Medscape EDUCATION

Healthy Kidneys, Healthy Heart: Reducing Cardiovascular Risks in Patients With Chronic Kidney Disease CME/CE

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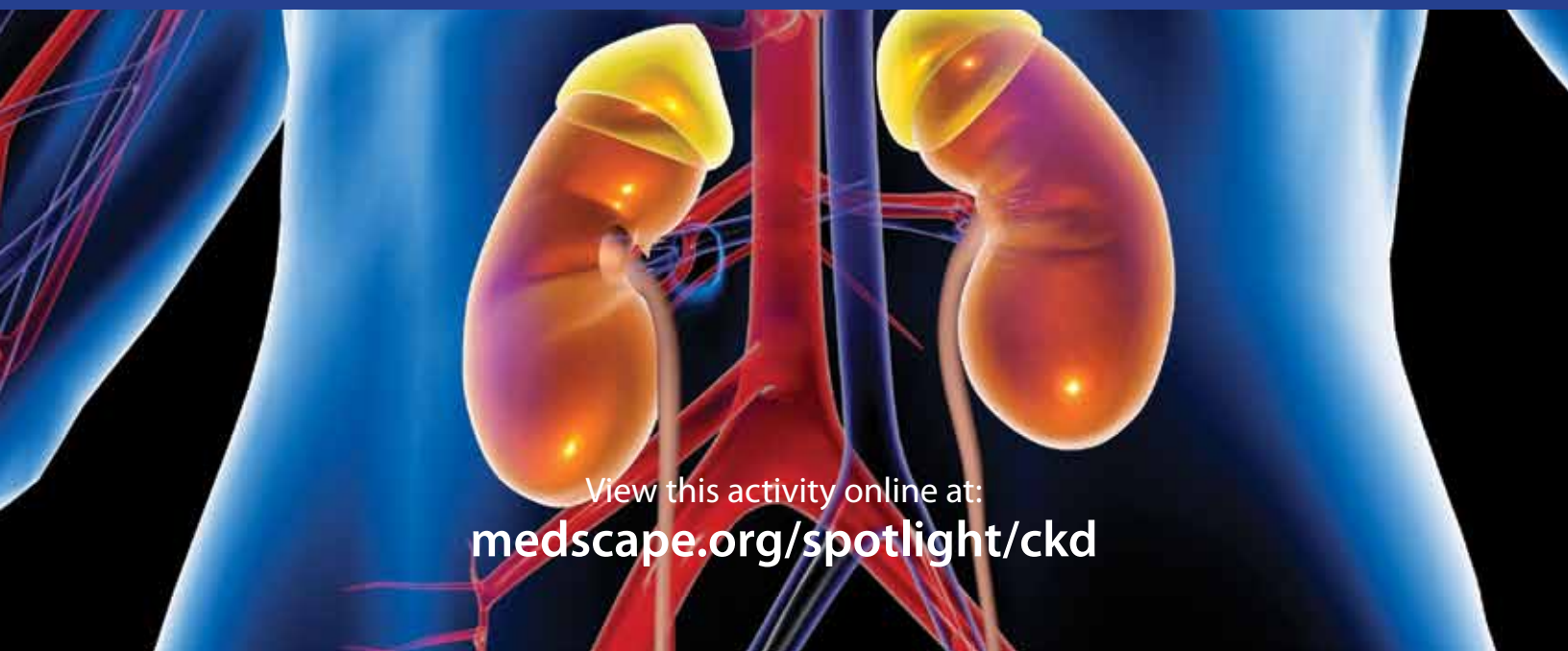

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Target Audience

This activity is intended for nephrologists, cardiologists, nurses, and other healthcare professionals involved in the treatment of patients with chronic kidney disease (CKD).

Goal

The goal of this activity is to summarize the cardiovascular risk factors associated with CKD and the strategies for reducing these risks.

