DEPARTMENT OF HEALTH AND HUMAN SERVICES
UNITED STATES FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CARDIOVASCULAR AND RENAL DRUGS ADVISORY COMMITTEE

Tuesday, October 16, 2007

8:00 a.m.

National Labor College
10000 New Hampshire Avenue
Silver Spring, Maryland

PAPER MILL REPORTING
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Robert Temple, M.D.

P R O C E E D I N G S

Call to Order and Introductions

DR. HARRINGTON: Why don't we go ahead and get started. My name is Bob Harrington from Duke University. I will be the Acting Chair for this meeting of the Cardiovascular and Renal Drugs Advisory Committee meeting.

Why don't we start with introductions and then we will have Cathy read the conflict-of-interest statement.

John, why don't we start with you.

DR. NEYLAN: Yes, I am John Neylan. I am the industry representative. I am Vice President of Medical Affairs at Wyeth Research.

DR. PROSCHAN: I am Mike Proschan. I am a statistician with NIAID.

DR. FLACK: John Flack, Chairman, Department of Medicine, Wayne State University.

DR. PAGANINI: Emil Paganini. I am a nephrologist at The Cleveland Clinic, Cleveland, Ohio.

DR. LINCOFF: Mike Lincoff. I am an interventional cardiologist and Director of Cardiology Research at The Cleveland Clinic.

DR. BLACK: I am Henry Black. I am a nephrologist

and preventive cardiologist at New York University.

MR. FINDLAY: I am Steve Findlay. I am from Consumers Union. I am the consumer representative on this panel.

DR. WEISE: I am Kathryn Weise. I am a pediatric intensive care physician and bioethicist at The Cleveland Clinic and I am here as the bioethicist.

MS. MILLER: Cathy Miller with the FDA.

DR. HARRINGTON: Again Bob Harrington. I am an interventional cardiologist at Duke and Director of the Duke Clinical Research Institute.

MS. SCOTT: I am Malazia Scott. I am the patient rep.

DR. STEVENSON: Lynn Warner Stevenson, cardiologist from Brigham and Women's Hospital in Boston.

DR. WATTS: Nelson Watts, endocrinologist, metabolic bone diseases, University of Cincinnati.

DR. TEERLINK: John Teerlink, cardiologist, from the University of California at San Francisco and the San Francisco VA Medical Center.

DR. STOCKBRIDGE: I am Norman Stockbridge. I am the Director of the Division of Cardiovascular and Renal

Products at FDA.

DR. HARRINGTON: I have been asked to read officially into the minutes, for topics such as those being discussed at today's meeting, there are often a variety of opinions, some of which are quite strongly held.

Our goal is that today's meeting will be a fair and open forum for discussion of these issues and that individuals can express their views without interruption. Thus, as a gentle reminder, individuals will be allowed to speak in the record only if recognized by the Chair.

In the spirit of the Federal Advisory Committee Act, and the Government in the Sunshine Act, we ask that the Advisory Committee members take care that any conversations about today's topic take place in the open forum of the meeting, and not during breaks or lunch.

We are also aware that members of the media are anxious to speak with the FDA about these proceedings, however, like the Advisory Committee meetings, FDA will refrain from discussing the details of this meeting with the media until its conclusion.

Finally, I would like to remind everyone present to please silent your cell phones and pages if you have not

+already done so. We look forward to an interesting and productive meeting and thank you for your participation and cooperation.

I have also been asked to note that we will be moving the open public hearing from 8:30 until after the formal presentations later this morning unless there are objections.

So, hearing none, we will move it to after the formal presentations.

Cathy.

Conflict of Interest Statement

MS. MILLER: The Food and Drug Administration is convening today's meeting of the Cardiovascular and Renal Drugs Advisory Committee under the authority of the Federal Advisory Committee Act (FACA) of 1972.

With the exception of the industry representative, all members and consultants of the Committee are special Government employees or regular Federal Government employees from other agencies and are subject to Federal conflict of interest laws and regulations.

The following information on the status of this Committee's compliance with Federal ethics and conflict of

interest laws covered by, but not limited to, those found at 18 U.S.C. 208 and 712 of the Federal Food, Drug, and Cosmetic Act are being provided to participants in today's meeting and to the public.

FDA has determined that members and consultants of this Committee are in compliance with Federal ethics and conflict of interest laws. Under 18 U.S.C. 208, Congress has authorized FDA to grant waivers to special Government employees who have potential financial conflicts when it is determined that the Agency's need for a particular individual's service outweighs his or her potential financial conflict of interest.

Under 712 of the FD&C Act, Congress has authorized FDA to grant waivers to special Government employees and regular Government employees with potential financial conflicts when necessary to afford the Committee essential expertise.

Related to the discussions of today's meeting, members and consultants of this committee who are special Government employees have been screened for potential financial conflicts of interest of their own as well as those imputed to them, including those of their spouses and

minor children and for purposes of 18 U.S.C. 208, their employer.

These interests may include investments, consulting, expert witness testimony, contracts/grants/CRADAs; teaching/speaking/writing; patents and royalties; and primary employment.

Today's agenda involves the regulatory considerations for extending the use of phosphate binders from the dialysis population (where they are approved) to the pre-dialysis population (where no products are approved).

The Committee will hear presentations on this topic from Shire Development, Genzyme Corporation, and Fresenius Medical Care. This is a particular-matters meeting during which specific matters related to the use of phosphate binders in the pre-dialysis population will be discussed.

Based on the agenda for today's meeting and all financial interests reported by the Committee members and consultants, conflict of interest waivers have been issued in accordance with 18 U.S.C. 208(b)(3) and 712 of the FD&C Act for Dr. Nelson Watts. Dr. Watts' waivers involve

unrelated consulting with an affected firm for which he received less than $10,001.

The waivers allow this individual to participate fully in today's deliberations. FDA's reasons for issuing the waivers are described in the waiver documents, which are posted on the FDA website at www.fda.gov/ohrms/dockets/default.htm.

Copies of the waivers may also be obtained by submitting a written request to the Agency's Freedom of Information Office, Room 6-30 of the Parklawn Building.

A copy of this statement will be available for review at the registration table during this meeting and will be included as part of the official transcript.

Dr. John Neylan is serving as the industry representative, acting on behalf of all regulated industry, and is employed by Wyeth Pharmaceuticals.

We would like to remind members and consultants that if the discussions involve any other product or firm not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement and their exclusion will be noted for the record.

FDA encourages all other participants to advise the Committee of any financial relationships they have with any firms at issue.

Thank you.

DR. HARRINGTON: Norman, it looks like we are turning it over to you.

Introduction and Background

DR. STOCKBRIDGE: Good morning. I want to thank the Advisory Committee members, the Advisory Committee staff, special members of the Advisory Committee who are participating today, and, in particular, I would like to thank John Neylan. This is his last meeting with the Advisory Committee.

He has served from 2004 to 2007 and I know Cathy has got a plaque to present to him and I hope all of you will join me in thanking him for his three years of service.

Thank you.

[Applause.]

DR. STOCKBRIDGE: I would also like to take an unusual step and express my appreciation to the three sponsors who are participating in today's meeting, who have managed to put aside their competitive interests in this

area and they have put together a coordinated presentation to discuss the indication that is under consideration.

I think regardless of what happens during the course of this meeting, this whole field will be better off because of this rather critical path-like cooperation that they have done.

Today's topic sits in a somewhat larger context for us at FDA. Cardio-Renal has long managed the products that raise and lower serum potassium and the regulatory decisions on those products have been predicated on the belief that even brief excursions outside of the normal range had immediate life-threatening consequences, so that the demonstration of real clinical benefits has never been a part of the evaluation of those products.

Cardio-Renal has recently assumed responsibility for the indication of hyponatremia where the consequences of excursions in serum sodium have to be pretty extreme for there to be any clinical consequence, and yet there is at least one product approved again without the demonstration as part of the development program of clinical benefits.

The three products under consideration today address abnormalities in a third electrolyte and I think we

are looking for the Advisory Committee's insight into how well it is necessary to show that treatment effects on some endpoint have direct consequence that is of concern to patients directly, the things we would usually think about clinical endpoints.

This is specifically in the area of an extension of use of these products into a somewhat earlier stage of renal disease, but I think we are also interested in the principles that might be applicable to the other products that we managed.

Thank you.

DR. HARRINGTON: Why don't we move to the presentations by the sponsor. I will ask Dr. Pratt to introduce the speakers. As I said, we are going to move the open public hearing to the end of the presentations.

Sponsor Presentations

Introduction of Invited Speakers

DR. PRATT: On behalf of Shire Pharmaceuticals, Genzyme Corporation, and Fresenius Medical Care, I would like to thank the FDA and the Advisory Committee for the invitation to participate in this meeting to discuss the use of phosphate binders in patients with chronic kidney disease

who are not on dialysis.

My name is Raymond Pratt. I am a nephrologist and I am Vice President of Research and Development at Shire Pharmaceuticals. It is my job this morning to introduce the agenda and to provide a brief biography of the presenters.

After my talk is finished, Pamela Williamson, who is Senior Vice President of Regulatory Affairs and Quality for Genzyme Corporation, will provide an introductory overview of the topic.

She will be followed by a presentation by a representative of the National Kidney Foundation, who is an invited speaker of the FDA Cardio-Renal Division. This presentation will be given by Dr. Kerry Willis, who is Senior Vice President, Scientific Activities, National Kidney Foundation.

It is her responsibility for overseeing the National Kidney Foundation's professional education activities, and during the past nine years she has managed the development and dissemination of clinical practice guidelines developed under the auspices of the Kidney Disease Outcomes Quality Initiative, or KDOQI.

Her presentation will cover chronic kidney disease

as a public health concern and what the National Kidney Foundation is doing to attempt to improve the lives of patients with chronic kidney disease.

[Slide.]

The first scientific presentation of the morning will be presented by Professor Keith Hruska, who is Professor of Pediatrics, Medicine and Cell Biology at the Washington University School of Medicine in St. Louis.

Dr. Hruska is an active nephrologist, as well as a cell biologist, and he has published extensively on translational models as experimental systems for the study of kidney disease. His main research interest is using these models to study the pathogenesis of extraskeletal manifestations of CKD.

