question about doing trials in this patient population. Since Renagel was approved in 1998, and this also addressed a question that Dr. Neylan asked earlier, you know, we have conducted a series of prospective randomized trials in the dialysis population.

We have looked at, for example, the treat-to-goal story that was published in 2002 in the prevalent dialysis population at the progression of calicification between sevelamer and active comparator, 200 patients for a period of one year.

We also had looked at the same situation in a study that Dr. Block published in 2005 with a follow-up in 2007. The first part of the study was to follow 18 months looking at the progression of cardiovascular calcification in incident dialysis patients, patients that were just new to dialysis. This is some of the data that Dr. Bushinsky presented just recently.

Additionally, those patients were followed up for up to 44 months from the start of treatment, and they were followed up in terms of the mortality based on the coronary calcification score and also mortality based on the binder choice.

Just recently, just published in Kidney International in August of 2007, the largest outcome trial that has been conducted in the dialysis population that actually we did, looking at basically 2,100 patients, randomized to either sevelamer or comparator, look at all-cause mortality.

The median follow-up of the patients in that trial were 45 months. Unfortunately, we followed the patients for 45 months, 2,100 patients and we lost approximately 46 percent of the patients to follow-up. The results, you know, the primary outcome is highly different between the treatments.

I just want to mention that to you, just kind of like show you some of the difficulties that we have had in terms of conducting this trial. This is not that we don't necessarily want to do any further trials.

I think that what we are asking for is like there is a need to treat these patients now, and I think that as a company, we certainly will be in a position to discuss what other trials are needed in the future.

DR. TEERLINK: I think it was droll that you guys felt that it was okay to have the NIH sponsor these trials

for you. I thought that was magnanimous of you.

[Laughter.]

DR. HARRINGTON: More questions?

DR. MALLUCHE: I would just like to comment on the same point. Since he is throwing in the NIH, I would be very negative that the NIH will ever fund these studies. It is extremely difficult.

DR. TEERLINK: I agree, nor do I think it necessary that they should.

DR. MALLUCHE: That's on the side, just a personal gripe.

I agree with you these studies should be done, and they can be done. They are difficult, but they can be done. But I think that, again, we are talking about the patients here with a GFR between 60 all the way down to maybe 25 or so where these abnormalities really take place and develop, and as you have heard, if you go from Stage 3 to 4, you come from 8 million people down to 400,000, because they all die.

This is a group of patients that needs to be treated, deserves to be treated, but studies need to be done, and according to our data, phosphorus control is one of the mainstays in the prevention of the cardiovascular

death in these patients. I fully agree with you.

But then there is another entity. Those are the patients who make it, the lucky ones, those 400,000 that survive, and the percentage of those who become then clearly hyperphosphatemic, really, there is very little that distinguishes these patients from the dialysis population in whom hyperphosphatemia is accepted as an entity that deserves to be treated with phosphorus binder.

So, my personal idea of all this, what we are trying to accomplish here is to give those poor patients who are awaiting dialysis the same chance to be treated the same way as the dialysis patients, because they have a tremendous drawback. The dialysis patients have 3 out of 7 days, the help from the dialysis phosphorus that is being removed.

So, 45 percent of the time, the phosphorus in these patients being removed. The patients with 25 percent of kidney function have less ability to get rid of the phosphorus, and only for those I think we are asking here to extend the label.

DR. HARRINGTON: Are you good, John? We will come back to you, because I want to give other people a chance.

Jeff, you had your microphone raised, and then I

want to get over to this side of the table.

DR. KOPP: I will just make a point briefly, that we have been told that hyperphosphatemia tends to begin between a GFR of 60 and 30 or 25, and the point I would like to make is that the rate of progression in a diabetic, shall we say, with good blood pressure control or ACE or ARB is now about 5 mL/min/year.

So, if somebody develops hyperphosphatemia at 30, then, potentially, they have three years to get from 30 to 15, at which point in the diabetic dialysis would begin, but if it begins at 40, they have five years, and if they are progressing slower, even longer, so I think multi-year therapy is a distinct possibility if approval is given up to a GFR of 60.

DR. HARRINGTON: Good point. Lynn, and then we are going to come to Dr. Weise and go down.

DR. STEVENSON: I think it is clear that we are not going to be able to assemble a base of data to convince us that the phosphate binders affect cardiovascular endpoints although there is some plausible rationale.

The mineral and bone disease issue, frankly, I am a little surprised by the lack of data on that. I had

assumed from the guidelines, in fact, that this was pretty clear, that if you treat with phosphate binders, you decrease the mineral and bone disease in the dialysis patients.

If you do, then, I think it is a relatively reasonable extension to say so we should start that just a little bit before dialysis. However, what I would like to hear from the groups is what is the data that at any time, including dialysis, that these phosphate binders actually affect the mineral and bone disease.

DR. HARRINGTON: I want to clarify. You are referring to the specific clinical entities of the diseases.

DR. STEVENSON: Exactly, things that we can measure that say that the mineral and bone disease is better with phosphate binders, which I had assumed it was from the guidelines, but I actually haven't heard that.

DR. HARRINGTON: You mean things like osteoporosis, fractures, et cetera, not something in your blood.

DR. STEVENSON: Yes.

DR. HRUSKA: This issue has come up and is extremely poignant. The basis for the approval is a

reduction in PTH levels, so there were two factors that went into approval, a reduction in phosphorus and a reduction in PTH.

When actually you begin to think about it, nothing is approved for renal osteodystrophy. Actually, having just made this statement, I now realize that I am wrong. Dr. Malluche will tell me that calcitriol was approved for renal osteodystrophy.

But the difficulty of actually doing a renal osteodystrophy trial, you know, it is doable, but it has not been done. The problem that we have with renal osteodystrophy is that it is characterized completely by histomorphometry, a bone biopsy, and we don't do bone biopsies these days.

So, exactly how are we to follow renal osteodystrophy in the CKD-MBD? In fact, we are in the process of having to recharacterize that disease or that problem simply because it is not going to be feasible for us to actually now start doing many more biopsies, so what KDIGO and KDOQI have done here is increase the pressure on the clinician to actually follow accurately the skeletal status of the patient.

Basically, we are not able to do that now because we never have done trials on renal osteodystrophy specifically. The trials are simply as I have stated in the second slide, decrease serum phosphorus and treat secondary hyperparathyroidism.

[Slide.]

Secondary hyperparathyroidism was thought to represent renal osteodystrophy. What we know now is that inherent in renal osteodystrophy is a low turnover disorder that is directly caused by the kidney disease. So, we actually need much better means of actually focusing on the renal osteodystrophy, and CKD-MBD finds this woefully deficient in scientific data.

DR. HARRINGTON: Dr. Weise, let's move over. This side of the table we have ignored for a while, so we will start with you and work our way down.

DR. SHURIN: I would like to follow up on some of the previous comments. I am very concerned about the lack of data. I am in Heart, Lung, and Blood, and we support a lot of studies on the cardiovascular implications of disorders of other systems including diabetes, stroke, and chronic kidney disease.

I am not aware of any serious attempt to look at either calcium scores or phosphate as part of the ongoing studies on cardiovascular disease and kidney disease. Now, my ascertainment may be incomplete and we only fund applications that we have received, but we run very, very complex studies.

We have got the ACCORD study going on right now, which has got 10,400 people with diabetes looking at intensive versus standard control of glucose, blood pressure, and cholesterol in terms of cardiovascular endpoints.

I don't see this as an undoable question at all from the standpoint of clinical trial, and I guess my concern about it is that if we accept a probably questionable surrogate outcome or surrogate measure as the outcome for this, is that we may never really have the opportunity to gather these data.

The proposal makes a huge amount of sense given that no study is actively ongoing, that it will take 5 or 10 years to get any data. It doesn't seem to be immediately coming down the pike, and I guess what I would really like to hear from our industry colleagues is if the labeling were

changed, how would you propose to look at some of these outcome data, what could we expect in postsurveillance marketing, because that actually isn't the NIH's job.

That would be something that we would rely on you to do and also to sort of make the point that I think Peter commented there would be multiple sponsors or the NIH. It isn't going to be multiple sponsors or the NIH.

If the NIH is involved, it will be with other multiple sponsors, but I would really like to hear what you are proposing concretely in terms of the postmarketing survey, that it will mean that five years from now when we hit 2012, are we going to be a little bit better off than we are right now.

MS. WILLIAMSON: Thank you for that question. It brings us back I think to the basis of what we are trying to accomplish here today.

All of the sponsors have demonstrated, and again we have just said this afternoon that we do continue to study these drugs both in the dialysis and pre-dialysis population, and we are interested in continuing to gather the data on long-term outcomes and safety including in the pre-dialysis patient population.

We welcome the opportunity to discuss long term how we collected those data, but we are concerned with the fact that these patients need, as you said, they need to be treated sooner rather than later, because they don't make it to the point where they actually get onto dialysis.

So, we are trying to come up with a reasonable approach that allows for the evidence that exists while not perfect, to allow for these patients to be treated. It is not a huge number of patients by any stretch of the imagination, but it is a very important segment of the patient population.

The use of phosphate binders in the dialysis population has become a routine standard of care, and no one is suggesting otherwise at this point. We are simply asking that those Stage 4 patients that are hyperphosphatemic be allowed to be treated on label and be informed.

We can talk about the potential for long-term follow-up. We don't have access to these patients postmarketing right now, because we are not allowed to speak to any of the physicians that may be treating these patients.

Ray, would you like to add to that?

DR. PRATT: Yes. I think that again to get to the questions, which Drs. Stockbridge and Temple have brought together, is that, you know, we are asking for the hyperphosphatemic link here.

We have seen some very intriguing ideas in terms of when these processes start, and I think an important question from the Committee here is, you know, what type of outcomes would be acceptable and when to start in terms of being able to work with the FDA to achieve the proper goals.

Nobody wants to do a study which we think may actually be failed, not because the drug is ineffective or something else, but because the process that you are looking at has taken so long to get there, and you may not reverse it as quickly as you would like to see.

I mean I think Dr. Hruska's data in terms of reversal of calcification in rats and mice is intriguing, have we seen that in human studies to date, and so I guess the question comes in when would be appropriate to start, and we do need to get some guidance from the Committee as to what types of outcomes could be potentially done.

DR. HARRINGTON: Dr. Shurin.

DR. SHURIN: We wouldn't necessarily expect that

industry per se would do the studies, would probably be collaborating with others, but both the numbers of patients I think, you know, groups where you are comparing fewer than 30 patients can't possibly achieve statistical significance is obviously of concern, the serious issue of potential drug interactions with the multiple other agents that people may be on, and sufficient follow-up to be meaningful would be absolutely essential.

