patients will be recruited from a WUH private and secure nephrology patient database.

13 Process of Consent

Consent will be obtained by the principal investigator and sub-investigators listed on the protocol and consent form. Each page of the consent will be reviewed with the patient. Patients will be given an opportunity to ask questions after each page. Patients will be asked to repeat pertinent parts of the consent to ensure comprehension. The patient will be offered and given an opportunity to take the consent home for further review as needed. The PI will be responsible for ensuring that valid consent is obtained and documented for all subjects.

14 Cost to the Subject

The study medication (Ferric Citrate) will be supplied by Keryx Biopharmaceuticals at no cost to the patient. All study costs including any tests, examinations, or other procedures associated with this study that are not a part of the patients routine medical care will be paid for by Keryx Biopharmaceuticals. The rest of the medical care that the patient will receive in this study will be considered standard care and thus would be recommended regardless of the patient's decision to participate in this study. These costs will be billed to the patient or the patient's insurance carrier. The patient will be responsible for any co-payments and/or deductibles as required by your insurance that are associated with routine medical care.

15 Payment for Participation

The patient will not be paid for participation but will receive a one-time $50.00 compensation for their expenses and time spent directly related to this study. To protect the subject's right to withdraw without penalty, the patient does not have to complete the entire study to be eligible to receive payment.

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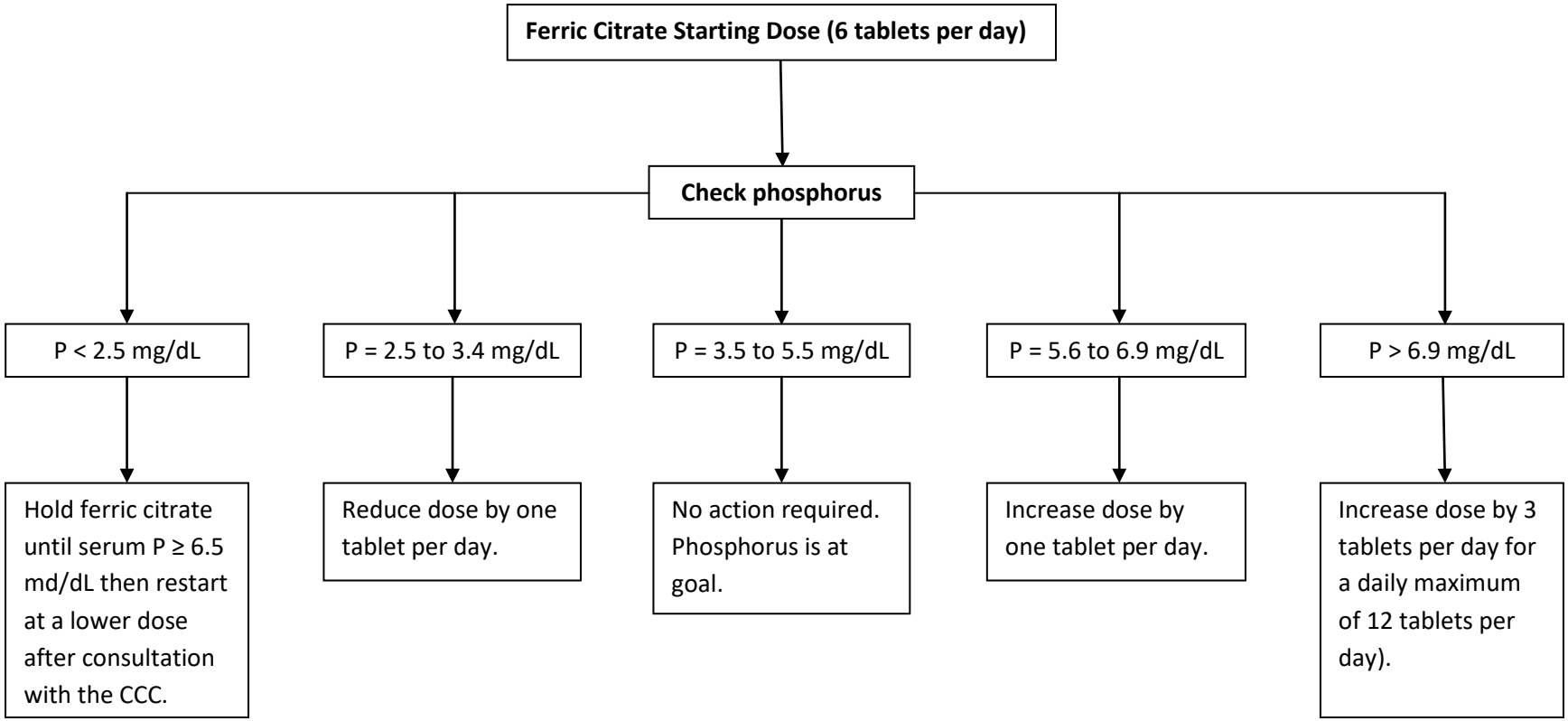
Appendix 1. Ferric Citrate titration schedule



Adapted from Appendix 1: J Am Soc Nephrol. 2015 Feb;26(2):493-503