Dr. Hruska will review the pathogenesis of hyperphosphatemia and what has been learned about the molecular pathogenesis and cell biology of phosphate and its influence on extraskeletal calcification.

He will be followed by Professor Peter McCullough, who is Chief of Nutrition and Preventive Medicine at the William Beaumont Hospital in Royal Oak, Michigan. Dr. McCullough is a cardiologist and has published over 500

articles on the diagnosis and management of cardiovascular disorders in patients with chronic kidney disease.

He is on the board of directors of the Kidney Disease Improving Global Outcomes group, KDIGO, and is a member of the KDIGO-CKD Mineral Bone Disorder Guidelines Workshop.

Dr. McCullough's presentation will review the associations between hyperphosphatemia in chronic kidney disease patients and cardiovascular outcomes.

The third speaker of the morning will be Professor David Bushinsky, who is Professor of Medicine, Pharmacology, Physiology, at the University of Rochester School of Medicine and Chief of the Nephrology Division at the Rochester Medical Center in Rochester, New York.

Dr. Bushinsky's clinical and research interests revolve around the effects of acidosis on bone remodeling and the regulation of divalent-ion metabolism in humans. Dr. Bushinsky will review the benefit-risk profile of phosphate binders and present the current clinical perspectives on the treatment of patients with chronic kidney disease not yet on dialysis who have elevated plasma phosphate levels.

At the conclusion of these presentations, the sponsors' conclusions will be presented by Dr. Jose Diaz-Buxo, the Medical Director and Senior Vice President at Fresenius Medical Care.

During the question and answer session, we have an additional invited expert who will be available to answer questions. This is Professor Hartmut Malluche, who is the Robin Luke Chair of Nephrology and Professor of Medicine at the University of Kentucky School of Medicine in Lexington.

Dr. Malluche is an expert on the pathogenesis of bone disease in patients with renal failure and has extensively published on this topic both in clinical and experimental models of kidney disease.

He has authored over 400 articles in peer-reviewed journals and has been a member of NIH and FDA scientific advisory councils.

Ms. Williamson, if you could do the introduction, thank you.

Overview

MS. WILLIAMSON: Thank you, Ray. Good morning.

I would like to add my thanks to Dr. Stockbridge and the members of the FDA for convening this committee

meeting here today. We believe that the subject to be discussed is extremely important in terms of potential benefits for those hyperphosphatemic patients who are not currently treated by phosphate binders.

[Slide.]

As Dr. Stockbridge mentioned, we are here today to talk about the regulatory pathway for the potential expansion of the indication for the use of phosphate binders from dialysis patients to CKD Stage 4 pre-dialysis patients with hyperphosphatemia.

We are essentially seeking an alignment between current clinical practice, which is consistent with the KDOQI guidelines and the current labels. Estimates vary, however, it is reasonable to project that Stage 4 and 5 hyperphosphatemic pre-dialysis patient population is between 80,000 to perhaps 120,000 patients in the United States.

The current labels include utilization of these products for those patients that were originally treated in the clinical trials who were on dialysis. However, we believe that no distinction should be made in treating patients with hyperphosphatemia based solely on dialysis status. Stage 4 patients who are hyperphosphatemic should

not be excluded from treatment.

[Slide.]

The three companies, Fresenius Medical Care, Genzyme Corporation, and Shire Pharmaceuticals agreed to participate in this meeting and provide pertinent information, expert testimony, and an industry perspective supporting a label expansion.

Just a quick note. Given the fact that we are three companies here today, we are going to do our utmost to facilitate the question and answer period in the afternoon, so bear with us if we need to consult for just a moment.

[Slide.]

Today, we are talking about three products that are currently marketed and commercialized, and in fact have been on the market for a considerable period of time for treatment of those patients who are on dialysis.

These products include calcium acetate under the brand name of PhosLo which has been approved in the United States since 1990, sevelamer hydrochloride, or Renagel, approved in the U.S. since 1998, and lanthanum carbonate, or Fosrenol, approved since 2004 in the U.S.

All of these products have been approved based on

their ability to lower serum phosphorus in dialysis patients. To be clear, none of the companies have a claim in their label for long-term outcome, nor are we seeking such a claim.

These products bind phosphate in the gastrointestinal tract and they decrease absorption and reduce dietary phosphorus burden. This is one of several components that are critical in terms of treating these patients who present with comorbidities.

[Slide.]

With respect to long-term safety information and postmarketing surveillance, I do want to bring to your attention the fact that there is extensive information available in terms of patient exposure.

For example, there are more than 850,000 patient years of exposure for calcium acetate, sevelamer more than 485,000 patient years, and lanthanum more than 27,000 patient years. All of these phosphate binders are well characterized and all of these phosphate binders have favorable safety profiles that are well understood.

Most of the side effects, as you will see, are GI related and are very manageable, so importantly, we are not

here today seeking approval of a new product, nor are we here today seeking a new or different use for the existing products.

We are talking about three products in a class that are already approved for treatment of hyperphosphatemic patients on dialysis and what we are here to consider is whether or not these products in terms of their labels should be extended for use in the pre-dialysis patient population.

[Slide.]

We know currently that these products are prescribed on label for patients with hyperphosphatemia who are on dialysis. We also know that these products are routinely prescribed off label for CKD patients with hyperphosphatemia who are not on dialysis.

Data will be presented today that show that the decision to treat should not be made solely based on the patients' dialysis status, and therefore, a label expansion would allow for access to FDA-approved treatment.

[Slide.]

Consistent with what you will hear from Kerry Willis from the National Kidney Foundation, chronic kidney

disease progresses as a continuum of stages resulting in deterioration of renal function. This is a growing global health concern.

Phosphorus imbalance occurs before the need for dialysis in CKD. The need for treatment is when hyperphosphatemia begins. By the time this determination has been made, the compensatory mechanisms that the kidney uses to preserve certain phosphorus levels have been exhausted.

We will also present data that support the premise that hyperphosphatemia is an independent risk marker for cardiovascular morbidity and mortality and progression of renal disease in the pre-dialysis patient population. We have three external clinical experts, as Dr. Pratt described, today who will provide a significant amount of detail on these topics.

[Slide.]

As we consider a potential label expansion, we realize that it is important to consider safety. The three phosphate binders have been on the market beginning in 1990. Prior to and since approval, there have been multiple well-controlled clinical trials that demonstrate efficacy and

safety.

Years of extensive use and postmarketing surveillance demonstrate a well-established safety profile, and when considering patient safety, one should also consider the risk of delayed therapy. These risks include vascular calcification, inadequate nutrition, morbidity and mortality. We believe that delayed treatment provides a greater risk than earlier treatment.

[Slide.]

Our presentation is structured to assist in providing the information necessary to answering the questions that have been posed by the FDA.

A key question is one of surrogate markers. All three products have been fully approved based on their ability to control serum phosphorus with the most recent product being approved in 2004.

Hyperphosphatemia is one of several conditions that is critical to treat in patients who present with comorbidities and therefore we maintain that lowering serum phosphorus is a valid and appropriate endpoint for phosphate binders in dialysis patients.

[Slide.]

We will provide today information that supports the need to treat CKD-4 patients. We believe there are no relevant differences between the dialysis and the pre-dialysis patient population with respect to hyperphosphatemia.

However, once patients reach dialysis, the magnitude of hyperphosphatemia and the associated multi-organ dysfunctions are amplified, so based on the evidence that is available today, we believe that it is important to treat hyperphosphatemia when it clinically presents regardless of dialysis status.

[Slide.]

You are going to be asked to evaluate the risks of early treatment with phosphate binders. As you can see, the risks of phosphate binder treatment in the dialysis population are well known and, in studies conducted to date, the risks of treatment in the pre-dialysis population are similar to those for patients who are on dialysis.

[Slide.]

There is sufficient evidence to support expansion of the current labels to the pre-dialysis patient population. All three companies continue to do research in

this area and, contrary to what had been posted in a draft agenda, we do continue to do clinical trials both in the dialysis and pre-dialysis patient population.

However, we also believe that clinical trials requiring long-term outcomes as endpoints should not be a prerequisite to expanding the label indication.

Finally, Stage 4 and 5 patients with hyperphosphatemia need to be treated and, based on presentations this morning, you will see that many of these patients are being treated albeit off label, and, therefore, if we could include the pre-dialysis patients in the label, label expansion would allow for FDA-approved treatment of hyperphosphatemia in CKD patients.

We would propose this morning an amendment to the indication to include "prior to and following initiation of dialysis."

Thank you very much. I believe next to speak is going to be Dr. Kerry Willis from the National Kidney Foundation.

DR. HARRINGTON: I have just been asked to make a quick announcement to remind the audience that Dr. Willis is an invited guest of the FDA.

FDA Guest Speaker Presentation

Chronic Kidney Disease-Related Mineral and Bone Disorders: Public Health Problem

DR. WILLIS: Good morning. On behalf of the National Kidney Foundation, I would like to thank Dr. Stockbridge and the FDA for inviting us to be here today.

[Slide.]

I am going to describe for you the scope of the chronic kidney disease and bone and mineral complications as a public health problem and then tell you about the strategies the NKF has developed to improve outcomes in this very large, high-risk population.

[Slide.]

I would like to first give you a brief background. This graph shows the first year adjusted patient death rates by treatment modality over the years 1986 to 1996 from the U.S. Renal Data System.

What you can see is that, while the overall rate of first-year death on dialysis for patients has dropped substantially, it is still above 20 percent per year. We found that unacceptably high and decided to see what we could do to help address the problem.

[Slide.]

The other compelling observation was the cardiovascular mortality is extremely high among dialysis patients in all age groups, and in some groups, 1,000-fold higher than in the general population.

So, we postulated early on that improving cardiovascular outcomes would be key to improving survival in this group, and you will see that this is a consistent theme in our guideline development activities as we go forward.

[Slide.]

In 1995, the National Kidney Foundation established a program which is now known as KDOQI or the Kidney Disease Outcomes Quality Initiative to develop evidence-based clinical practice guidelines.

Our clinical practice guideline development process relies on an independent workgroup under the guidance of expert methodologists who rigorously review the literature according to a process recommended by the U.S. Agency for Healthcare Research and Quality.