Certainly, I think it would be something we would want to hear fairly strongly from you.

MS. WILLIAMSON: And the three sponsors have talked about what the possibilities might be to gather these data in a postmarketing setting.

One of the options that we have discussed--and again we would need to drill down into the specifics on how this would be conducted--would be to collect these data through some sort of a broader registry approach where we have the opportunity to actually capture a large amount of information in the postmarketing setting that we don't have the opportunity to do right now.

DR. BUSHINSKY: If I can just comment on the drug-drug interactions, it is clear that the dialysis patients

are taking the last I saw a mean of 12 medications on a daily basis including medications on dialysis and multiple times off dialysis.

They are managing quite well taking their phosphate binders and their medications. So this patient population, if anything, might be on fewer medications and should be able to manage in the same way.

DR. HARRINGTON: Well, wait a minute. What do you mean that they are doing quite well, how do you know that?

I mean I am not being silly, it is just how do you know that they are taking 12 medications, that if they weren't taking phosphate binders, they might actually be responding better to their aspirin, their statin, et cetera? You don't know that.

DR. BUSHINSKY: We don't know that.

DR. HARRINGTON: And that's the point, right? We don't know a lot of this stuff, and it sounds good, but we don't know.

DR. BUSHINSKY: Right, but we know, in fact, that they are bringing their blood pressure down with their anti-hypertensives, we know they bring their LDL down with their statins. We know these drugs are working.

Your point that they could be working better if they weren't on this is something we can't address.

DR. McCULLOUGH: Bob, before you kind of run away with that one, you would have to ask yourself do the observational data show right now, among our common cardiovascular medicines, that they have a decreased reduction just in the observational data with respect to any forms that you could go through ACE inhibitors, beta blockers, et cetera. I have done a lot of these publications, and so far everything we see in CKD, if anything, there is an amplified benefit what we see in these patients including on dialysis.

So, there is no signals of attenuation. The only areas where I think things get unstable with respect to therapeutic benefit have to do with anti-thrombotics, and not aspirin. But there could be one with clopidogrel and certainly with the heparin substances, and that probably has to do with kind of the uremia environment that influences thrombosis in the platelet.

But if you are saying, wow, these phosphate binders really blunt the impact that beta blockers can have, seen in the population, we don't see that in the

observational data. The observational data show, if anything, a magnified benefit.

DR. HARRINGTON: Susan?

DR. SHURIN: I think the clear evidence is that we don't have enough information to make a statement about that, and I don't know that I would count on a lot of these patients being on fewer medications.

Many of them have chronic kidney disease as a consequence of other organ dysfunction. I think they are going to be on a lot of medications, and I think we need to know a lot more.

DR. HARRINGTON: Dr. Weise, we will finally make it to you here.

DR. WEISE: Just a few comments. I think we are all swayed somewhat by the compelling appeal to patients needing treatment and to the thought that renal disease is a continuum and when to begin dialysis is a fairly arbitrary thing, but I think what we haven't shown is that this is the treatment that these patients need, this treatment in isolation.

It is certainly not based on evidence that has been presented today, and I find it concerning that we heard

that there are not ongoing outcome studies in the post-dialysis or the ongoing dialysis patients being done currently. It makes me skeptical that similar studies would be done after approval of this class of drugs for these indications.

It particularly worries me that if a drug becomes approved, it becomes a self-fulfilling prophecy and I think achieving equipoise in a study or a series of studies like this would be almost impossible once approval is granted, because it says that this is now the standard of therapy that should be in place, not just the standard of therapy that people have migrated towards.

DR. HARRINGTON: Go ahead.

DR. MENOYO: Thank you. I have got two points. Number one is that there are some treatments already approved for the treatment of secondary or an aspect of secondary hyperparathyroidism in the patients on Stage 3 and 4 CKD, and that is basically the vitamin D analogs, basically approval of reduction of PTH.

So, we are asking to expand the indication of phosphate binders that treat another aspect of secondary hyperparathyroidism to a Stage 4, that we are talking about

GFR less than 30, not less than 60 like another member was mentioning.

The other thing is that we actually just published an outcome study of 2,100 patients looking at all-cause mortality in the dialysis population, not in the CKD population pre-dialysis.

So, we continue to do further studies on the population that we have the indication on at the current time. As I mentioned before, we also have done other studies looking at the prospective randomized studies looking at vascular calcification in patients prevalent to dialysis and also patients incident to dialysis.

DR. HARRINGTON: Dr. Weise, did you have any more?

DR. WEISE: No.

DR. HARRINGTON: Steven?

MR. FINDLAY: Just a clarification. One of the sponsors mentioned compliance problems as one of the reasons that 60 percent of the pre-dialysis patients don't get or take a phosphate binder.

Is that because of the GI side effects? There was a glossover a little bit of the compliance problems for that 60 percent. Could there just be a little bit more

discussion of that 60 percent and why don't they get or take these medicines, and is that compliance in GI side effect problems?

DR. PRATT: I mean I think compliance, actual compliance and actual adherence to therapy, are major issues in not only the dialysis patient population, but obviously in this patient population, when you are asked to take a medicine or multiple pills with each meal that you take, you get tired of it pretty quickly I think.

One of the things I think at least in our short-term study in CKD patients, you know, intolerance or GI side effects was not a major issue. GI side effects are not a major issue in terms of dropping from our clinical studies that we have conducted.

There have been some issues in terms of the way the studies were designed, like when you are doing an active comparator study and patients can switch amongst phosphate binders ad lib, you know, for whatever reason, whether they are tired of taking them or intolerant, and then in the active arm, where you have to drop from the study because you don't have another choice to go to, you are certainly looking at a little bit higher rates there.

When we actually adjust for that, looking at patients who switch therapies because they may have been intolerant to the first standard binder they took, and going to a second, the rates become much equal, and it is about 15 percent of the patient population actually do this.

So, I think that, you know, this is a major issue that again has to be addressed, and it is important in addressing a long-term treatment trial where you want to keep people on one specific therapy for a number of years.

DR. HARRINGTON: Steven, do you have a follow-up?

MR. FINDLAY: No.

DR. HARRINGTON: Henry.

DR. BLACK: Thanks, Bob. I have a series of questions, many which have been asked already, but I want to emphasize some things.

I also think that some of the things I am hearing today sound like excuses to me. This is no more complicated a trial than we undertake all the time, and a 46 percent dropout rate over five years is not that different from things that we do. We just plan for it and build it accordingly.

Secondly, we need hard endpoints for people who

are at lower risk, and I don't think that we can get by without that. I am hesitant to give a free pass right now because I think that is what it would be.

The non-nephrologists seem to take care of a lot of these people, so guidelines aren't going to matter, and to say we need more research, you know, we always say that. Well, that is not good enough either. We do always say that, but that is five years ago, and I think we really do need this.

I think there are a lot of things that aren't done, poorly done trials that haven't shown anything, well, that is not a good excuse either, and I think right now you made a very strong case that this is a complicated disease with multiple factors, only one of which you are doing anything about. That also would be a very hard trial to interpret if other things weren't controlled for or dealt with in some way.

So, I would be very hesitant right now that I have enough information. I am not secure that we know all the drug interactions, adding additional pills to a daily regimen isn't likely to improve compliance. It is likely to make it worse.

So, I really don't know where we stand, and I am just a little bit nervous to go on with this right now. That is not a question.

DR. HARRINGTON: I was going to say that was a series of statements. Do you have any questions for the group, Henry?

DR. BLACK: No. I think the things that I wanted to ask have been addressed and I am just commenting on those.

DR. HARRINGTON: Michael.

DR. LINCOFF: Many of the previous speakers have addressed issues around this. I just want to clarify one point and then a follow-on to that.

In the dialysis or pre-dialysis population, any population of patients receiving these, is there any data that the treatment influences any endpoint other than the phosphate and the PTH levels--I mean the phosphorus, because we have heard impassioned pleas that patients need this therapy.

I believe the association between the phosphorus levels and the bad outcomes, but as we have all said, that doesn't prove causation, and it doesn't prove that changing

the phosphorus levels is going to change the outcome.

So, for any endpoint, in any population of patients, is there any prospective data, because unless I am wrong, I don't believe I have heard of any that suggests that any endpoint aside from a blood test is effective, and if that is not the case, then, I have a follow-on.

DR. BUSHINSKY: Perhaps I can review a few trials that are not double-blind, placebo-controlled trials. They are trials comparing an active comparator to, in this case, sevelamer. If I can have the first slide.

[Slide.]

This was the first study that showed--was the treat-to-goal study. It was done in prevalent dialysis patients. They were treated with either a calcium-containing phosphate binder or sevelamer.

They found that with respect to coronary artery calcification and aortic calcification, there were statistically less progression in those patients who had baseline calcification, in the patients treated with sevelamer compared to the comparator, which was calcium.

That was the first study in prevalent dialysis patients.

DR. LINCOFF: We don't have that reference. How many patients were there?

DR. BUSHINSKY: It's about 200 patients.

We need the treat-to-goal, it's about 200 patients. Yes, slide on, please.

[Slide.]

So, there was a washout period of two weeks. Patients were then randomized to sevelamer or to calcium-containing phosphate binder for 12 weeks. There was a baseline EBCT, EBCT at 26 weeks, and an EBCT at 52 weeks.

On this slide you had just seen were the results.

DR. STEVENSON: I am sorry, but might not there be some reason to think that the control arm, the active control of taking calcium might, in fact, also increase calcium?

DR. BUSHINSKY: As I started out by saying, this is not double-blind, placebo-controlled. There were two drugs, both phosphate binders. You could make that argument.

The other argument you could make, and let me make it before the cardiologists make it, is that sevelamer also lowers LDL cholesterol, and this might, in fact, be a

cholesterol effect.

Against that is that there is a 4D study published in the New England Journal with prevalent dialysis patients showing active statin therapy does not influence outcome.

The next study that we can talk about is the RIND trial, which was a similar study in incident dialysis patients.

[Slide.]

This is the RIND trial, 385 patients were screened, 148 were randomized to calcium and again to sevelamer. You can see what happened, and again the EBCTs were done.

The next slide.

[Slide.]

You can see the RIND trial, which shows the progression of calcification in those patients who again had baseline calcification, and again there was statistically less progression in those patients treated with sevelamer compared to calcium.

The same criticisms that you could make before. There was no placebo arm and sevelamer does lower LDL cholesterol. This study was followed up on this year. We

have that data.

DR. HARRINGTON: While you are looking for it, you might comment. I think the cardiologists would agree that there is an association between coronary artery calcification and clinical outcomes, I still wouldn't call coronary artery calcification a clinical event.

DR. BUSHINSKY: No, I didn't say that. I clearly said coronary artery calcification.