Learning Objectives

Upon completion of this activity, participants will be able to:

1. Identify risk factors that contribute to the development of cardiovascular disease in patients with CKD
2. Compare available therapeutic options for the treatment of comorbidities in patients with CKD and the effect of these therapies on cardiorenal outcomes
3. Describe the role of therapies that are directed at preventing vascular calcification to reduce cardiovascular risk in patients with CKD

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CONTENT:

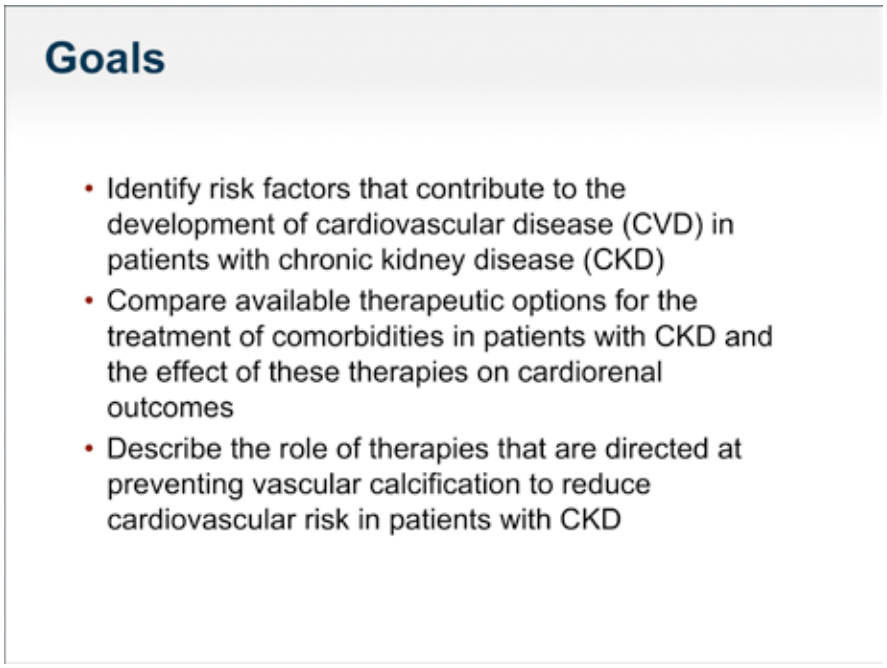
Introduction

Slide 1.

Kevin J. Martin, MB, BCh: Hello. I'm Dr. Kevin Martin, Professor of Internal Medicine and Director of the Division of Nephrology at St. Louis University. I'd like to welcome you to this Medscape panel discussion titled *Healthy Kidneys, Healthy Heart: Reducing Cardiovascular Risks in Patients With Chronic Kidney Disease.*

Slide 2.

Joining me today is Dr. Geoffrey Block, who is Associate Clinical Professor of Medicine at the University of Colorado Health Sciences Center and Director of Clinical Research at Denver Nephrology. Also joining me is Dr. Matthew Budoff, who is Professor of Medicine in the Division of Cardiology at David Geffen School of Medicine at UCLA and Director of Cardiovascular Imaging at Los Angeles Biomedical Research Institute and Harbor-UCLA Medical Center.