To begin, all relevant English language literature is retrieved in a comprehensive search using keywords

supplied by the workgroup, and then roughly 10,000 to 30,000 articles per guideline are screened and their applicability to the study population and quality of their conclusions is assessed.

Based on those results, a chain of logic is constructed by the workgroup that ties into the supporting evidence and the evidence statements, which then become our guidelines.

After external peer review by interested agencies, practitioners, medical societies, and patients, the guidelines are finalized and published in the American Journal of Kidney Diseases.

As part of the dissemination process, we develop a series of secondary publications in peer-reviewed medical journals and post the guidelines on the Internet.

In the implementation phase, there is an ongoing active process of helping patients and practitioners understand and apply the guidelines in real world practice settings, and once implementation has begun, we can assess the impact of the guidelines both in terms of how they are used and their impact on patients.

We look at large databases and assess these

practice changes, and use that as part of the evidence to update the guidelines, which happens about every three years.

[Slide.]

This is a summary of the guidelines we have published to date with the first guidelines in 1997 under the Dialysis Outcomes Quality Initiative, which gradually became KDOQI and now KDIGO, which is our global initiative for guideline development.

Today, I will focus mainly on two guidelines, the chronic kidney disease and bone and mineral guidelines that were initially published in 2002 and 2003.

[Slide.]

Consistent terminology has been a key goal for KDOQI. A disease needs to be clearly defined in order to be detected and treated appropriately.

So, chronic kidney disease is structural or functional abnormalities of the kidneys persisting for greater than 3 months, as manifested by either kidney damage, with or without decreased glomerular filtration rate, or GFR, which is a direct measure of kidney function and can be estimated based on a prediction equation from

serum creatinine values and defined by pathologic abnormalities or markers of kidney damage, such as urinary protein, blood abnormalities, or imaging abnormalities, or kidney transplantation, which results in reduced function and the ongoing impact of immunosuppressive drugs.

Then, in the later stages, CKD is defined by a GFR less than 60 ml/min/1.73 m^2, with or without kidney damage.

[Slide.]

These are the stages defined in our 2002 guidelines and I want to emphasize that chronic kidney disease is a continuous and progressive condition for most patients. These stages were devised for data collection and classification of disease and to help standardize communication between health care providers and patients.

The first two stages represent kidney damage defined by abnormal findings, such as proteinuria. Stage 3 and 4, moderate and severely decreased GFR are the stages at which you start to see significant complications, and finally, Stage 5, a GFR less than 15 is kidney failure.

[Slide.]

We have established that CKD is a major public health problem. It is common, it is harmful, and we have

treatments that we can implement, and we believe that implementation of these treatments earlier will improve outcomes and lower the mortality rate of patients at all stages of disease.

[Slide.]

This is our conceptual model for chronic kidney disease, going from normal all the way through kidney failure and death due to CKD.

In the normal population, it is important to screen for chronic kidney disease particularly where there are risk factors in the diabetic patient, patients with hypertension, the elderly population, patients with a family history of kidney disease, and importantly, racial and ethnic minorities who often have multiple CKD risk factors.

Once increased risk is observed, risk-reduction methodologies can be implemented and more frequent screening for chronic kidney disease, which can lead to early diagnosis and treatment.

[Slide.]

When kidney damage is evident, as it is in 11.3 million adult patients, active treatment of comorbid conditions that can slow progression before GFR rate has

declined significantly is required.

[Slide.]

At Stage 3 and 4, which affect about 7.7 million people, glomerular filtration rate has declined significantly. However, it is still important to estimate the progression of the disease and treat for complications, as well as preparing the patient for renal replacement therapy.

[Slide.]

Once kidney failure occurs, replacement by dialysis and/or transplantation can be implemented. About 300,000 patients are currently at this stage. So, what happens to all of those people who have decreased GFR and then don't make it into dialysis and transplant?

The majority of them die and the mortality rate of patients with CKD is similar to that of patients with many cancers. Another important thing to note is that these deaths are largely due to complications, not kidney failure per se.

[Slide.]

Because we are here today to talk about phosphate, the prevalence of abnormal mineral metabolism is important

to recognize. This slide shows the prevalence of abnormal serum calcium, phosphate, and parathyroid hormone by GFR level.

As you can see, patients with mildly decreased GFRs, even in the 60 to 69 mL/min range, approximately, 20 percent of these patients already have intact PTH levels over 65 picograms/mL, which is the upper limit of normal, and these values continue to increase as the GFR declines.

Elevated calcium, phosphorus, and PTH occur with increasing prevalence as GFR declines and are associated with serious comorbid conditions including bone pain, fractures, and muscle pain, as well as increasing mortality.

[Slide.]

Bone and mineral disorders were prioritized to be our first interventional guideline that covered all stages of chronic kidney disease, and this prioritization was based on patient surveys that ranked bone disease highest in terms of adverse impact on their quality of life and also on observed variability in practice, which is a measure of the potential for improvement.

[Slide.]

This is the bone workgroup. We assembled 14

leading experts including some who are here today. These were investigators from the major clinical trials in this area and included representation of pediatric nephrology and renal dietetics.

[Slide.]

Here are the recommended target levels established by the workgroup for phosphorus, calcium, and PTH. So, starting with phosphorus, the workgroup stated in the Background Section of the guideline that, "It is imperative to prevent hyperphosphatemia and maintain serum phosphorus levels within the normal range."

So, in Stages 3 and 4, the target range is essentially the laboratory range of normal values. This was based on opinion because there was very little evidence.

In Stage 5, the target range is a little higher. The 3.5 to 5.5 range was arrived at based on strong evidence that 6 mg/dL was deleterious and other evidence that 3.5 to 5.5 might be the lowest achievable range in these patients.

The reasoning was similar for calcium, and as you see, normal in Stages 3 and 4, and a little higher in Stage 5. The recommended PTH levels progressively elevate as CKD progresses because of the association between PTH and bone

turnover.

[Slide.]

These are the corresponding treatment recommendations for Stages 3 and 4. Decrease total body phosphorus burden by dietary restriction and phosphate binder therapy, 2.7 to 4.6 mg/dL, and this should begin when either elevated serum phosphorus or elevated serum PTH is observed.

Treat elevated PTH with active oral vitamin D sterols to a target of 35 to 70, or 70 to 110 pg/mL, and normalize serum calcium.

[Slide.]

So, in Stage 5, normalize serum phosphorus by diet and phosphate binder therapy, as much as possible, to 3.5 to 5.5 mg/dL, and limit elemental calcium intake from binders to 1,500 mg/day.

Treat elevated PTH with active vitamin D sterols to a target of 150 to 300 pg/mL, and normalize serum calcium ideally to 8.4 to 9.5 mg/dL, and always less than 10.2. And, in addition, control the calcium phosphorus product to less than 55 mg/dL to prevent soft tissue calcification.

[Slide.]

So, while we were working on these, we were also continuing to look at cardiovascular disease in chronic kidney disease, and, in fact, published guidelines on the three biggest risk factors - diabetes, hypertension, and dyslipidemia.

Meanwhile, data started to accumulate that began to shed some light on how abnormal mineral metabolism might lead to either bone disease or cardiovascular disease or both.

[Slide.]

So, again, we began to focus on how we could come up with a consistent terminology. The term "renal osteodystrophy" is used to describe different entities, and the predominant use is to describe a disorder of bone remodeling.

However, this does not take into account new data that there is increased morbidity and mortality of abnormal serum biochemistries, such as phosphorus, nor increased awareness of vascular disease related to bone and mineral disorders in chronic kidney disease patients.

[Slide.]

To address these issues and see if we could come

up with definitions more closely linked to clinical outcomes, we assembled the leading experts in bone and mineral disorders and came out with a position statement last year, the Definition, Evaluation and Classification of Renal Osteodystrophy, under the auspices of KDIGO, which as I mentioned earlier is an international guideline group.

[Slide.]

The KDIGO workgroup recommended that the term "renal osteodystrophy" should be used exclusively to define the bone pathology based on biopsy that is associated with chronic kidney disease, and that the clinical, biochemical, and imaging abnormalities previously identified as correlative renal osteodystrophy should be defined more broadly as a clinical entity or syndrome called chronic kidney disease-mineral and bone disorder, or CKD-MBD.

[Slide.]

So, CKD-MBD is a systemic disorder of mineral and bone metabolism due to CKD manifested by either one or a combination of the following:

Abnormalities of calcium, phosphorus, PTH, or vitamin D metabolism;

Abnormalities in bone turnover, mineralization,

volume, linear growth, or strength;

Vascular or other soft tissue calcification.

[Slide.]

This is a proposed framework for classification based on the presence or absence of laboratory abnormalities, bone disease, and vascular calcification.

This framework is being used as the basis for new clinical-practice guidelines being developed by KDIGO. It is hoped that this classification will aid in selecting therapies more specific and appropriate to the various clinical states found in chronic kidney disease patients.

[Slide.]

So, in schematic form, the CKD-MBD is an intersection of these three different classes of abnormalities - laboratory, bone, and vascular calcification, which ultimately result in cardiovascular disease, fractures, and increased mortality.

By detecting these abnormalities early and treating them, we can reduce the incidence of these severe adverse outcomes.

[Slide.]

In summary, CKD is defined using estimated GFR and

classified into five stages. This classification can help predict clinical outcomes.

Early detection and treatment, and this certainly includes hyperphosphatemia, can improve patient outcomes.

There is a link between cardiovascular disease and bone and mineral disease in CKD, and the new CKD-MBD classification will form the basis for updated international clinical practice guidelines.

Thank you.

DR. HARRINGTON: I think we have a following speaker from the sponsor.

Sponsor Presentations (Continued)

Pathophysiology of Hyperphosphatemia

DR. HRUSKA: Good morning. I am Keith Hruska and Dr. Pratt introduced me.

[Slide.]

Hyperphosphatemia is associated with significant pathophysiology in chronic kidney disease. This pathophysiology contributes to the high rates of mortality seen in the disease. However, in the 20th century, the pathophysiology was that of secondary hyperparathyroidism.

[Slide.]

Phosphate binders were originally approved in chronic kidney disease Stage 5 on dialysis for hyperphosphatemia, and hyperphosphatemia was a major cause of secondary hyperparathyroidism, and hyperparathyroidism was considered equivalent to renal osteodystrophy.