DR. LINCOFF: I would actually be willing to accept that coronary calcification has some predictive value. We know that is has predictive value for coronary events, and it is a measurement of a direct, it's not a surrogate, it's a measure of plaque or at least plaque presence and to some degree the advanced state of plaque.

I am willing to accept that this is certainly better than a blood test.

DR. BUSHINSKY: As a non-cardiologist, I would rather my patients have less coronary calcification than more regardless of where that calcium is.

[Slide.]

This is the best data that we have on mortality. Again, it was the study that I just showed you, just

published, showing a difference, trend of a difference between sevelamer and the active comparator. Again, it is not a double-blind, placebo-controlled study, showing less mortality.

You notice there are a few patients at five years, a few more patients at four years, again, not the perfect study. There is no placebo arm.

[Slide.]

This is the best data that we have.

Also, there is a DCOR study which was done.

The DCOR study design, multicenter, randomized, again open label, and let me just discuss the three different binders. We have one binder that must be chewed. We have another binder that can't be chewed. We have a third binder whose smell gives it away. So, it is going to be difficult, but not impossible, to certainly do the studies that you are looking for.

The other caveat that I have, seeing patients with a high phosphorus. I am basically a basic scientist. I am NIH funded. I do work in genes and cells. When I see a high phosphorus, and I see the calcification that it does in vitro, I am afraid for my patients to have that

calcification, and I would be loathe to not treat these patients.

So, I personally, and I think many of my colleagues would be loathe not to participate in the trials. I understand, we learn a lot from trials. But the evidence to me is so overwhelming. I personally would have trouble enrolling a placebo group.

[Slide.]

That said, this is the DCOR study. Primary endpoint was all-cause mortality.

[Slide.]

Secondary study endpoints you see.

If I could have the results.

[Slide.]

The first result was the all-cause mortality was not different. This started out with an enrollment of over 2,000 patients, as was said, dropped down to--you can see the numbers. There was no difference in all-cause mortality.

[Slide.]

In a pre-defined subgroup analysis, there was, in fact, a significant difference with patients greater than 65

pre-defined, there was a difference, but that is the state.

You have now seen the four studies done post-approval by these companies to try to understand what you are looking for today, but there is no perfect study.

DR. LINCOFF: I am pleased actually to see that there has been some evidence of a treatment effect with some therapy compared to control or placebo.

That implies the part of the loop that we would really like to see more data on, interfering with the phosphorus levels are actually having an effect on a clinical outcome.

Given the difficulties that you saw particularly with the enrollment and the dropout in the dialysis population, we have heard talk now of the willingness of the sponsors to conduct postmarketing studies if the indication were expanded to the pre-dialysis patients.

Do you anticipate, though, that it would be possible to do a placebo-controlled study? Again, not necessarily blinded, recognizing the limitations, but a placebo-controlled maybe with a variety or all three of the different phosphate binders as a control group, but do you think it would be practical, because I think without

randomization, just following patients, you are never going to know what--you are never going to get an answer.

DR. BUSHINSKY: I, too, understand that a randomized trial would be perfect, but if I give a calcium binder, the serum calcium goes up, and the PTH goes down, I, as a clinician, have to follow that. I know the patient is getting a calcium binder.

If I give the patient sevelamer, the LDL cholesterol goes down. I know that the patient is getting sevelamer. So, it would be very difficult for a placebo to be done while I was following the laboratory values that I have to follow for dialysis quality outcomes.

DR. LINCOFF: But I said not blinded.

DR. BUSHINSKY: I am sorry?

DR. LINCOFF: I did say not blinded.

DR. BUSHINSKY: Oh. I suspect it could be done, I think nephrologists would have great hesitancy given the KDOQI's recommendations for years now to control phosphorus. As the data collects in the basic science literature, that of the evils of phosphorus, I think it might get harder to enroll patients.

Could it be done? Virtually, anything could be

done, but I think it would be difficult. I wouldn't enroll patients, but I suspect others might.

The other aspect of it is that many of these patients are followed by primary care physicians who perhaps aren't aware of the data, aren't aware of the necessity for controlling phosphorus, the perceived necessity for controlling phosphorus.

Once those patients are referred to nephrologists, who would almost certainly do the study, they would be put on a phosphorus binder.

DR. BLACK: I would just like to make a comment I wanted to make before. Everyone is talking about placebo control. Here, we have a very obvious place for active controlled studies where you wouldn't have the issue of enrolling a patient.

As far as chewing and not chewing, it's a double-dummy design where you wouldn't have that issue either.

As far as primary care people being involved, in many of the studies we do, we have a center and we send them back for routine care, and as far as watching lipid levels or phosphorus levels, the early studies of statins, there were people who were not involved who gave recommendations.

So, I don't any of those are even difficult to surmount. I think they are relatively easy to surmount.

DR. BUSHINSKY: Well, we showed you the active comparator studies.

DR. BLACK: Not with outcomes.

DR. HARRINGTON: I suspect Henry is not counting coronary imaging as a clinical outcome.

DR. BUSHINSKY: I see. Okay.

DR. HARRINGTON: Emil, let's go down to you and then John, Michael, John, and we will try to get all of this in by 2:30.

DR. MALLUCHE: Are you interested in further studies?

DR. HARRINGTON: Sure.

DR. MALLUCHE: I just wanted to add studies that we had done with bone biopsies since this was brought up before. There were 22 patients were biopsied at baseline and again after one year. They were treated with active comparator. Twenty-four patients were biopsied at baseline and again after one year.

Another 33 patients were biopsied at baseline and after two years of treatment. Another 36 patients were

biopsied at baseline and after two years of treatment. Again, one group with lanthanum, the other one with active comparator.

It was very interesting that in the bone biopsies, after one year, we saw that there were clearly less patients with adynamic bone in the lanthanum treated compared to baseline, and compared to the active comparator. Then, after two years, bone volume, there were significantly less patients with low bone volume in the patients treated with lanthanum.

So, we had some evidence that lanthanum had a beneficial effect on the bone formation and keeping up the bone activity and. as you have heard here this morning, the low bone turnover, the inability of bone to contribute to mineral homeostasis and the loss of bone is associated with calcifications.

Even the individual postmenopausal osteoporotics have been shown that those who lose more bone have more progressive calcifications than those who lose less bone. So, here we have the outcome bone volume and bone activity.

DR. HARRINGTON: Peter, did you have a quick comment?

DR. McCULLOUGH: Yes, a quick comment just to help, I think, clear up some question marks being a consultant on the industry side here.

Because of the three-company agreement, there have really been a tremendous amount of attempts to suppress product-specific comparisons, and that is one of the reasons why the presentation didn't have a flow of a clinical trial.

So, what David has shown you, there is a fourth trial. If I can have the fourth trial, which is CARE-2, which has been presented and under review right now.

Since the 2003 guidelines, there have been four prospective randomized trials of phosphate binders in patients on dialysis. The RIND study, which showed with sevelamer that there was an attenuation of the progressive calcification and a reduction of mortality although a very tenuous mortality conclusion as the secondary endpoint in small endpoints.

DCOR, much larger, didn't measure coronary calcification, but didn't show a reduction in overall mortality with a high dropout.

There is the CARE-1 study, which was prospective, randomized, double-blind just with respect to phosphate

control in dialysis patients, but it's the only head-to-head comparison of two approved drugs on the market.

Then, the fourth one is CARE-2. This is under review at the journals and I have asked the sponsors if I could just fully disclose it, so you guys can see all the trials.

[Slide.]

These are patients on dialysis. They are washed out and now they are randomized. Because of the LDL-lowering effect of sevelamer, the design of this trial is to try to equalize both groups with statins, so try to keep the LDLs as a control on this process, because there is an interaction with respect to lipids and progression of calcification, and then do EBCT at baseline. And then, in follow-up, they had a strict control with respect to use of vitamin D and control of PTH and not letting PTH go greater than 300.

So, this is the best--out of all the trials presented, this is the best in terms of blindedness maintained. This is what Henry is asking for, an active control arm, and then this is the third thing we have been talking about is control of yet another metabolic factor

which is part of the atherogenic process in these patients.

[Slide.]

This is what was shown with respect to calcium acetate, not a mixture of calcium carbonate, which the other studies, as Lynn pointed, are kind of contaminated by high amounts of elemental calcium and calcium carbonate, and this is calcium acetate.

These are two approved drugs for use in dialysis, and here you can see the median percent change in coronary artery calcium score from baseline, at 6 months, 20 and 14 percent respectively, and then at 12 months, about a 20 or 30 percent rate.

So, this doesn't declare a differential among the treatment groups, but it is an attempt, and the reason why I am showing this, it is an attempt long postmarketing, long post guidelines of an industry-sponsored trial where one industry now is making a comparison and trying to tightly control it.

It is not definitive, and it doesn't show--none of these trials, by the way, the phosphorus in all these trials is actually the same, they are tightly controlled the same, so we are it is in a sense kind of a conundrum. What we

really need is a metabolic control versus no metabolic control arm to really go after and answer the outcome issue.

DR. HARRINGTON: Peter, if you could stay, Henry has a quick question.

DR. BLACK: If I am interpreting that properly, there was no reduction in progression with either drug, it continued on. Is that less than you would have expected or more than you would have expected?

DR. McCULLOUGH: To be fair, Henry, it is about on par.

DR. BLACK: It didn't seem to have affected the natural history.

DR. McCULLOUGH: I think it's a fair interpretation.

DR. TEMPLE: So, is that discouraging? I mean why didn't it improve all that?

DR. McCULLOUGH: I think this basically goes to my point. I think the pivotal question is, the real biologic question, is this metabolic bone and mineral disorder really a cardiovascular risk state or not.

If we equalize all the factors that we can in the equation, in this case we are equalizing phosphorus, we are

equalizing calcium, equalizing PTH, equalizing LDL cholesterol, boy, we can make two groups look the same.

The trial that we need is a metabolic-controlled trial versus no metabolic control. We are in that conundrum now because some of these products are approved and labeled for use, the vitamin D in this group. The guidelines are already telling the doctors to use it. That is the conundrum that we are in.

The trial we really need, and I think there is equipoise to do it, but if a single sponsor steps up and does it, it is going to have to be very complex. It is going to involve multiple medications. It is going to have a lot of issues to it. It will be a blockbuster trial and we are going to have to solve the lost to follow-up issue in these renal patients.

DR. HARRINGTON: Michael, are you done? Emil, are you okay? So, let's go to John.

DR. FLACK: I want to make a couple of points briefly. One, I think that the burden of proof for safety, efficacy, effectiveness is really on the sponsor when they come and ask for approval.

I certainly can speak for myself and I think for

others that there is a certain willingness to accept, extrapolate and not necessarily hold your feet to the fire to do necessarily mortality and morbidity endpoint trials. But I think a big chunk of why we have seen the arguments come as they have, and a lot of it has been mental jousting to really sort of kind of making an excuse about why we haven't done the studies.

That has left us in a conundrum because I am probably willing to accept the fact that I think that there is a benefit signal there on something important. But you haven't studied it in enough people and it is easier to study a group than dialysis patients.

Dialysis patients, because they already have so much going on, you could easily miss something in that group of people. You can get at it better in this Stage 4 group of people, and blinding, if looking at responses like blood pressure prevented us from doing placebo-controlled trials, we would have never done it, and it is really not very convincing at all when people get up and say, you know, we can't do it because we know what the LDL is going to do or whatever.

They are clever ways to blind the data and rig

your study to the point that you can do that. The whole notion about safety is, to me, real important, because you get these drugs out here and you haven't studied them in enough people, and it takes studying a fair amount of people for safety particularly for low prevalence things.

I think an important thing that is going to happen here is these drugs are going to start being marketed to primary care providers. They are going to have to, because a lot of these patients are not going to be in a nephrologist's care, because nephrologists don't even want to see them until they get ready for dialysis in many areas in the country.

Now, I work in an academic institution that is not that way. But I have sat on panels with national groups coming in basically saying they don't want to see the patients literally until they are ready to go to dialysis. Taking this drug kind of like cholestyrine is potentially going to create issues in both the nephrologists and probably even more so in a primary care setting.

I am sort of left with the conundrum here of very convincing pathophysiology plausibility, et cetera. But we spend a lot of time explaining why we haven't really done

studies, and a lot of the arguments really kind of detract, I think. from the story that is really pretty positive and some of it probably doesn't have a lot of substance to it.

I have been doing clinical trials for 25 years and some of the stuff I have heard today just defies logic about why you can't do it.

DR. HARRINGTON: Go ahead, Bob.

DR. TEMPLE: I just wanted to briefly comment on blinding. There are some very important trials in this world that have been done that weren't blinded. GISSI was never blinded and there are a number of them. It really all depends on the endpoints. You can do a lot if the endpoints are clearly objective.

Also, in trials, people have hidden uric acid when the uric acid went down. You can do a fair number of things that make a trial possible I think.

DR. HARRINGTON: I think we would all agree. Henry brought up some others. John brought up some ideas.

Go ahead, Michael.

DR. PROSCHAN: I have some of the same comments that have already been made. To me, it seems like it is just a little bit too convenient to argue, well, we don't

need these trials, the evidence is in, and then to also imply that if you did do the trial, it might not come out significant, because there are all these other factors going on.

I don't know. That bothers me. If I had to guess whether phosphate binders were good or not, you know, the evidence that I have seen probably sways me more than 50-50, but the point is I shouldn't have to guess.

I mean this should not be a guessing game, there should be a clinical trial done to answer the question, and I think all the evidence that has been presented today would be a wonderful thing to put in the background and significance of the protocol, you know, justifying a large trial.

It has already been said, I forgot who said this, but even if you accept a cause and effect relationship between phosphorus and cardiovascular events, that doesn't necessarily mean that, you know, taking these phosphate binders will necessarily improve things.

I mean I think there is a cause and effect relationship between cardiac arrhythmias and cardiac arrests and sudden death. But that didn't mean that using these

drugs to try and eliminate the cardiac arrhythmias improved things. In fact, it made it worse.

As I say, I have probably tipped more than 50-50, but that shouldn't be the basis for approval as far as I am concerned.

DR. HARRINGTON: Any specific questions for the sponsor, Michael?

DR. PROSCHAN: Well, one thing. I guess that plot that was shown at the end about sevelamer versus the active control. It was significant in the age greater than or equal to 65, and they mentioned that that was a predefined subgroup.

I am just wondering, first of all, was the treatment by subgroup interaction significant, and, second, how many predefined subgroups were there.

DR. HARRINGTON: So, if one of the investigators that showed that piece of data--

DR. CHASEN-TABER: I was the statistician on the study. We had six subgroup factors that we considered as part of our plan, and as a gating criteria, we did exactly as you suggested. We required a treatment by age interaction, the cut point, and everything was predefined.

DR. PROSCHAN: So that was significant?

DR. CHASEN-TABER: Right, that was significant as a gating factor. I think that is what you are getting at.

DR. HARRINGTON: Thank you.

Michael, did you have any other questions or comments? I am sorry.

MS. WILLIAMSON: That's okay. I didn't want to interrupt.

I wanted to go back to something that we started the day with, which is I think relevant to the most recent questions. These products, all three of these products have been approved and on the market for many years for treatment of hyperphosphatemic patients on dialysis.

I hope we are not suggesting that those patients shouldn't be treated because we do not have any long-term placebo-controlled, double-blinded studies. We are seeing evidence, I think reasonably rational evidence, albeit in the face of those hard-outcome data that Stage 4 patients who present similarly should be treated and should have the opportunity to be treated within the context of the label.

Again, I don't want it to seem that studies have not been done or not ongoing, or that we are not interested

or willing to look at clinically meaningful information that we think will benefit the physicians in their treatment of the patients.

We are looking at these patients that present similarly to those patients for which the products are already approved, yet they are just not on dialysis.

DR. HARRINGTON: The question wasn't asked, but I will look down at Norm and Bob. Norm very specifically said that Cardio-Renal inherited this product. One of the questions we weren't asked is was the body of evidence that led to the initial approval satisfactory.

I suspect from the remarks you have heard today that the Committee, you would probably not have us discuss that today, but, Norm or Bob, do you want to comment?

DR. TEMPLE: We didn't ask and if I were you, I wouldn't have raised it, but that is another question.

DR. HARRINGTON: That is why I made my opening remark there.

DR. TEMPLE: It takes a fair amount for us to reverse a previous decision. We would have to be really nervous about it or something like that. Whether in the modern era, we would have done the same thing, I think is

open to question.

We might well have asked for outcome data, but, you know, we might have considered it more obvious that it was trouble for those people, so I don't want to really speculate, but we were not asking that now. We were asking about the extension to a much less ill population or a somewhat less ill population.

DR. HARRINGTON: Go ahead, Lynn, and then I am going to go to John and then maybe finish up the questions.

DR. STEVENSON: I am very encouraged that you have been able to do these trials. As a pragmatist, I share your concern it would be very difficult to do a placebo-controlled trial when the kidney guidelines say we recommend doing this.

What I would like to know, though, is would it be feasible to do essentially a dose-ranging trial where you aim for 5.5 in one group, and you aim for 4.5 in the other group, and basically, if it works, then, it should work better in the group that you get to 4.5.

If we found that there is absolutely no difference, then, we may need to go back to the drawing board and figure if anybody should get it.

DR. HARRINGTON: Kathryn, why don't you weigh in while the sponsors are figuring out who is going to answer that.

DR. WEISE: Is there a way to measure whether patients are actually taking drug? It seems that there was a fair number of patients who could be treated, but were not taking drugs. It was a little hard to interpret.

The 100 hundred percent of nephrologists said they treated, but only 39 percent of patients were treated? Is there a subset in there of patients who were prescribed drugs, who did not take it, who could serve as your control off of drug?

DR. BUSHINSKY: Clearly, all patients don't take all prescribed drugs. Most nephrologists, when they prescribe drugs, hopefully, the patients take it. We do have indices that they are taking it. For example, with sevelamer, if the LDL cholesterol falls dramatically, we can assume--and they are not started on a statin--we can assume they are taking the medication.

The same with the calcium-containing binders and we see the primary endpoint, which is the phosphorus goes down. These drugs are quite effective in lowering

phosphorus. So, we have a good sense of who is taking the medication and who is not, and most patients take it.

DR. WEISE: I am being a little bit facetious, but I think if your problem ethically is designing a trial where you don't give drug, you choose not to give drug, could you perhaps instead have a population of patients who choose themselves not to take drugs, and that is your untreated group.

DR. HARRINGTON: Go ahead.

DR. PRATT: Just one comment again, too, is that the most recent approval for a phosphate binder was in 2004, with Fosrenol, and it was through the Cardio-Renal Division, not a previous division, so just to clarify that.

DR. TEMPLE: Just to be clear, we try not to change in midstream unless there is a reason. That had been the basis of the previous one, so we stick with it, whatever nervousness we might have had.

DR. MALLUCHE: Can I make a comment in defense of the FDA decision approving the phosphate binder? I mean it is in textbooks that if phosphorus goes up, parathyroid hormone goes up.

You can do this in the normal individual and the

patient with renal insufficiency is even more magnified. I don't think there is any question that higher phosphorus is associated with high parathyroid hormone.

You have seen today a patient who lost her kidney because of excessive parathyroid hormone activity, so I think it is perfectly justified to allow the clinician to reduce phosphorus and avoid hyperparathyroidism with the bad clinical outcome.

As nephrologists, we do it, we will continue to do it, and I would have tremendous difficulties to get a study through my IRB where I say I let parathyroid hormone go wild.

DR. HARRINGTON: John, do you have a final question or two?

DR. NEYLAN: If you don't mind, a comment and a question.

DR. HARRINGTON: Sure.

DR. NEYLAN: The comment is to everyone, the question is actually to Norm and Bob.

The comment--I am putting on my nephrologist hat--that I think the discussion this afternoon has been very instructive.

I have seen the Committee go from questioning whether any substantial research has been done in this population of patients to now understanding that, indeed, there is an emerging body of research here, that there are real challenges and that the practice is in some way conspiring against some of the classical designs of clinical research, namely, the ability to enroll a placebo control group.

I think that is a conundrum of modern therapeutics that we are seeing across the board and one that I know FDA is grappling with. I know FDA, as well, has talked about using the product label and the information within as a way to enhance the quality of care delivered in this country through a broader understanding of the potential, as well as the limitations of therapeutics.

I am concerned a bit as we talk about the levels of evidence here needed to justify expanding this indication to this pre-dialysis population of advanced renal disease, whether we are potentially throwing the baby out with the bath water and holding the sponsors to a very high hurdle that may take very many years to achieve.

Knowing the FDA also is concerned about this

through the critical path and such, and is entertaining innovative ways to conduct clinical research, whether that might be possible for the sponsors to work with FDA in a postmarketing commitment, that would devise a trial or a series of trials that might implement some of the things we have learned with regard to imbalanced randomization or adaptive trial design, allowance of cohorts of patients to come in and rapidly drop out for futility or safety issues, dose-ranging studies rather than placebo controlled.