This original indication for phosphate binders remains relevant, but the pathophysiology of hyperphosphatemia is much more than secondary hyperparathyroidism.

[Slide.]

Today, approximately 11 million Americans have chronic kidney disease and excessively high mortality risk due to cardiovascular disease.

As just mentioned, most patients with chronic kidney disease die before reaching end-stage kidney disease and requiring dialysis.

The risk of death in the survivors that reach dialysis is extreme, such that a 30-year-old on dialysis has the risk of death of a 90-year-old with normal kidney function.

[Slide.]

The mechanisms of this excess mortality in chronic

kidney disease include hyperphosphatemia and vascular calcification.

The standard risk factors just presented by the National Kidney Foundation don't explain cardiovascular risk in chronic kidney disease. Studies by Gerard London's group have demonstrated that vascular calcification is a cardiovascular risk in chronic kidney disease, and their group has linked vascular calcification to hyperphosphatemia.

Multiple observational studies have demonstrated that hyperphosphatemia is an independent cardiovascular risk marker in chronic kidney disease. Furthermore, chronic kidney disease causes an imbalance of phosphorus resulting in phosphorus retention.

The heterotopic mineralization induced by phosphorus retention is not a passive process and will show you that phosphate actually is a signaling molecule driving vascular calcification through stimulating the activity of a sodium-dependent phosphate transport protein Pit-1 in the vascular smooth muscle cell.

[Slide.]

To describe the pathophysiology of phosphate as a

cardiovascular risk in chronic kidney disease, I am going to take you through four discussion points: an imbalance of phosphate homeostasis, the contribution of the skeleton to hyperphosphatemia, that hyperphosphatemia causes vascular calcification, and that phosphorus is a signaling molecule through Pit-1.

[Slide.]

First, the imbalance of phosphate homeostasis.

[Slide.]

This slide describes phosphate balance. We take about 1,200 milligrams of phosphorus in our diet and we absorb a net of 800 milligrams from 950 milligrams absorbed and 150 milligrams secreted into an exchangeable phosphorus pool that represents three components.

The largest component is intracellular phosphorus involved in phosphorylation reactions. The second component is the mineralization front in the skeleton. This is a significant component of exchangeable phosphorus. And then there is a very small component that we measure, the serum phosphorus, which represents less than 1 percent of the total body phosphorus.

The kidney excretes the absorbed phosphorus such

that balance is maintained, 800 and 400 equals 1,200.

A component of phosphate balance physiology that is normally ignored is the skeleton. This is because the adult skeleton is in balance through bone formation equaling bone resorption on a daily basis. However, the skeleton functions as a phosphate reservoir and 85 percent of the total body phosphorus exists in this reservoir.

The function of this reservoir is to assimilate phosphorus when balance is positive. An example of this is an infant, say, a 3-month-old, whose serum phosphorus is quite high. The function of the skeleton is assimilating this positive balance, and we call this assimilation growth. This is the normal function of the skeleton as a phosphate reservoir.

[Slide.]

Phosphorus balance is lost in chronic kidney disease. Intake is the same and absorption is maintained essentially the same. However, the kidney now fails to excrete the absorbed phosphorus, resulting in a positive balance. In chronic kidney disease, there is a unique feature to this positive balance.

[Slide.]

This feature is that the function of the skeleton as a reservoir for the positive balance is blocked. I have described that on this slide showing that bone resorption exceeds the rate of bone formation. This effectively blocks the skeleton from functioning as a phosphate reservoir.

[Slide.]

As a result, a new reservoir for the positive balance is required. In chronic kidney disease, the new reservoir is multiple soft tissues including the cardiovascular system.

This cardiovascular calcification is shown to take in the 100 milligrams of excess balance that I show in this diagram, 50 milligrams positive from the failure of the kidney, 50 milligrams being contributed by the skeleton, and 200 milligrams moving into the heterotopic sites. But, as I will demonstrate, this heterotopic mineralization is not simply a passive process.

It is an active process and I will demonstrate the capability of these heterotopic sites to actually lose phosphorus, so I have shown it as a bidirectional process with 200 going in and 100 coming out.

In this final balance slide, I have also adjusted

for the effects of a decrease in phosphorus intake from 1,200 milligrams to 1,000 milligrams, showing that despite the decrease in absorbed load, the kidney still fails to excrete the absorbed phosphorus.

Now, how is phosphate balance regulated in chronic kidney disease?

[Slide.]

As a beginning, consider the decrease in calcitriol production that occurs in Stage 3 chronic kidney disease.

In response to the decrease in calcitriol production, there is a decrease in calcium absorption leading to hypocalcemia, which stimulates secondary hyperparathyroidism.

The increase in PTH levels acting at the level of the kidney stimulate an increase in the reabsorption of calcium, an increase in calcitriol synthesis, and a decrease in phosphate reabsorption.

This decrease in reabsorption maintains balance until kidney failure is too severe. When excretion failure occurs, an increase in the serum phosphorus results. The effects of hyperphosphatemia represent an additional

stimulus to decrease phosphate reabsorption.

As a result of the decrease in calcitriol, at the level of the skeletal osteocyte, there is a decreased stimulus for production of FGF-23. FGF-23 is a small molecule that is handled largely by glomerular filtration and proximal tubular reabsorption so, in chronic kidney disease, the switch occurs from a decrease in stimulus to increased levels through the effects of kidney failure.

FGF-23 is also a potent stimulus to decrease phosphate reabsorption. So, in chronic kidney disease, phosphate excretion failure occurs in the presence of tremendous phosphaturic stimuli, hyperparathyroidism, the serum phosphorus itself, and FGF-23.

Now, as I have shown you three slides ago, this excretion failure results in heterotopic mineralization.

[Slide.]

Vascular calcification in chronic kidney disease comes in two forms, atherosclerotic calcification, which represents calcification of the arterial intima of atherosclerotic plaques, and secondly, Monkeberg sclerosis, which represents arterial medial calcification.

In chronic kidney disease, both forms are observed

in the large arteries. Calciphylaxis in chronic kidney disease is mainly a Monkeberg type process in smaller arteries and, in coronary artery calcification and cardiac valve calcification, are mainly atherosclerotic, if not completely so.

[Slide.]

Vascular calcification in chronic kidney disease causes cardiac disease. Vascular calcification leads to vessel stiffness and vessel stiffness increases pulse wave velocity. Since coronary flow or coronary artery perfusion is mainly a diastolic event, this increase in pulse wave velocity causes a chronic ischemia, leading to left ventricular hypertrophy.

In addition, the vessel stiffness causes an increase in pulse pressure, and in chronic kidney disease we see a change in the phenotype of hypertension in our patients. It begins largely as a diastolic hypertension and converts to a systolic hypertension due to this increase in vessel stiffness.

The increase in pulse pressure observed in chronic kidney disease leads to an increase in afterload, and this is an independent contribution to left ventricular

hypertrophy, leading to the events of chronic kidney disease on the heart, cardiac disease events, and mortality.

[Slide.]

The complexity of human disease required a translational model to dissect the role of phosphorus in chronic kidney disease caused vascular calcification and cardiac disease.

The model that we chose was a model of atherosclerosis, the low density lipoprotein receptor deficient mouse fed a high fat, high cholesterol diet.

This mouse develops hypercholesterolemia, insulin resistance that progresses to type 2 diabetes, obesity, and hypertension. In other words, it is a mouse model of the metabolic syndrome of humans.

These mice developed vascular calcification. When chronic kidney disease is added to the model, there is a major increase in vascular calcification and the development of hyperphosphatemia at the equivalent of about Stage 3 chronic kidney disease.

[Slide.]

This slide depicts the effects of high-fat feeding and chronic kidney disease on vascular calcification.

Reproducibly, in this model, at the aortic root shown on these slides, stained with alizarin red for calcium, there is a large atherosclerotic plaque, and you can see that high-fat feeding causes deposition of calcium within the plaque and in the arterial media below the plaque shown by the arrow.

When chronic kidney disease is induced, the number and size of there calcium deposits is markedly increased. Treatment of these animals with phosphate binders diminishes the number and size of calcium deposits.

In addition, we began these studies as a trial of bone morphogenetic protein 7 toxicity, and we were surprised when we found that BMP-7 was actually efficacious. When we examined the mechanisms of BMP-7 action, we observed that BMP-7 corrected hyperphosphatemia.

It was the mechanism of correction of hyperphosphatemia that represented the initial link between the skeleton and vascular calcification in chronic kidney disease. The mechanism by which BMP-7 decreases serum phosphorus is stimulation of bone formation.

Since this observation, all studies of vascular calcification in chronic kidney disease have demonstrated

this link between the skeleton and vascular calcification. This has led the KDIGO change that you have seen in the previous talk in the definition of renal osteodystrophy.

The development of vascular calcification in these mice occurred over 8 weeks, from 14 to 22 weeks of age. This is equal to about 5 to 8 years of human life.

[Slide.]

Human clinical experience is similar to the observations made in our animal studies. For instance, the status of skeleton in a metabolic syndrome is similar to the skeleton in our fat-fed, low-density lipoprotein receptor deficient mice.

To characterize this statement, consider obesity. Obesity alone is associated with an increase in bone mass and no increase in fracture risk. However, patients with a metabolic syndrome have an increased risk of osteoporosis and poor fracture healing.

Chronic kidney disease stimulated vascular calcification in our model mimics the prevalence of vascular calcification and insulin resistance in type 2 diabetes especially when it is complicated by diabetic nephropathy.

Chronic kidney disease and type 2 diabetes is

associated with the adynamic bone disorder as is our animal model, and treatment of hyperphosphatemia diminishes vascular calcification.

[Slide.]

So, I have said then that the skeleton contributes to hyperphosphatemia.

[Slide.]

Let me enlarge on this statement. Both forms of osteodystrophy in chronic kidney disease contribute to hyperphosphatemia. In low turnover osteodystrophy, characterized by insufficient levels of parathyroid hormone to maintain normal bone remodeling rates, movement of phosphorus and calcium from the exchangeable pool into the skeleton is diminished.

The reductions in bone formation in low turnover osteodystrophy exceed the reductions in bone resorption. As a result, low turnover osteodystrophy, because of excess bone resorption, contributes to hyperphosphatemia and metastatic calcification or heterotopic calcification.