Now, I know FDA, at least some divisions are a little bit wary about adaptive design at the Phase III level, preferring to see it at earlier stages, but given the conundrum here of emergence of the practice, seeing this is being done, is even promulgated by a national society like NKF, I am wondering if it might be possible for FDA to also be open to some innovative thoughts here and working with these sponsors in devising a rational postmarketing strategy and risk management.

DR. HARRINGTON: Bob or Norm?

DR. TEMPLE: I am not sure what postmarketing means here. If that means do the studies after we buy the surrogate, that is one question. You know, we have to look

at the particular proposed adaptive design and see how it works.

Actually, let me throw back at various people the possibility, which we did once for nitrate patches, that a possible study might be to use all three currently marketed products in a single trial.

You could look at the subgroups, too, but your primary endpoint would be for all of them. That might make something feasible that might not be, so I would be interested in how people thought about that. I guess if you really think the effect on lipids is very important, you might not think that was such a great idea.

We are prepared to look at a wide variety of designs. I think the possibility of a dose-response design makes a lot of sense. If you are nervous about leaving people untreated, you could still go to 2.5, 3.5, 4.5, and see if you can detect a slope. That would be informative.

So, those possibilities all exist. That might allow the conduct of a rather larger study than would be possible if you had to leave people untreated, so maybe that would work out.

DR. HARRINGTON: Susan.

DR. SHURIN: I would like to endorse that concept because then what you are looking at is a strategy for treatment rather than a specific treatment. I mentioned the ACCORD trial. This is looking at control of hypertension, cholesterol, and glucose in diabetics, and all of the patients are treated with something.

If they have got hypertension, they are treated for their hypertension, and if they have got hyperglycemia, they are treated for that, they are treated for hypercholesterolemia, but it is a strategy approach, so it varies.

So, you are looking, not specifically, it is more of a practice question than it is of an FDA approval question, but it enables you to go at this issue, is if a lower phosphorus is better, how much difference does that make and how do you then use these drugs.

I think these are very important postmarketing questions and, given that we are not going to have evidence in the near future that is going to impact this, and the use is already expanding, it may be very important to consider it and it would be an important thing to build into the approval up-front.

DR. HARRINGTON: It is looking like we could use a five-minute break, so let's take just five minutes and then we are going to come back and do the questions.

[Break.]

Questions to the Committee

DR. HARRINGTON: We are going to move to the part of the committee meeting where the Committee is asked to weigh in on a series of questions put together by FDA. I have been asked to remind the Committee, some have been involved in meetings recently, that there is a new voting procedure.

The new voting procedure is that it used to be we went around the table and asked people to vote one by one. Instead, what we do now is I read the question, and I ask you to vote, we will say yes, everyone raise their hand, and when you raise your hand, I ask you to keep your hand up and then we will go around the table one by one and ask the voting members to state their name and their vote for the record.

So, a little different procedure. We will remind you when we get to the questions.

The Questions to the Committee. There is a

preamble here that I won't read the details of, but I will read a couple of sentences, because I do think it may inform the Committee's discussions as to what FDA is looking for from us.

The first is the Division does not question whether these drugs, phosphate binding agents, are effective in lowering serum phosphate in pre-dialysis patients; they are effective in so doing in patients on dialysis and in normal volunteers. The question is whether there is adequate evidence of net clinical benefit to warrant recommending such use.

There is then a series of statements about the discussion of surrogacy, which is what our questions will be around, and the final paragraph in the opening is that in the questions that follow, you are first asked whether surrogacy has been established in the setting for which the indication is sought, and then, if not, whether there is an adequate basis for belief that benefits in the dialysis setting lead to incremental benefits when the treatment is applied at an earlier stage of renal disease.

Cathy will put up the first question. As is frequent in these sorts of questions, there is a series of

what I will call introductory questions, so let me read the first.

Questions No. 1. One possible theory for approving phosphate binders for use in pre-dialysis patients is the following:

Serum phosphate is a valid surrogate for clinical benefit in pre-dialysis patients.

For what clinical outcomes is serum phosphate plausibly part of the pathogenesis?

Let me read all three and before the vote, we can have a discussion on all three at the same time.

The first is again: For what clinical outcomes is serum phosphate plausibly part of the pathogenesis?

Considering only the variability related to the natural history of the disease, for which clinical outcomes has serum phosphate been shown to be predictive of risk?

For which clinical outcomes have interventions targeting serum phosphate in the pre-dialysis setting been shown to alter risk in the manner predicted by the change in phosphate?

I will open up the floor and ask for comments, clarifications, discussion, et cetera.

I know this is not a quiet group. Emil.

DR. PAGANINI: We are, first of all, commenting that I think one of the biggest advances here has been the definition of a syndrome or disease entity of CKD-MBD, so that now allows us to stratify and better identify the patient population and its specific subgroups.

I think we have seen the benefit of binder wars between the companies after approval in the ESRD population where those postmarketing, quote, unquote, "studies" have shown one marker may be better, one product may be better than the other product, one form of therapy may be better than the other form of therapy.

So, that is a positive thing and I think also the positive thing that we have seen with the three companies coming together and saying listen, children, can we do this as a group as opposed to trying to do it individually is a positive thing.

I think we have seen that all of the therapies lower phosphorus. I think that is clear whether it be in the ESRD population or in the pre-dialysis population, the therapies do lower phosphorus.

Where they may have a benefit, we have seen in

both basic and clinical work in vascular calcification, metastatic calcification, bone disease, and cardiac dysfunction, but we haven't seen this as a single entity, but rather a piece of many, many other elements that are involved in the CKD population and the ESRD population.

So, phosphorus per se and its lowering per se, while it is effective by the drugs, are not cause and effect to improvement in outcome at all.

So, the comparator data I think may in fact raise some questions on risk.

The comparator data actually has more of a risk as a risk modification than effectiveness I would say. So, if you are using calcium versus something else, a calcium binder with calcium in it may have more progression, higher rate of progression than something without calcium in it, so that really shows that two things don't really seem to help, or they help partially.

There is still progression of calcium deposition and problems with calcium-phosphorus deposition; however, one versus the other, maybe one has less risk than the other, so it is more of a risk ratio rather than an effectiveness outcome.

I don't see any long-term--again, to finish up on this one question--I don't see any long-term outcome with either calcium, especially the thought process of calcium versus others with lanthanum, and what has not been brought up, but it is in the same class as gadolinium, and that was approved a while ago and now we are finding problems. I don't know if we are going to see something. Remember this only opened up in '04, so long-term care there.

Also, the other gel binder, we have no real good long-term outcome data. So, with that I would say I don't see that phosphorus per se and its control is a valid marker for pre-dialysis patients.

DR. HARRINGTON: Bob.

DR. TEMPLE: Just to make the question clear, and this may be over-refined, but the first question is a mechanistic question; where do you think phosphate might fit in, animal data, all kinds of other stuff. It doesn't mean it does, where might it?

The second question is if you look just at the epidemiology, what is phosphorus associated with, you know, the way HDL is associated with stuff. That doesn't prove changing HDL does anything. That is the next question.

Then, the third question is have they actually shown that changing it or any measure makes any difference. I don't know if that helps.

DR. HARRINGTON: It does.

DR. TEMPLE: I think all of those things were touched on, but that was the idea.

DR. HARRINGTON: I mean what you have done here is you have just taken the Prentice criteria for surrogacy and peeled them apart and want to make sure that we think about each of the pieces.

Mike Lincoff.

DR. LINCOFF: I will try to take a shot at this in the formalized manner that you have presented it.

I think the pathogenesis has supported an association between phosphate or phosphorus levels and vascular calcification, perhaps valve calcification, the bone disease, and survival, and mortality outcomes.

Similarly, I think in the pre-dialysis population we have seen evidence that variability has been associated with coronary calcification. Actually, we haven't seen much with bone disease per se, but I don't know if that just wasn't presented, and long-term mortality outcomes.

As for the third in terms of an intervention linked to an outcome, I think that is what we have been saying all day today is that there is nothing for that third criteria that connects an intervention on phosphate with outcome, which is always the toughest of the topics to address.

DR. STOCKBRIDGE: Mike, could you quickly tell us why you thought ectopic calcification and bone disease were clinical endpoints?

DR. LINCOFF: I am convinced, not just on the basis of the data here, but on the basis of data that we have collected for a number of years, it is calcification, CT, et cetera, in coronaries at least is a predictor of outcome.

DR. STOCKBRIDGE: Okay. So, you think that is a better surrogate.

DR. LINCOFF: I agree, and to an extent I am trying to be practical here, recognizing the difficulties of doing a mortality or myocardial infarction study. A study with those as the endpoints, I am more willing to accept coronary calcification as a surrogate that I believe has value than a laboratory test, but I will agree it is a

surrogate.

DR. STOCKBRIDGE: So, if somebody came in next week with a treatment that reduced ectopic calcifications by, I don't know, 5 percent, you would say, hey, congratulations?

DR. LINCOFF: I would. Well, then, of course, you are always getting back into the risk-benefit analysis.

DR. STOCKBRIDGE: How would you do that computation?

DR. LINCOFF: Well, I mean in this case we have much, much safety data than we have for most sets of drugs.

I mean let's be realistic, this is a drug being used in large numbers of patients for many years. We have more of a safety database for this drug than we would have, say, for PPAR accessed or something like that.

DR. STOCKBRIDGE: But you think you know how to predict what events you will have prevented with a 5 percent reduction in ectopic calcification?

DR. LINCOFF: Well, the first question here was, is there a linkage, not is there--

DR. STOCKBRIDGE: No, my first question was whether or not we had something that linked, mechanistically

linked phosphorus with some clinical endpoint.

DR. LINCOFF: Right, and just as this discussion has been brought up with neointimal hyperplasia--but intravascular ultrasound, I mean that is a measurement of atherosclerosis. Calcification is a measurement in a way of atherosclerosis.

I mean it is then a leap to take what does atherosclerosis do to something that a patient feels. But I don't think it is controversial that it is better not to have atherosclerosis than it is to have atherosclerosis.

I think we can call that a clinical outcome, or you call it a surrogate, because it is not associated with, you know, how a patient feels, but I think it is a more tightly linked clinical outcome than is a blood test.

DR. HARRINGTON: Do you want to call even calcium in the artery a surrogate, or do you want to call it just another biomarker?

DR. LINCOFF: Those are almost the same.

DR. HARRINGTON: No, I think of them as--and maybe Michael will help me out here--but I think of them as much different. A biomarker can raise to the level of a surrogate, but a biomarker is just some measure that--you

know, LDL is a biomarker that has risen to the level of a surrogate, but there is not many others in at least cardiovascular disease.

Michael, am I off base here? Blood pressure would be another?