The proof of this is that our patients with low turnover osteodystrophy develop osteoporosis, in other words, they lose skeletal mass. This demonstrates the role

of excess bone resorption in low turnover osteodystrophy.

In high turnover osteodystrophy, because of the influence of excess parathyroid hormone, high levels of rank ligand develop and there is excess osteoclast activity. Even though the bone formation rates are increased, bone resorption rates are excessive and the high turnover osteodystrophy contributes to hyperphosphatemia, which contributes to heterotopic mineralization including vascular calcification and stiffness.

[Slide.]

This places hyperphosphatemia central to the failure of a multi-organ system that we have been discussing and is operative in chronic kidney disease. This multi-organ system begins with renal injury.

Renal injury leads to phosphate excretion failure and hyperphosphatemia. Intestinal absorption is maintained near normal as an important component leading to hyperphosphatemia. But, in addition, chronic kidney disease directly damages the skeleton, leading to the adynamic bone disorder. The adynamic bone disorder contributes to secondary hyperparathyroidism and both high turnover and low turnover osteodystrophy contribute to hyperphosphatemia.

This hyperphosphatemia causes vascular calcification, as I have alluded to, and so we have a failure of a four-organ, multi-organ system: the kidney, the skeleton, the parathyroid glands, and the vasculature.

Each of the organs are directly influenced by others in the system. One of the direct wires from the skeleton to the vasculature is hyperphosphatemia.

[Slide.]

So, we have just reviewed how the skeleton contributes to hyperphosphatemia. Now, I would like to discuss how hyperphosphatemia causes vascular calcification.

[Slide.]

In demonstrating this, let's review a study we performed where we demonstrated the ability of phosphate binders to treat, not prevent, but treat vascular calcification.

Here, we allowed animals to progress with chronic kidney disease to the state of very significant established vascular calcification. As you can see on the left they were hyperphosphatemic and, when treated with vehicle in the yellow bars, there was no change in the serum phosphorus, but when we treated with the phosphate binder, there was

significant normalization of the serum phosphorus, shown here by the orange and gray bars.

When we looked at the aortic calcium levels, the vehicle treatment was characterized by a continuous accretion of calcium, whereas, the phosphate binder caused a significant reduction in the aortic calcium level compared to baseline, representing a partial reversal of established calcification.

Furthermore, in this study, we were able to demonstrate that the control of serum phosphorus prevents cardiac hypertrophy. This is a hard cardiac endpoint in this translational animal model. Thus, the demonstration of reversal of calcification is a clear proof that hyperphosphatemia is a direct cause of vascular calcification.

The effect of phosphate binders in this study occurred over 6 weeks of treatment; in other words, we established vascular calcification at 22 weeks and treated until 28 weeks and, as previously alluded to, this is equivalent to several years of human treatment.

[Slide.]

To further look at the mechanism of

hyperphosphatemia causing vascular calcification, we went on to in vitro studies and then applied this in vitro data back to the in vivo situation.

In our in vitro model is human atherosclerotic aortas from which we isolate smooth muscle cells and expand them in culture. When we look at these isolated smooth muscle cells, we observe that they have a significant phenotypic drift. They are no longer contractile cells, but rather they are beginning to exhibit osteoblastic differentiation.

They have significant levels of the osteoblastic morphogens BMP-2 and BMP-4. They express the osteoblastic specific transcription factor RUNX2 and yet when we put them in culture, they do not mineralize, however, when we increase the media phosphorus concentration from 1 to 2 millimolar equivalent to a change in the serum phosphorus from 3.1 to 6.2, there is marked matrix mineralization.

This matrix mineralization occurs due to the stimulation of a second osteoblast-specific transcription factor osterix, so the effects of phosphorus is to induce osterix expression, which is the mechanism of phosphate stimulated matrix mineralization.

Now, taking this data back to the in vivo situation, we can demonstrate that chronic kidney disease induces expression of osteoblastic transcription in the aorta.

RUNX2 levels, shown here, are increased in chronic kidney disease and phosphate binders produce a dose-dependent inhibition of aortic osteoblastic gene expression, shown here using lanthanum carbonate.

This demonstrates the mechanisms by which phosphate binders diminish vascular calcification in chronic kidney disease.

[Slide.]

Finally, I would like to review how phosphorus is a signaling molecule through Pit-1.

[Slide.]

In the in vitro studies just described, the vascular smooth muscle cells, diagramed here, have a sodium-dependent phosphate transport protein Pit-1. The effect of phosphorus occurs through a Pit-1 associated signal generating complex.

Shown here is the yellow boxes. The signaling complex is activated by the engagement of sodium phosphate

within the transport protein. The signal generating complex results in cell signals activating the transcription of RUNX2 and osterix, leading to matrix mineralization.

The effect of phosphorus is to directly stimulate osterix expression. This occurs within minutes. It is inhibitable by occlusion of the sodium-dependent phosphate transport protein with phosphonoformic acid, and it is inhibitable by an inhibitory RNA and RNAi to Pit-1.

Inhibiting Pit-1 blocks the effect of high media phosphorus or a high serum phosphate, therefore, phosphorus is a signaling molecule.

[Slide.]

The translational studies that I have described are in agreement with the new clinical consensus, the chronic kidney disease-mineral bone disorder, or the CKD-MBD as defined by KDIGO.

Abnormal laboratory values including hyperphosphatemia lead to abnormal skeletal metabolism, which is renal osteodystrophy. This comes in either a high turnover or low turnover variety. Both forms of renal osteodystrophy contribute to hyperphosphatemia and vascular calcification.

In addition, the direct effects of phosphorus itself on vascular calcification have been reviewed. Thus, you can see from the diagram, then, that the relationships between these three parameters lead to the clinical outcomes of increased morbidity and mortality in chronic kidney disease.

[Slide.]

In conclusion, hyperphosphatemia is a loss of homeostasis, a loss of skeletal reservoir function, a contributor to vascular calcification. As a result, hyperphosphatemia is a cardiovascular risk factor in chronic kidney disease.

The function of hyperphosphatemia is not simply passive, related to an increase in calcium phosphorus product, but it is an active principle, a signaling molecule that directly directs heterotopic osteoblastic differentiation.

The control of hyperphosphatemia by phosphate binders diminishes vascular calcification and the translational animal models that I have described reflect clinical experience.

Translational models have hyperphosphatemia, and

hyperphosphatemia is a determinant of vascular calcification.

Thank you.

I would like to introduce Dr. Peter McCullough, who will discuss the epidemiology and cardiovascular mortality associated with hyperphosphatemia and the CKD-MBD.

Cardiovascular Consequences of

Chronic Kidney Disease-Mineral and Bone Disorder

DR. McCULLOUGH: Good morning, Mr. Chairman, ladies and gentlemen.

[Slide.]

This segment is going to review the cardiovascular aspects of chronic kidney disease-mineral and bone disorder. I just want to start out by recognizing the contributions that many in this room, including many of the panel members, have made with respect to understanding the puzzle between how chronic kidney disease works to amplify and accelerate many aspects of cardiovascular disease.

I believe part of this puzzle has to do with this risk condition or risk state of CKD-MBD and the data behind it will be the subject of this presentation.

[Slide.]

So, let's go first to the definition of chronic kidney disease, mineral and bone disorder, which has been explicitly stated by Kerry Willis.

[Slide.]

I just want to point out and emphasize that clinicians are asked to measure these biochemical parameters, calcium, phosphorus, PTH, and vitamin D and to recognize abnormalities on the lab values, and understand that this is integrated with respect to bone and soft tissue and vascular calcification.

When we go over the studies in the next two segments, phosphorus, as the biochemical parameter, has been the one that has been most consistently related to manifestations of cardiovascular disease probably due to the fact that when phosphorus is elevated, it represents a loss of control of multiple systems, in particular the loss of the ability of parathyroid hormone to reduce phosphorus and cause phosphaturia.

I will show you data that the biologic plausibility that Dr. Hruska has gone over integrates nicely with the clinical data with respect to the hypothesis of how this kidney, mineral, and bone disorder relates to

cardiovascular disease.

[Slide.]

There is amplification of calcification in atherosclerosis. And I should just state at the outset every autopsy study ever done of human atherosclerosis has found calcium in the atheroma. It is part of the atherogenic process.

Everything I know about this from the autopsy studies, studies taking atherectomy specimens and now imaging studies using non-invasive ways of evaluating calcification have related the atherosclerotic process in calcification to be one and the same in the coronary arteries.

[Slide.]

We recognize that the conventional cardiovascular risk factors have all been shown in studies to be related to coronary calcification--i.e., atherosclerosis. But importantly, in chronic kidney disease, one could find studies either in the dialysis population or in the pre-dialysis population relating the calcium phosphorus product, exogenous calcium intake particularly when patients are exceeding the guidelines' recommendations of oral calcium

intake, calcium carbonate as a form of an off label use of a phosphate binder, hyperphosphatemia. We will go over this, chronic inflammation, exogenous vitamin D in some studies, oxidative stress strongly related to the duration of dialysis.

That means the longer patients are on dialysis, the greater the probability and the greater the intensity of the calcification that will be found in the coronary arteries, and then secondary hyperparathyroidism in some studies.

So, it is a complex puzzle. This discussion today relates phosphorus as part of this complex discussion, but represent that this is a very dynamic milieu in which we believe coronary atherosclerosis is both amplified and accelerated.

[Slide.]

This is a recent depiction of atherosclerosis as shown in a publication, in Circulation, showing a lot of the familiar components to this process including ingress of LDL cholesterol, inflammatory cells, inflammatory factors, participation of the renin angiotensin system and oxidative stress, but importantly, demonstrates the metamorphosis that

occurs with vascular smooth muscle cells, which can move into the atheroma, can be activated very importantly by phosphorus via the Pit-1 receptor, and Dr. Hruska has gone over this.

This is a relatively new understanding and many depictions of atherosclerosis have really been devoid of demonstrating how the calcium actually becomes part of the atherosclerotic process.

The clinical studies and the basic science studies would support that there are promoters of this calcification process, most importantly phosphorus, but the calcium phosphorus product has been related, forms of bone morphogenetic protein, leptin, vitamin D, reactive oxygen species, and there are also inhibitors of the calcification process which have been I think very promising in terms of being potential treatment targets in the future including fetuin-A, osteoprotegrin, matrix, a GLA protein, osteopontin, bone morphogenic protein 7, and pyrophosphate.

So, the biologic plausibility of having a dysmetabolism of calcium phosphorus, parathyroid hormone, and vitamin D, if you will, and its connection to atherosclerosis is reasonably strong, and that is actually

part of the chain of logic that we have used in the guidelines panels to build our rationale statements and ultimately lead to what we believe are recommendations for the best practice of this.

[Slide.]

Now, a recent technology approved for use in clinical medicine predominantly by cardiologists and radiologists is CT angiography, and this slide shows just an example of what one of these images looks like. As shown here, this is the left anterior descending artery and it has contrast in it. That is what makes it white. There very bright white specks are calcifications seen in the human coronary artery.

Basically, what this represents is the location where atherosclerosis is. Now, roughly, 96 percent of human atherosclerotic plaques have some degree of calcium in it, about 6 percent will be found to be devoid of calcium, and the calcification pattern can be basically blotchy, as shown here, or as shown in the right coronary artery, down here, be circumferential when we look at it in cross-section.

The CT angiography also has the ability--this is the 64-slice example--most institutions are now at a higher

resolution to actually give the degree of stenosis.

A lot of the slides in my presentation, the ones that follow, will focus on a measure of vascular calcification called the coronary artery calcium score.

This is the sum total of the calcium content that is found in the coronary arteries as represented in Agatston units, and, in general, represents a burden of atherosclerosis in the human coronary arteries. I think that is the best way to think about it.

The technologies used in previous studies prior to multi-slice CT were electron-beam computed tomographies, and I think the way to think about it is that the calcium score that is generated is basically the same between these two forms of technologies.

The reason why I am showing this is that this is now in clinical use and has appropriateness criteria, and many institutions now across the United States are using this as a form of non-invasive imaging in making decisions regarding patient care.

[Slide.]

So, as general of rule of thumb, with respect to coronary artery calcification, this table shows integration

of several studies demonstrating that a calcium score of zero, which would for the majority of patients represent the absence of significant atherosclerosis, is related to a very low probability of any form of significant stenosis and a very low cardiac risk status, less than 1 percent chance per year of death or non-fatal myocardial infarction.

Then, you can see the idea here. As the calcium score becomes greater, there is a greater probability that somewhere in the coronary artery tree, there is a significant stenosis, and studies using stress MRI have shown that once we get to a calcium score over 100, and certainly over 400, somewhere in the left ventricular myocardium there is a reduction in myocardial blood flow, abbreviated here MBF.

That is a general framework to understand the data that we are going to show with respect to coronary artery calcification.

[Slide.]

The prevalence of coronary artery calcification, as you can see here, varies according to the general population and certainly with respect to the chronic kidney disease stages.

Now, here is a study in the general population where the mean age is 44. In these other studies, and these are different populations represented in these bar graphs, the mean ages are greater.

Calcium scores go up with age, that has been clearly shown, but there is a marked increase in the prevalence of calcification in the coronary arteries, and all the studies agree on this, long before the patients end up on dialysis.

So, it is making the case that we believe the imaging studies are supporting the biologic rationale that Dr. Hruska has gone over, that this process is active as a part of chronic kidney disease-mineral and bone disorder.

[Slide.]

Now, there have been 14 different studies that have evaluated the burden of calcification in patients with chronic kidney disease, and the majority of these have been patients on dialysis, but have clearly linked the burden of calcification in the human body with mortality.

In this study, this is an ultrasound study where calcification is looked for in the common carotid, the aorta, the iliofemoral, and the popliteal arteries, and

patients are given a severity score based on the overall burden of calcification in the body.

The outcomes are clear. Over the long haul, on dialysis, patients that have no calcification to begin with have an excellent survival. There is almost no other group that we can identify in patients in the dialysis population that will live this long and be free of morbidity as the group that has no calcification to start the dialysis process.

As you can see here, patients who have calcification through multiple sites in the human body have a much worsened survival.

Now, let's be fair to the data. These patients here are younger and the patients who are more heavily calcified throughout their vasculature are older. There is a lower prevalence of established cardiovascular disease to start with, and in this group of patients, these patients are already on dialysis, and the dialysis vintage, that is, the duration of dialysis differs.

[Slide.]

However, in this study, patients are new to dialysis, so this is a randomized clinical trial where

patients are followed over time, they are all new to dialysis, and they are stratified by their baseline coronary artery calcium score at the start of the trial.

You can see here the same principle. Those individuals who had a calcium score of zero, had an outstanding survival over the five years on dialysis compared to their counterparts that would have significant coronary artery calcification.

As I have stated, this is something that we found very solid in the medical literature, this link between the burden of coronary calcification, the burden of atherosclerosis in survival in patients with significant chronic kidney disease.

[Slide.]

Now, in patients before dialysis, there are a variety of studies to mention that have evaluated chronic kidney disease in the various stages before dialysis and made comparisons with respect to the presence of vascular calcification and have measured serum phosphorus.

Let me just state at the outset not all of these studies are entirely consistent because of phosphorus, PTH, and the regulation and the suppression of phosphorus until

relatively late in the process of CKD-MBD, but what I will show you I think is a fair representation of what exists in the literature.

That is, as compared to those with normal renal function at baseline, patients with chronic kidney disease, this is Stages 3 through 5, not on dialysis, have a much higher coronary artery calcium score. It makes sense, because these patients, through the stages of CKD, have had an accrual of calcium to a greater degree and probably at a faster rate.

[Slide.]

At 2 years, the calcium score is even greater, and you can see here the annualized progression--that is mean coronary artery calcium score divided by the baseline--is greater than those with normal renal function in this observational study.

[Slide.]

In terms of the severity of coronary artery calcification, as they progress in terms of chronic kidney disease, not only is the prevalence greater, as I have already shown you, but the severity, the proportion of individuals who have high scores, scores over 400, where we

would expect them to be in a risk zone for cardiovascular events.

[Slide.]

Now, some studies have linked phosphorus to the degree of calcification, and in this study, patients who had a calcium score over 400, on average had a higher mean phosphorus over time, but I have to remark, 60 percent of patients in both groups were on phosphate binders in this study, so the elevation in phosphorus really represents a loss of control or even the inability in some circumstances in chronic kidney disease for the phosphate binders to bring their phosphorus level down.

Now, both of these phosphorus levels would be in the range that has been suggested by the guidelines' experts, but I think does point to the biologic connection, the clinical connection between phosphorus and coronary artery calcification.

[Slide.]

Now, intriguingly, recent studies have shown that the data on phosphorus also relate to the general population, and this is in patients who have basically preserved renal function, so let's go over this.

[Slide.]

This is the Framingham Offspring Study. These are patients in their young 40s. The estimated GFR across these ranges here is over 100. It is 108 here and it is 117 here, and you can see the adjusted hazard ratio for cardiovascular disease, a standard Framingham defined endpoint is, in a graded fashion, increased for those individuals with the higher mean phosphorus at baseline.

What the authors speculate is that this probably represents, not chronic kidney disease, but represents an interaction between genetic--there are genetic polymorphisms in several of the factors that Dr. Hruska showed and serum phosphorus levels in the normal population--probably an interaction between genetics and diet.

The American diet has steadily progressed in terms of its phosphate intake primarily because of the influx in the last two decades of processed food. So, it is intriguing data in the general population to suggest that phosphorus is somehow related to cardiovascular disease.

[Slide.]

Now, let's go to the clinical trial. This is the CARE trial of statins in patients with established coronary

artery disease followed over time, and in this analysis, they measured serum phosphorus at baseline.

You can see the groupings here. This is phosphorus through the normal range, and in this example, the mean age is in the high 50s. The estimated GFRs are pretty similar, 68 through 72 in the groupings.

You can see the mean phosphorus levels below the estimated GFR, but the same epidemiologic concept shown through a range of normal phosphorus levels, you can see a graded increased adjusted hazard ratio for all of these meaningful endpoints, coronary death or non-fatal MI, fatal or non-fatal MI.

Both of these, by the way, were secondary endpoints in the CARE trial, and then new heart failure. Patients with prior heart failure were excluded from this study, so this is new heart failure, which was a tertiary endpoint.

Let me state in the CARE study, there was no cutoff for creatinine. The only exclusion criteria in this trial was nephrotic syndrome, or based on the judgment of the investigators, a severe kidney disease.

This is another look, and I think fairly

supportive of what had been shown in the Framingham data, that phosphorus probably not as a manifestation of chronic kidney disease in phosphorus retention, but probably more of a manifestation of a gene environment interaction, may be playing a role in cardiovascular outcomes. This is a relatively new idea in terms of the pathogenesis of atherosclerosis, and I think certainly intriguing.

[Slide.]

Now, in a large study in the Pacific Northwest, in the Veterans Administration system, 6,730 patients were screened based on their serum creatinine, so a man with a creatinine over 1.5 in this VA system, or a woman with a creatinine greater than 1.2, was included in this analysis.

The relationship between the risk of incident myocardial infarction or the combined endpoint of death or non-fatal MI--and these were defined by ICD codes in this administrative database--were evaluated and adjusted for all the baseline factors.

All the hazard ratios I have shown you so far are adjusted, and they are certainly adjusted for baseline renal function, the estimated GFR, age, diabetes, all the usual confounders that we recognize in cardiovascular

epidemiology, but finding the relationship between an elevation in serum phosphorus, now, this is the serum phosphorus out of the normal range, greater than 4.6, and the risk of incident cardiovascular events followed over time through this administrative database.

[Slide.]

Well, the coronary arteries are not the only part of the heart that can become calcified. There is one study evaluating the calcium content that can accrue within the myocardium.

It was done using an energy-subtraction radiography technique that measures the sum total calcium content--ctually, both in the heart in lungs--so this represents myocardium, which is the greatest mass of the heart, valves and coronary arteries, in 43 patients undergoing dialysis, 32 controls, and nine patients with advanced cardiomyopathy, but with normal renal function.

What we have shown is that the dialysis patients had the greatest myocardial calcium content compared to controls, about a 1.5 fold increase.