DR. PROSCHAN: Right, I think you are right. There are a lot of criteria that are required for surrogacy, and not so with just a biomarker, so I think you are right.

DR. TEMPLE: From a narrow point of view, it is a surrogate if we use it as an endpoint and base approval on it. Whether we should or not is another debate, of course. Until then, they are plausible biomarkers.

DR. HARRINGTON: Other comments around the table? Lynn.

DR. STEVENSON: In thinking about this, to the degree that we are talking about plausibility now, and nothing that has really been demonstrated, I would wonder if we need to separate these two major things, the metabolic bone disease and the vascular calcification, because it seems like maybe the PTH level is the more relevant thing for the metabolic bone disease than the serum phosphate, because the PTH can go high while the serum phosphate is

still okay, and yet you are absorbing too much phosphate, whereas, I think that the phosphate level itself may be more directly related to the vascular calcification.

I don't think we know that, but I would just suggest that it is not clear that it is necessarily the same surrogate for both of those endpoints.

DR. HARRINGTON: Nelson, you are the expert on bones. Do you want to help us out?

DR. WATTS: I don't think we have heard anything that establishes phosphorus levels as a surrogate for anything. If we had, we wouldn't be having this discussion, because we have endpoint data at least with something.

But having said that, I have a brother who is a criminal attorney, which I tell him is redundant, and he specializes in the penalty phase of capital crimes. And, for him, he has to prove something beyond a shadow of a doubt.

In a civil case, you need a preponderance of the evidence. So, while I don't think phosphorus levels rise to qualify as a surrogate, I think that it is a reasonable marker for bad things happening.

The KDOQI guidelines are already saying do

something about it. The drugs are already on the market and approved based on this surrogate in patients with end-stage renal disease. They are already being used, and it seems to me, unless there is somebody planning a large trial that is going to look at all three of these drugs head to head, or in a dose-response, that it is simply a matter of some patients may get insurance coverage for it and others won't, but it is going to be used.

DR. HARRINGTON: So, you are jumping ahead. Let me go back to Norm's line of questioning.

DR. WATTS: But I think for what Lynn is saying, I don't think PTH is an adequate surrogate for bone problems either.

DR. HARRINGTON: So, from your perspective, from your area of expertise, you have not seen data that would elevate hyperphosphatemia to a level of surrogacy.

DR. WATTS: No.

DR. HARRINGTON: What about the first question, do you have evidence that serum phosphate is part of the pathogenesis of either bone diseases or cardiovascular disease?

DR. WATTS: I can't add to the list that Mike

made.

DR. HARRINGTON: Go ahead, John.

DR. TEERLINK: One of the questions, one of the things that is interesting as I am thinking about the intracoronary calcification, and maybe Mike can help with this, but it is plausible that one could reduce calcification of the coronary artery without changing or perhaps even increasing the atherosclerotic load or atheroma in the coronary vessels.

So, you could have actually an increase especially--I don't know if we know this in renal disease--you could actually increase the atherosclerosis, the soft plaque while reducing the calcium, and you are actually perhaps increasing your overall cardiovascular risk.

DR. LINCOFF: Except that studies have shown CT calcification to be as strong as or stronger of an independent predictor of cardiovascular events than is stress testing or other factors.

Now, that doesn't mean that if you could make it go away, that you would make that risk better. But having gotten to that level of calcium, you then have a risk associated with it, so that is the first step.

DR. HARRINGTON: Other comments around the table? Yes.

DR. KOPP: Just to follow up on that point, I take it the studies you are referring to are cardiologic studies of people with normal calcium and phosphorus metabolism. So, if the kind of calcification that we are seeing in renal patients is somehow different, because it is driven by an excess of calcium and phosphorus, a high product, its manifestations and its consequences may be different than in the prior situation.

DR. HARRINGTON: Norman, as I look at these questions, the data that we have seen today, particularly some of the translational data, might suggest that there is a biological plausibility that phosphate is involved with the atherosclerotic process.

I think that we have heard I think an elegant description from one of the scientists that this may well be the case. The Framingham data to me is at least another piece of evidence that hyperphosphatemia may, in fact, be a reasonable biomarker and that it does appear to be associated with cardiovascular risk in a well studied, ongoing epidemiologic project.

But for me, it really falls short on the third one here, that there are no clinical outcome interventions targeting serum phosphate in the pre-dialysis population which have shown to alter risk.

I loved Michael's comment earlier which he said what we have heard today is a great prelude to the study, that we could include that in the background material. I thought that was nicely said.

I have heard great science, great description, and a hypothesis that deserves to be tested in a major day.

Other comments? Seeing no comments, let's go to the voting question. Again, remember, we will go for the yes votes first. Raise your hand, leave them up, and we will go around the table.

The vote is: Is serum phosphate a validated surrogate for clinical outcomes among pre-dialysis patients? Yes votes first.

[No response.]

DR. HARRINGTON: No votes?

[Show of hands.]

DR. HARRINGTON: Leave your hands up and let's start with you, John. State your name and your vote.

DR. TEERLINK: John Teerlink. No.

DR. WATTS: Nelson Watts. No.

DR. KOPP: Jeffrey Kopp. No.

DR. STEVENSON: Lynn Stevenson. No.

MS. SCOTT: Malazia Scott. No.

DR. HARRINGTON: Robert Harrington. No.

DR. SHURIN: Susan Shurin. No.

DR. WEISE: Kathryn Weise. No.

MR. FINDLAY: Steve Findlay. No.

DR. BLACK: Henry Black. No.

DR. LINCOFF: Michael Lincoff. No.

DR. PAGANINI: Emil Paganini. No.

DR. FLACK: John Flack. No.

DR. PROSCHAN: Michael Proschan. No.

DR. HARRINGTON: I guess, Norman, we don't need the question if you voted yes. There were no yes's, so let's move to Question 2.

Again, the early questions, we will put them all up there at once before we get to the voting question.

Question No. 2. A second theory for approving phosphate binders for use in pre-dialysis patients is the following:

Serum phosphate is a valid surrogate for clinical benefit in dialysis patients, and earlier intervention is beneficial.

Let us first consider whether serum phosphate is a valid surrogate in dialysis patients.

In the previous question, you described where you thought serum phosphate was in the pathophysiologic chain to particular clinical endpoints. Please add anything you think relevant to distinguish pre-dialysis and dialysis.

For which clinical outcomes have interventions targeting serum phosphate in the dialysis setting been shown to alter risk in the manner predicted by the change in phosphate?

Again, we will open up the floor for a discussion around, I guess, Nelson, to use your analogy, the chain of evidence here that we are trying to build the story for surrogacy in the dialysis patients.

Does anyone want to open up? Michael, go ahead.

DR. PROSCHAN: I think it is the same problem, with the second one, that there aren't such studies, and what I would like to see is a trial that shows that when you intervene, you see a benefit on the clinical outcome, and

then when you try and adjust for the change in the phosphate, that benefit goes away.

I mean to me that is what I would like to see, and I haven't seen that.

DR. HARRINGTON: Lynn.

DR. STEVENSON: I would like to say I do think there is a big of an artificial distinction between the dialysis and pre-dialysis particularly when we talk about the people with creatinine clearances of, say, less than 20.

So, whatever we do, I am a little reluctant to say that at that point of beginning dialysis is the point where you do something entirely different. If anything, I think once they are on dialysis, things are better controlled, better supervised, so I could like to try to muddy a little bit that distinction at the point of dialysis.

DR. HARRINGTON: John.

DR. TEERLINK: Yes, so actually, that is my exact point, because the patients are better controlled and are under more careful supervision and intensely followed during dialysis. They have been more established in terms of what the safety record is.

I am a little more concerned actually about what

happens in the pre-dialysis patients where it may not be as clear. So, I am not sure which way that cuts.

DR. STEVENSON: I guess I was leaning more towards the idea that if we think it is beneficial in the dialysis patients and the people who have similar renal function, but for whatever reason they haven't quite gotten to dialysis yet. I am not sure that I would necessarily want to deny them something that we are giving to dialysis patients.

DR. HARRINGTON: Let me go over to Emil first, Nelson, and then I will come back. Go ahead, Emil.

DR. PAGANINI: I would be very careful about not, about combining those two groups. The dialysis patient is exposed to a series of interventions that are not exposed to the CKD population. There is exposure to membrane, there is exposure to dialysate, there is back diffusion, there is a whole series of issues in the dialysis population that are not exposed in the CKD population, so don't mix the two.

The phosphorus controlled by dialysis is really very poor, otherwise, we wouldn't need binders. Because of the kinetics of phosphorus, within the first hour or hour and a half, you have lost any further--and it was well described here--any further removal, because of charge

effect and its movement away or across membranes. It really doesn't move very well across membranes.

So, within the first hour and a half, you will take all your serum phosphorus out, and then that's it, and then you are finished with your dialysis in four hours, and then it just sort of reclaims, so, dialysis addition of phosphorus control is minimal at all.

In the CKD-5, which are the folks that are pretty close to dialysis but haven't gotten there, I think their physiology is perhaps a little bit more similar to the chronic dialysis population, but without all of the other attributes that dialysis brings.

In the CKD-4, I think they are a different population, and that population is at least in equilibrium over time with whatever it is that you are doing with a fixed outcome as far as their GFR is concerned.

If you look at dialysis as we currently practice, and say the equivalent GFR delivery of dialysis somewhere around a GFR of 12, and not as effective as a natural kidney would be at that GFR, and then you go back down and you say someone between 30 and 15, they are a different set of population, they have a different kinetics of things, so I

think there is a distinction.

One further comment and then I stop. To extrapolate from the dialysis population back, I think is going to be problematic, because I think the dialysis population is different. However, to not control phosphorus, and again this is 30 years ago, 31 years ago when I went through my nephrology training, they said when phosphorus goes up, you control it, and that is just what we do.

Now, there is no label for it. One hundred percent of those 100 nephrologists out of the 5,800 nephrologists that are practicing said in that small group that they all do it, it is part of the training program, it is in all textbooks to control it.

But to confound that population with the dialysis population and say look how well it works in dialysis, but doesn't work--it should work just as well there, I think is totally different populations.

DR. HARRINGTON: Emil, let me again using Norm's questions here. In the dialysis population specifically, do you believe that we have enough evidence that serum phosphate is in the pathophysiologic chain to the clinical

endpoints? If so, what endpoints? You have nicely I think distinguished pre-dialysis and dialysis. And. No. 2, are you convinced that targeting serum phosphate alters risk in a predictable way?

DR. PAGANINI: I am and I think it is in a context of a series of other issues that you would do, in other words, lowering phosphorus as a be all-end all point will help in control of PTH and calcium.

Controlling calcium and as far as intake is concerned, controlling vitamin D is a very important issue. Vitamin D therapy will increase phosphate intake through the gut, and so you have to control that.