There was an inverse linear association between ejection fraction and the myocardial calcium content, and

the multivariable regression showed a strong positive correlation between myocardial calcium content, the calcium-phosphorus product, and the degree of vascular calcification in patients on dialysis.

The ejection fraction was associated with the calcium content, as well as the lung content in the calcium-phosphorus product.

This is the only study of its type, but it does suggest, at least not invasively, require confirmation that calcium could accrue within the left ventricular myocardium and may be part of the mechanistic explanation of how this mineral and bone disorder could be related to incident heart failure besides the standard understood mechanism of the contribution of coronary ischemia.

[Slide.]

Well, the coronary arteries, the myocardium, and also the valves can become calcified, and I think this is where the data in the cardiovascular literature is pretty strong.

[Slide.]

This is a standard echocardiographic depiction of aortic valve sclerosis, as shown here in Panel A, mitral

annular calcification in Panel B, and then another look at the aortic valve in cross-section in Panel C.

The nephrologists and cardiologists will recognize these are very common lesions in patients with chronic kidney disease, and extraordinarily common in patients on dialysis.

[Slide.]

So, as a general summary of the valvular literature, chronic kidney disease patients, approximately 25 percent when studied will have one form of the valvular calcification and about 50 percent in dialysis patients.

Valvular calcification and vascular calcification, when evaluated in the same patient populations, have been strongly interrelated.

All the dialysis studies that I was able to find and published in a review paper a few years ago have found associations between the phosphorus, calcium and calcium-phosphorus products in the dialysis population. When looked at, the valvular calcification has been related to all-cause mortality.

[Slide.]

Here are data from Framingham, a well-understood

epidemiologic data set demonstrating in patients with chronic kidney disease compared to those without chronic kidney disease have much higher rates, as I have mentioned, of mitral annular calcification, aortic valve sclerosis, aortic annular calcification, and at least one of the two.

The point prevalences range, but around about most, and we could look at a variety of NIH-sponsored epidemiologic studies, a West Coast community-based study, the Heart and Soul Study, all show the point prevalences are about the same for those patients with chronic kidney disease, much higher than the general population.

[Slide.]

When looked at, the link between mineral and bone metabolism and valvular calcification has been shown, and in this case, a measured inhibitor of the calcification process, a putative inhibitor, fetuin-A, was related to lower levels of prevalence of valvular calcification.

So, the biologic diagrams that you have been seeing showing transformation of a vascular smooth muscle cell basically into an osteoblastic-like cell, those same types of diagrams, same types of basic studies, apply to the myofibroblast, which is the vascular smooth muscle cell-like

component that exists in the cardiac valves.

[Slide.]

Now, Dr. Stockbridge mentioned this notion of fluctuations in terms of potassium and sodium and how could this possibly relate, and I do have a comment that addresses that with respect to arrhythmias.

[Slide.]

Now, ventricular tachycardia, ventricular fibrillation, asystole, atrial fibrillation, heart block, these are all roughly 2 to 3 to 4 times higher in the chronic kidney disease population than in the general population.

Having said that, the case reports of cardiac arrest attributed to severe acute or progressive chronic hyperphosphatemia are exactly that.

They are case reports and they are rare, so we don't think that phosphorus is itself arrhythmogenic or fluctuations in phosphorus, at least what we can see in the literature, and the mechanisms by which these arrhythmias are higher in this population are probably through the greater degrees of structural heart disease that occur in these patients.

Now, lastly, all-cause mortality, and I want to show you what exists with respect to all-cause mortality and how that relates to serum phosphorus.

[Slide.]

So, we will go back to the CARE trial. In the CARE trial, the adjusted hazard ratio for all-cause mortality was again in a graded fashion higher for higher phosphorus levels through the normal range.

So, this relationship between the non-fatal cardiovascular events and all-cause mortality was demonstrated. The same thing was demonstrated in the Veterans Administration study, all-cause mortality higher for basically the 7 percent of individuals where the phosphorus levels were actually out of the normal range.

I think these are some of the data that are weighing on individuals in the guidelines panels in terms of making the best reasonable recommendations where phosphorus ought to be in patients with chronic kidney disease.

Now, in the dialysis population, the risk relationships and the types of odds ratios or measures of association that you will see are greater.

[Slide.]

Now, in this population, and there are many data sets that look at this, basically, show a slightly U-shaped relationship, so very low levels of serum phosphorus have been related to protein, calorie malnutrition, and this is thought to probably explain any type of elevation down in the low range.

But in the high range, it represents very difficult-to-treat hyperphosphatemia. The vast majority of individuals in all of these dialysis data sets are on phosphate binders, so this represents the sum total of the difficulty to treat this patient population, patient compliance, as well as potentially dietary effects.

But the relationship to the relative risk of all-cause mortality, adjusted for almost all factors that are known and related to mortality in the dialysis population, I think is very strong.

[Slide.]

When we try to relate this to patients just before they go on to dialysis--because part of this discussion is should we generalize the treatment of hyperphosphatemia just back before patients go on dialysis, to these very advanced stages of chronic kidney disease--this study is relevant,

and it is the PREPARE study.

It is in patients--they recruited patients who they expected to go on dialysis within a year, and so the estimated GFRs are all below 30. In fact, the mean estimated GFR in this study is below 20.

For each mg/dL increase in serum phosphorus, there was a 25 percent increased risk of unadjusted mortality and a 62 percent increased risk for the adjusted mortality, so the epidemiologists in the room will recognize this phenomenon.

The only way the unadjusted risk can be lower than the adjusted risk is that there must have been a negative confounder, and there was in this study, something that related to high phosphorus, but actually made that mortality rate lower, and that was actually individuals who were younger in this data set with non-diabetic kidney disease, had higher levels of phosphorus, and that is just how the data are.

So, when adjusted for age and for the cause of kidney disease, the independent relationship between phosphorus and all-cause mortality is elevated and significant.

Over the short duration of this study, 30 out of the 448 patients died and 37 percent were related to cardiovascular disease, and I think this does--this clinical study, and just an observation, highlights to some degree the urgency that I think Kerry Willis and others have put in their presentations with respect to the treatment of these patients just before they go on dialysis.

[Slide.]

So, to finish and conclude, hyperphosphatemia is a component of chronic kidney disease-mineral and bone disorder and is associated with amplified atherosclerotic calcification. That is these higher coronary artery calcium scores.

Myocardial and valvular calcification, arrhythmias probably mediated through structural heart disease, and not actually the fluctuations of phosphorus levels themselves, the development of heart failure, whether that is via worsening cardiac ischemia or potentially structural involvement of the left ventricle and cardiovascular death.

Hyperphosphatemia is independently associated with all-cause mortality and, for these and other health reasons, the guidelines and expert panels have recommended treatment

of hyperphosphatemia in the CKD-MBD, in both the pre- and current dialysis populations, and the treatment targets in the pre-dialysis patients are to try to bring that phosphorus level down into the normal range.

For most labs, that is 2.5 to 4.6, and recognizing that an elevation in parathyroid hormone is also a treatment target, so we use phosphate binders in that group, the parathyroid hormone levels come down, and really what we are talking about today is patients that are very close to ultimately going on dialysis.

They are in a very high risk state, and the scientific exercise in my view is one of generalization, so hopefully, I have helped in terms of the thought process in terms of how do we generalize from the dialysis population, an established treatment, on to patients in the pre-dialysis stages of chronic kidney disease.

Thank you.

I will introduce Dr. David Bushinsky next.

Benefits and Risks of Phosphate Binder Therapy in Pre-Dialysis Patients

DR. BUSHINSKY: Good morning and thank you for allowing me to discuss the benefits and risks of phosphate

binder therapy in pre-dialysis patients.

[Slide.]

Over the next 30 minutes, we will discuss that serum phosphorus increases as patients lose kidney function, that patients with chronic kidney disease have increased vascular calcification and mortality.

We will discuss the potential risks of phosphate binder therapy, the potential benefit of phosphate binder therapy, and finally, we will discuss survey data on phosphate binder use by nephrologists already in CKD patients.

[Slide.]

First, that serum phosphorus increases as patients lose their kidney function.

[Slide.]

In a publication in the Journal of the American Society of Nephrology, Kestenbaum and colleagues have shown that serum phosphorus levels increase with decreased renal function.

In a retrospective cohort study conducted in eight Veterans Administration medical centers located in the Pacific Northwest, the authors analyzed over 3,000 patients,

made a serum phosphate measurement, two measurements of serum creatinine at least six months apart, and a measure of weight to calculate the estimated creatinine clearance.

They plot mean serum phosphorus levels as a function of baseline estimated creatinine clearance using the Cockcroft-Gault formula.

The black line represents the smooth mean serum phosphorus levels relative to estimated creatinine clearance. The gray shaded areas contain phosphorus measurements that are in the highest and lowest quintiles for estimated creatinine clearance. The white area contains serums phosphorus measurements within the 3 middle quintiles relative to estimated creatinine clearance.

On average, serum phosphate levels increased marginally with declining estimated creatinine clearance until creatinine clearance dropped below approximately 40 mL/min. At this point the mean serum phosphorus levels increased rapidly as kidney function declined.

The request before the panel today is to expand the label for the phosphate binders, which are already approved for use in dialysis patients, to those patients who are in Stage 4 or 5 CKD, but not yet on dialysis.

These patients have a creatinine clearance of less than 29 mL/min and who have a serum phosphorus level greater than 4.6 mg/dL, which is the upper limit of serum phosphorus recommended by the KDOQI for patients with this range of kidney function.

Note in the green outlined box there are not many patients with a phosphorus in this range, but for these patients, having a phosphorus binder will allow them to achieve a serum phosphate within the range suggested by the National Kidney Foundation and within the range of normal for most laboratories.

[Slide.]

Let us review why serum phosphorus levels increase as kidneys fail. In a publication in NDT, Carver and colleagues described mineral metabolism parameters in a cross-sectional study of 1,836 patients attending outpatient nephrology clinics.

In the upper left graph, they demonstrated that from CKD Stage 1 to CKD Stage 5, there is a significant increase in serum phosphorus, similar to the increase that was shown in the last slide.

Through mechanisms that have been described

previously by Dr. Hruska, serum levels of intact parathyroid hormone, shown on the graph in the upper right, also increased with declining renal function.