So, I see control of phosphate in the ESRD population having effects on bone. We have heard from Kentucky that that is true and there is some good data on that. Control of phosphate and that complex in the ESRD population for advancement or progression of coronary artery disease, there has been data on that.

However, that data has been with one phosphate binder versus the other, so it is probably a risk analysis of different therapies as opposed to a true therapeutic improvement, which I tried to say before.

So, I would yes in the dialysis population. I think there is enough evidence that control of serum phosphorus does have some clinical benefit.

DR. HARRINGTON: But the question I think, not to parse words, but the question becomes a bit more specific. In order to show that something is a surrogate, you have to be able to say that basically, you have got phosphate outcome and that that line is always preserved.

I hear you bringing in other lines that also affect the outcome. I also hear you saying that to establish surrogacy means that in a predictable way, you could raise or lower phosphate, and it would have a predictable raising or lowering of the clinical outcome.

Again, I hear you saying there are other things at play there.

DR. PAGANINI: Yes, I think that it is a complex. If you were to look at the classic ESRD population of patients, their phosphorus control is poor, and the reason why it is poor is on four levels: food, fluids, fun, and physiology.

The food, they will eat whatever they want. The fluid is a major issue for coronary disease, et cetera,

hypertension, et cetera, et cetera.

Fun, we all have fun. And physiology; it is just physiology of phosphorus per se and its control.

DR. HARRINGTON: Let me go to Henry, Jeff, Michael.

DR. BLACK: I just want to make one small comment, is how difficult it is to separate phosphate control from everything else that goes with it. I think it is very hard to answer that question as a result.

I don't think we want to say that you shouldn't worry about it, but I don't think we can necessarily say that it, by itself, is a surrogate that we should concern ourselves with.

DR. HARRINGTON: I think, Henry, for me, you articulated much better than I have what the issue is. I don't think it is something we don't want to worry about, but on the other hand, is it really a surrogate.

Jeff and then Michael.

DR. KOPP: The point I would want to make is that secondary, tertiary hyperparathyroidism and osteitis fibrosa cystica was a major problem in the hemodialysis populations in the 1970s,--not that I was practicing at that time,

because I am much too young for that--but from what I understand, and as a result of control of phosphate and PTH and the use of vitamin D, that has become much less of a problem.

Its manifestations were clearly important clinical outcomes, i.e., fractures. But the points that you have just made are correct. It is multifactorial how we have made that better, and phosphate is one piece.

So, using this very stringent set of criteria that we are applying, probably phosphate can't meet that. In a way we don't have to decide that today, because we are not going to take these agents off the market, I believe, for the ESRD population, and I don't think we are denying it to anybody at the present time unless including in the CKD population with a GFR of 15, unless there are insurance issues where they can't get it paid for.

So, these agents are still on the market, as I see it, after today, and still available.

DR. HARRINGTON: Mike Lincoff.

DR. LINCOFF: Well, I think we do have to grapple with it a bit today, because that would be one of the potential criteria by which the extension--as they have

said, one of the theories here or hypotheses we could extend on the basis of it is a valid surrogate for the sicker group of patients, so I think that that is an issue.

I, too, am convinced of the pathogenetic link, but on the other hand, we don't have I don't think good data for hard endpoints, but at least we have some data. We have data with what appears to be some effect on coronary calcification, some effect on bone, and we have the historical improvements in outcome with a combination therapy, a strategy of therapy, a control of minerals and metabolic risk factors.

So, it may be impossible to sort out the individual effect of just the phosphate. But then it is interlinked because, as well, if you are giving more vitamin D, you are absorbing more phosphate, so as a result, you may have to give the phosphate binder.

We may have to accept that they are interlocked and the strategy of this approach, including the phosphate binders, appears to be effective. And I think in the dialysis population, we have more evidence for that, for that linkage.

DR. HARRINGTON: John Flack.

DR. FLACK: I will say it again. I am real convinced with the plausibility, some of the animal data, some of the human data. At the end of the day, I think were I come down is that I think that correcting phosphate makes sense, like correcting potassium in hypertension, and I believe it has an effect on PTH bone disease.

Past that, I am not really sure. Maybe vascular calcification. And I think that a lot of the supporting data that was thrown out there today was kind of out there on the limb. But for me it gets back to when you are taking care of these patients with metabolic derangements, you know, it is going to affect their PTH, their bone disease, and start using these analogs. You are going to raise their phosphate. And I think, for me, that is enough to say to work on the PTH and the phosphate.

Some of you are going to need a binder to do it. I do think, though, that the body of data in regards to safety is inadequate and all. But I do think that correcting phosphate makes sense metabolically for bone disease and all.

I will say this about KDOQI guidelines or anybody's guidelines, when we write these guidelines, they

are not meant necessarily--they are meant to reflect what we have, sometimes what we have is not great. And it doesn't mean that once you write a guideline and put something in there, that it's the gospel and you can never challenge it again.

You can't wrap yourself and hide behind anybody's guidelines to do that. On the other hand, the KDOQI was probably a reasonable extrapolation that managing phosphate is important. They did it on imperfect data, but because they did it doesn't meant that the case is closed.

DR. HARRINGTON: Yes, John.

DR. NEYLAN: Just one minor point that I would kind of like to throw back at Jeff, and that is that the playing field is changing these days with regard to access to medications even in the U.S. so that it is becoming increasingly problematic in some sectors and with some third party providers and perhaps even Medicare Part D, that indeed, if an agent is not listed on the formulary, and specifically noted to be allowable for use in a specific disease entity, that patients who potentially could benefit by that may be denied access.

I think the committee here, it is probably not

entirely accurate to say that the practice is going on and regardless of what the committee decides today it will continue to go on unabated.

DR. HARRINGTON: Other comments, questions from the Committee? Go ahead, Lynn.

DR. STEVENSON: Again, I think, you know, we all come from a different kind of guideline experience. With the cardiology guidelines, this, I think would be something that is clearly not a Level 1, which means you kind of have to do it unless you have a good reason not to.

It might be a reasonable Level 2 in which it basically says it is reasonable to do this, but it is not mandated and it is not something where somebody will look at you askance if you didn't do it. I understand that the Kidney Foundation guide is a little different, but I think that is where I would put it is at Level 2. You can do it, but you don't have to.

DR. HARRINGTON: Other comments? Norman, have we had a discussion along the lines that you would like to hear?

DR. STOCKBRIDGE: Yes, that's pretty good. I just wanted to call attention to a characteristic of the question

that is coming up to vote.

DR. HARRINGTON: Go ahead.

DR. STOCKBRIDGE: That is that you are first asked whether serum phosphate is a validated surrogate, a very formal description of does it meet the usual criteria for that, and then if you say no, you get an opportunity to say whether or not you think there is some other reason for believing that the linkage is sufficient to support decisionmaking.

I don't know exactly how I phrased it, but there is a two-part here and I want to make sure that people understand the difference between these two parts before they vote.

DR. STEVENSON: So, we are actually going to vote on the second part, as well as the first part? I think that would make it easier. It is not written as a voting item, the second part.

DR. HARRINGTON: So, the voting question is serum phosphate as a validated surrogate, if you vote yes, you are done; if you vote no, you have any opportunity to weigh in on, as Norm said, what you believe are specific clinical benefits, nevertheless, attributable to that treatment.

DR. KOPP: Norman, could you clarify--I guess now I am confused--the difference between a validated surrogate and specific clinical benefits attributed to the treatment of elevated serum phosphate?

DR. STOCKBRIDGE: There were three things that you need to be able to establish to declare something a validated surrogate. That is sort of where we went through, you know, beginning in Question 1.

They were that you had a plausible--that it constituted a plausible step in a pathophysiological sequence. That is one. Two was that you had epidemiological data, had natural history data, that said when the biomarker went in some direction, you go a consistent effect on the clinical outcome.

So, the natural history of the biomarker and disease, the clinical outcomes seem to go together, they were correlated.

The third thing, the thing that I think is the major barrier to calling something a validated surrogate is the demonstration that regardless of how the biomarker is altered, by whatever mode of intervention you can name, that you get the same consistent relationship to outcome.

DR. KOPP: It is that third part that would be lacking from this definition, clinical benefits attributable to treatment of elevated serum phosphate.

DR. STOCKBRIDGE: That is the question to you.

DR. KOPP: I guess what I am saying is it seems awfully close to a surrogate, if it is attributable to the change in phosphate.

DR. STOCKBRIDGE: Again, you have to be able to point to the data that says when you modify this biomarker by any other variety of mechanisms, you get the corresponding change in the clinical outcome that you expect from it. It is, in fact, in that area that I think you don't have any data at all here.

DR. HARRINGTON: Go ahead, Bob. You want to clarify it?

DR. TEMPLE: I mean the first question is can you think of a reason why this might be a surrogate. It is not whether you documented human evidence that it is, but you have a mechanism, you have an animal model, you have some reason to think so.

The second is if you look among people with, say, a high phosphate, do they seem to do badly, and I think for

a lot of reasons, we have heard plenty of epidemiologic data that says they do.

The last question is does fixing it make a difference. Maybe it is true, true unrelated. Maybe they have high phosphates because they have bad something else, and that is always the question with surrogates, and it is a challenge to do it.

Norm said he doesn't believe a surrogate until it has been shown for multiple different mechanisms. I am not totally sure we insist on that. I think I believe some things for statins, and I don't know if I believe them for other things, but anyway you could argue that--you could argue that point, but certainly the best surrogate works no matter how you change it as long as you don't do harm.

DR. HARRINGTON: Go ahead, Michael.

DR. PROSCHAN: It seems like another way that that could be the case, that you would see specific benefits attributable, but not a surrogate, is if there is an effect of changing phosphate by a certain amount, that effect is not nearly as much as you thought it should be by changing phosphate by that amount, but there still seems to be some benefit.

DR. HARRINGTON: Good addition.

DR. TEMPLE: Actually, that goes to one of the hardest part of the Prentice criteria, which is that the change in the surrogate is supposed to fully account for everything.

I am not sure I totally believe that. Sometimes drugs do more than one thing, but anyway, that certainly has been frequently said.

DR. HARRINGTON: Go ahead, Mike.

DR. LINCOFF: Then, if we believe that an intervention works in the setting of a strategy of multiple interventions, but can't link it individually, Does that thus not qualify as a surrogate, but would qualify as the subsequent paragraph? I mean is that sort of one of the criteria?

DR. TEMPLE: Well, I mean that is thorny. Even if you had clinical benefit, if you had multiple interventions, you wouldn't necessarily know what to attribute it to, which poses major problems for us. We have actually never said anything official about this, but suppose you did five things to a cancer, and the cancer went away, do you want to be in the trial that finds out which of those things did it?