As you know, PTH is phosphaturic; that is, it leads to an increase in the fraction of filtered phosphorus that is excreted by the kidney. Others have shown that additional phosphaturic factors, such as fibroblast growth factor 23, also increase proportionally with the decline in renal function.

In this study, some of the patients had measurements of the fractional excretion in phosphorus. Indeed, as can be seen in the graph on the lower left, the fractional excretion of phosphorus increased as kidney function deteriorated.

In spite of the increase in the fractional excretion of filtered phosphorus, 24-hour urine phosphorus excretion, as show in the lower right graph, was actually lower in the patients with worse kidney function.

The fall in urine phosphorus, in spite of an increase in parathyroid hormone and FGF 23, with worsening kidney function, is clearly due to less phosphorus being filtered by the failing glomerulus. Even though the tubule

is excreting a greater proportion of the filtered phosphorus, the decrease in the amount of phosphorus that is filtered is causing a fall in the urine phosphorus.

As patients with greater stages of CKD continue to absorb intestinal phosphorus, whose absorption is poorly regulated and generally greater than 60 percent of intake, their inability to excrete this absorbed phosphorus invariably leads to phosphorus retention.

For example, in patients with CKD-1, absorption and excretion of phosphorus are in balance, however, with progressive stages of chronic kidney disease, there is less phosphorus excretion in spite of continued gastrointestinal phosphorus absorption.

Once the needs of the bone are met, the phosphorus, which cannot be excreted by the failing kidneys, has no place else to go, and must deposit in soft tissues including the vasculature.

[Slide.]

Our patients with chronic kidney disease have the traditional risk factors for cardiovascular disease. They tend to be older, have hypertension and diabetes, the leading causes of chronic kidney disease in America.

Unfortunately, many of them continue to smoke and have increased LDL cholesterol and obesity. A family history of cardiovascular disease is oftentimes present, as well as LVH.

In addition, our CKD patients have non-traditional cardiovascular risk markers. Block, Young and others have shown in retrospective analyses of large databases of dialysis patients that increased serum phosphorus, increased calcium, increased calcium x phosphorus product, and elevated PTH are each independently associated with an increased relative risk of death.

However, increased phosphorus has by far the greatest impact on mortality, and today we will concentrate on this factor.

[Slide.]

CKD patients have increased vascular calcification and mortality.

[Slide.]

In a publication in the New England Journal of Medicine, Go and colleagues have shown that there is increased risk of death, cardiovascular events, and hospitalization as renal function declines.

They estimated the glomerular filtration rate among over 1.1 million adults in Kaiser Permanente of Northern California who had a serum creatinine measured between 1996 and 2000, and had not undergone dialysis or transplantation.

The mean age was 52 years and the median follow-up was 2.8 years. There were approximately 51,000 deaths, 138,000 cardiovascular events, and 555,000 hospitalizations.

The age standardized risk of death from any cause, as seen on the lefthand graph, increased as the estimated GFR declined, ranging from a modest increase in risk with an estimated GFR of 30 to 44 mL/min to a 14-fold increase in risk of death with an estimated GFR of less than 15 mL/min.

The age standardized risk of any cardiovascular event also increased as the estimated GFR decreased, again from a modest increase in risk with an estimated GFR of 30 to 44, to a striking 36-fold increase in risk with an estimated GFR of less than 15.

Finally, the age standardized risk of hospitalization also increased markedly as seen on the righthand panel. It is clear that as kidney function declines, there is a marked increase in the rate of death

from any cause, a marked increase in the rate of cardiovascular events, and a marked increase in the rate of hospitalizations. Thus, our CKD patients are ill and clearly dying at an accelerated rate.

[Slide.]

In a publication in Archives of Internal Medicine, Keith and colleagues have shown that death is actually a more common outcome than dialysis or transplantation in patients with chronic kidney disease.

In an analysis of patients again from Kaiser Permanente, they identified almost 28,000 patients with an estimated GFR of less than 90 mL/min on two separate occasions. They followed these patients for 5 years.

With Stage 2 CKD, shown on the left, 1.1 percent of patients subsequently needed renal replacement therapy while almost 20 percent died. With Stage 3 CKD, 1.3 percent of patients subsequently needed renal replacement therapy, while 24 percent died.

With Stage 4 CKD, almost 20 percent of patients subsequently needed renal replacement therapy while 45.5 percent, almost half of the patients, died.

Thus, our patients with CKD have a far, far

greater chance of dying than reaching dialysis or transplantation.

[Slide.]

In a retrospective cohort previously described, Kestenbaum and colleagues did Kaplan-Meier survival plots by serum phosphorus relative to estimated creatinine clearance.

The normal serum phosphorus group in yellow refers to patients with phosphorus measurements in the middle three quintiles relative to estimated creatinine clearance.

The high phosphorus group in orange, and the low phosphorus group in blue, refer to patients with phosphorus measurements in the highest and lowest quintiles respectively relative to estimated creatinine clearance.

They found that Kaplan-Meier estimates of survival were significantly different among the patients with relative phosphorus measurements that were in the highest and lowest quintile predicted by their estimated creatinine clearance.

After 3 years of follow-up, survival was 72.2 percent among patients in the lowest phosphate quintile, 67 percent in patients in the middle 3 quintiles, and only 54.6 percent among patients in the highest phosphorus quintile

relative to estimated GFR.

After adjustment for 8 factors including renal function, serum phosphorus was associated with a 23 percent increased risk of death, an elevated serum phosphorus was associated with a 23 percent increased risk of death.

Thus, a higher serum phosphorus is associated strongly with increased mortality in CKD patients not on dialysis, the very patients that we are seeking approval to treat.

[Slide.]

Sharon Moe and colleagues wrote that an evaluation of CKD-MBD patients should involve measurement of parathyroid hormone, calcium, phosphorus, alkaline phosphatase, which is an index of osteoblastic bone formation, bicarbonate, an index of acidemia, and imaging for soft tissue calcification.

The increased emphasis on soft tissue calcification is apparent by these recommendations.

[Slide.]

As you have heard, the National Kidney Foundation gathered groups of experts to make recommendations pertaining to various aspects of care for patients with

kidney disease.

They recommended that the target phosphorus level in early stages of CKD be even lower, 4.6 mg/dL, than recommended for patients on dialysis, which were allowed to go up to 5.5 mg/dL.

The National Kidney Foundation recommends that phosphate binders be used in conjunction with dietary phosphate restriction to achieve these levels.

The goal of our presentation is to expand the use of phosphate binders to Stage 4 CKD consistent with the recommendations of the NKF and, as we will see, consistent with what many nephrologists are currently doing in practice.

[Slide.]

Potential risks of phosphate binder therapy.

[Slide.]

The most common adverse events with phosphate binders are all related to the gastrointestinal tract. Fosrenol, which is lanthanum carbonate, PhosLo, which is calcium acetate, and Renagel, which is sevelamer hydrochloride, are all listed on this table.

As indicated, the Fosrenol and Renagel comes from

their respective package inserts, and the PhosLo data is on file with the manufacturer. Any episode of nausea, vomiting, diarrhea, or constipation that occurred during administration of the medication is, of course, listed.

In general, the GI side effects are mild and resolve either spontaneously or after discontinuing or reducing the amount of the medication.

[Slide.]

Phosphate binders reduce intestinal phosphorus absorption and lower the level of serum phosphorus. However, the incidence of overt hyperphosphatemia is less than 1 percent in all studies of each of the compounds.

As a clinician, I can say that hyperphosphatemia is easily managed by reducing the dose of the medication or discontinuing it all together.

[Slide.]

The drug-drug interactions listed on the respective package inserts for each of the medications are shown on this table. Fosrenol has no effect on absorption of digoxin, metoprolol, or warfarin. Compounds known to interact with antacids should not be taken within 2 hours of dosing.

Renagel has no interaction with digoxin, metoprolol, warfarin, or iron. There is a 50 percent decrease in the area under the curve for ciprofloxacin. It said if a drug may have a clinically significant effect, it should be administered at least 1 hour before or 3 hours after sevelamer.

PhosLo affects bioavailability of tetracycline.

[Slide.]

So, what are the potential benefits of phosphate binder therapy?

[Slide.]

Perhaps we can attenuate vascular calcification, perhaps we can delay the decline of renal function, and reduce complications related to CKD-MBD.

[Slide.]

There have been a number of studies by a number of investigators on the efficacy of phosphate binders in patients with chronic kidney disease who are not yet on dialysis.

Many of these studies were performed with calcium carbonate, an over-the-counter medication that is often used as a calcium supplement. Calcium carbonate is not approved

for use in dialysis patients although it appears to be widely used perhaps due to its very low cost. Let us summarize these studies.

[Slide.]

In general, and as expected, each of the phosphate binders resulted in a lowering of serum phosphorus in CKD patients not on dialysis.

[Slide.]

As you have seen, the prevalence of coronary calcification in CKD patients not on dialysis ranges from 25 percent to a reported 93 percent. In general, non-diabetics have lower rates of coronary calcification than diabetics. Studies in non-diabetics range from 20 to 54, and in diabetics from 54 to 93.

We have seen that whether the calcification is in the media or in the intima or a combination of the two, the risk of death is far higher than in patients with no observed calcification.

[Slide.]

In a recent study in Kidney International, Block and colleagues have shown that baseline coronary artery calcification score is a significant predictor of mortality

in incident patients to dialysis.

These investigators assessed all-cause mortality in 127 patients new to hemodialysis after a median follow-up of 44 months from randomization to either calcium-containing phosphate binder or to sevelamer.

Baseline coronary artery calcification score was a significant predictor of mortality even after adjustment for age, race, gender, and diabetes with increased mortality proportion to baseline score.

With a coronary artery calcification score of greater than 400, the survival is abysmal. At 48 months, approximately, 50 percent of patients are alive, and at 60 months, only about 25 percent of patients survived.

As you heard from the National Kidney Foundation earlier this morning, this poor survival is far worse than that of many malignancies.

[Slide.]

In a recent study in Kidney International, Russo and colleagues evaluated the effect of calcium carbonate or sevelamer treatment on the progression of calcification in 90 pre-dialysis patients.

Inclusion criteria were stable, serum calcium,