No, you don't.

So, we have suspended out combination attitude or our combination policy in such cases, but you are asking a different question.

If you really knew that in a setting of multiple things, lowering phosphate and doing two other things, really improved survival, you would be pretty happy that the collection is doing something good and unless one of the drugs was very toxic, you wouldn't go and ask that question. You couldn't ethically do it.

In fact, that is not so much a surrogate question anymore, because you would have established that the surrogacy of the various interventions that you used, you just wouldn't know which one did it, a somewhat different question.

DR. HARRINGTON: Let me then read the question and we will vote. Again, we will do the yes votes first. Leave your hands up.

Is serum phosphate a validated surrogate for clinical outcomes among dialysis patients?

Yes votes first.

[Show of hands.]

DR. HARRINGTON: Let's start with you, John. State your name and your vote.

DR. FLACK: John Flack. Yes.

DR. PAGANINI: Emil Paganini. Yes.

MS. SCOTT: Malazia Scott. Yes.

DR. HARRINGTON: Okay. No votes.

[Show of hands.]

DR. HARRINGTON: Michael, let's start with you.

DR. LINCOFF: Michael Lincoff. No.

DR. HARRINGTON: Oh, no, one down, I am sorry.

DR. PROSCHAN: Michael Proschan. No.

DR. HARRINGTON: It's not Chicago, don't vote twice, Mike.

DR. BLACK: Henry Black. Yes and yes, from my Chicago days.

DR. HARRINGTON: You are voting no you mean.

DR. BLACK: No and No.

MR. FINDLAY: Steve Findlay. No.

DR. WEISE: Kathryn Weise. No.

DR. SHURIN: Susan Shurin. No.

DR. HARRINGTON: Robert Harrington. No.

DR. STEVENSON: Lynn Stevenson. No, but I am very

nervous to be going against the vote of a nephrologist who knows this a lot better than I do.

DR. KOPP: Well, I am doubly nervous, but I am still going to vote no. Jeffrey Kopp.

DR. WATTS: Nelson Watts. No.

DR. TEERLINK: John Teerlink. No.

DR. HARRINGTON: Okay. So, now all of those who voted no, we will start with you, John. If you voted no, please say whether you believe specific clinical benefits are nevertheless attributable to treatment of elevated serum phosphate in the dialysis patient.

DR. TEERLINK: I am still not sure. When I look, there seems to be conflicting evidence even amongst the coronary calcification with the CARE-2 data, and I don't believe necessarily--there was still progression of the disease despite the phosphate lowering that was about 30 percent increase over one year.

So, I don't know what the baseline rate of increase in coronary calcification is in this population, but if you have a 30 percent increase in one year that is unaffected by being on phosphate binders, I can't see that.

In terms of the other endpoints, we haven't

looked, so I don't know.

DR. HARRINGTON: Nelson.

DR. WATTS: I think what it takes to be a surrogate is a real high hurdle, and I don't think that this gets there. But I think it is awfully hard to dismiss the evidence and the improvement in bone disease that we have seen in these patients with not only phosphate binders, but also other interventions.

So, I am convinced in my heart that it makes a difference, and most of what I do every day is not evidence based, and I think it would be a shame for this to go away, but I don't think we have a surrogate.

DR. HARRINGTON: Jeff.

DR. STOCKBRIDGE: Wait. What improvement in bone disease did you see?

DR. WATTS: The secondary hyperparathyroidism that kept us busy in the '70s and '80s has virtually disappeared. Now, it is not just phosphate binders, there are other things going on. I thought I added that.

DR. KOPP: I would echo those sentiments as well. It clearly plays a beneficial role as part of a package, but if the definition of surrogate in this context requires both

a quantitative analysis of the nature of the benefits and some sort of linear or similar predictive relationship or a certain decrement in phosphate translate to a certain benefit, I don't think it has met those standards.

DR. STEVENSON: I am going to say yes for metabolic bone disease although I think it is very difficult to know what role the vitamin D therapies have played, and I think that the vascular calcification if incredibly complex and I would be very reluctant to say that we have any impact on that yet.

DR. HARRINGTON: I, too, voted no, and I like both John Teerlink and Jeffrey's description that this seems to be part of a package, but I couldn't tease out what lowering phosphate by itself does to specific clinical outcomes. So, I liked the description that Jeffrey provided, and I cannot provide you with what I believe are specific clinical benefits.

DR. SHURIN: I will just echo that. I think, yes, it is beneficial. The major evidence is for bone disease and the complications thereof with tissue calcification.

DR. WEISE: I voted no and I am unable to tease out phosphorus alone from other effects within the package,

and don't know what happened untreated in terms of other safety issues, because we don't do it anymore.

MR. FINDLAY: I agree the benefit is evident, it has been shown in the evidence presented today.

DR. BLACK: I also agree. I am reasonably strict about a validated surrogate and what exactly that means, but I also do a lot of things that I don't have evidence for, and I think it is part of a collection of therapy, a group of things we do especially for metabolic bone disease.

I am not at all convinced what EBCT means and what it is going to turn out to mean. I guess MACE is close to being done, and maybe we will see when that is.

DR. HARRINGTON: Michael.

DR. LINCOFF: I agree. I do believe that there is some evidence for the points that you brought up, as well as Dr. Kopp and Dr. Watts.

DR. HARRINGTON: Michael.

DR. PROSCHAN: I feel confident in my vote that it is not a valid surrogate because of that third condition. I don't feel confident about whether or not it has any other specific clinical benefits.

DR. HARRINGTON: Emil, you were a yes vote, but I

will let you talk anyways.

DR. PAGANINI: Absolutely. I just want to point out to the Committee that they are very foolish, that without controlling phosphorus in that triad of a control in these patients, you will in effect almost negate some of the benefits that you would have with the other two treatments that are involved.

So, while from answering the question from an FDA point of view, posing a question like that, to me may, in fact, send a very poor message out there, and I don't think, as you hear the reluctance around the table, of people saying, you know, I am going to say no, but that is not the way I practice, gee whiz, kids.

DR. HARRINGTON: I don't think, well, I will speak for myself, I will let others weigh in, I don't think you are hearing us say, well, we are voting against something, but we are doing it anyways.

I think what you are hearing, at least what you have heard me say, is that there are criteria for establishing a biomarker as a surrogate, which I don't believe has been met to my satisfaction in this setting, but I do believe that lowering phosphate is part of a

therapeutic strategy that is beneficial to patients.

I just couldn't tease out for you in the data that is currently available, and you nicely said it yourself, Emil, there are other things going on.

So, for me it is the surrogate no, part of a strategy yes.

John.

DR. FLACK: You ended up like I was hoping you were going to end up with your final comment there. You know, we get sometimes hung up on trials, and I love trials, and we like evidence, and we like things to fit nice, neat definitions. But this is a very tough population of patients, and everything doesn't fall out neatly.

Part of the problem we have got is that some of the studies have not been done, but for bone disease, and part of managing bone disease and dealing with calcium, vitamin D, phosphate, it makes no sense not to manage phosphate when you are trying to deal with hyperphosphatemia in these patients, and not a lot of the Stage 4s are going to have it. I think the book said about 8 percent or so.

But I think it would be a really weird message to say manage the stuff and all but don't manage the phosphate

when you need it in that small group of people, despite the fact that it doesn't quite the fit the real neat definition of maybe a strong surrogate marker is.

I think here we just have to read between the lines and look at the totality of evidence. The totality of the evidence is convincing to me managing the stuff for bone disease and keeping people's phosphate in check makes sense, but not necessarily for the reasons that were presented today elaborately and sometimes dodging the question about why you can't do studies or looking at mortality and vascular calcification. I think that is mostly it's plausible, but mostly unproven.

DR. HARRINGTON: I think, John, in part, we are building up to where you want people to comment, which is, you know, does the Committee feel that there is an indication here. So, I think everything up to this point is trying to establish what the bar is and how people feel about that.

Lynn had a comment, but let me go to Michael and then I will come back to Lynn.

DR. PROSCHAN: I was going to say, you know, that this wouldn't be the first time that the questions that the

FDA posed are not necessarily the ones that, you know, we all think are the best questions, but every time that issue has come up before, they basically said, well, nevertheless, we want you to answer them.

So, there are certain times when I think, gee, I would have asked a different question, but I don't know if we are really supposed to go there.

DR. HARRINGTON: Bob.

DR. TEMPLE: Well, we are always interested in other questions, but let's make something clear. If there isn't a clear clinical benefit from a treatment, and you don't believe the thing that is measured is a surrogate endpoint, it is very hard to think how we have a basis for approval even if people's emotional content is that I am probably doing good.

I just wanted to offer a comment. I mean everybody does things that they think are likely to be good even before the evidence is in. I put myself on folic acid for a while, and I am not proud of it, but I did, knowing that the data weren't in, and what I am hearing people say is this seems sensible, it makes sense.

I mean the first two parts of the paradigm Norm

was asking about are sort of there. There is plausibility, there is massive epidemiologic data, and that makes me want to take action even before I have the evidence. And there is nothing wrong with that thinking. You have to do that all the time. You know, you have to do marrow transplants for breast cancer even before you have the data--oh, wait a minute.

So, everybody does that, but I guess from our point of view, it is important to keep in mind that even if that is true, that is not necessarily a statement about evidence or it is a different kind of statement about evidence, and even though I don't for a second doubt the legitimacy of needing to behave in ways before you have all the evidence. That happens all the time.

DR. HARRINGTON: I was going to point out to you, John Flack, when you made your comment about guidelines, remember, even in cardiology, which has very much had a long history now of practicing by guidelines, more than two-thirds of the recommendations are Class II, so despite an enormous body of evidence to guide what we do, it is the minority of things which fall in the I's and the III's.

It shows that, you know, we do a lot of things

because we think they are the right thing, but the evidence may be lacking.

Lynn, I know you want to make a comment about voting.

DR. STEVENSON: I just wasn't exactly clear from all the conversation what the vote was on the second part of that.

DR. HARRINGTON: Norm, if you voted no, we were asked to comment, but did you want us to vote on this ancillary part?

DR. STOCKBRIDGE: I was not particularly seeking a vote on the "if you voted no" part of this.

DR. STEVENSON: I have to say from my standpoint, I would have been uncomfortable voting no in the surrogate unless I knew I had a chance to vote yes on the following one.

DR. STOCKBRIDGE: What I heard a variety of people around the table say is that even though this wasn't a valid surrogate, they couldn't name the clinical benefit that this was established as a surrogate for, that they nevertheless felt that either alone or in combination with various other interventions, there seemed to be less bone disease,