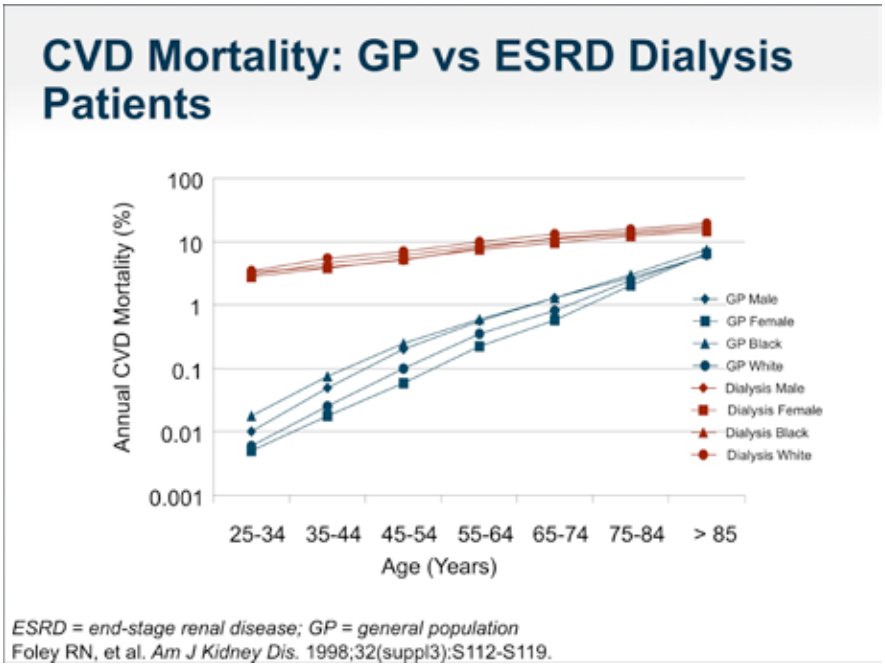
Slide 3.

The goals of the activity are to identify risk factors that contribute to the development of cardiovascular disease in patients with chronic kidney disease (CKD), to compare available therapeutic options for comorbidities in patients with CKD and the effects of these therapies on cardiorenal outcomes, and to describe the role of therapies that are directed at preventing vascular calcification to reduce cardiovascular risk in patients with CKD.

How often do you think vascular calcification is clinically significant in patients with CKD?

- Never
- Rarely
- Occasionally
- Frequently
- Always

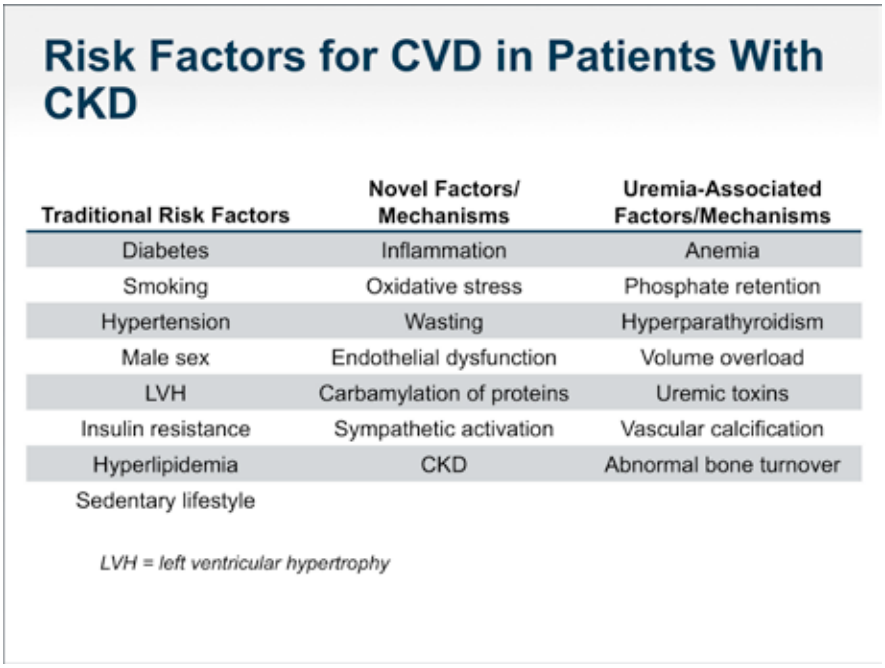
Overview



ESRD = end-stage renal disease; GP = general population
Foley RN, et al. *Am J Kidney Dis.* 1998;32(suppl3):S112-S119.

Slide 4.

First, I'd like to provide an overview of this issue. It has been realized in the past 10-15 years that cardiovascular disease is a major contributor to mortality in patients who have kidney disease, such that the mortality of those in their 20s and 30s can be equivalent to that of 80-year-old persons who don't have kidney disease.[1-3] Of course, this provoked a lot of investigation to try to understand what it is about kidney disease that contributes to the high incidence of fatal cardiovascular events.



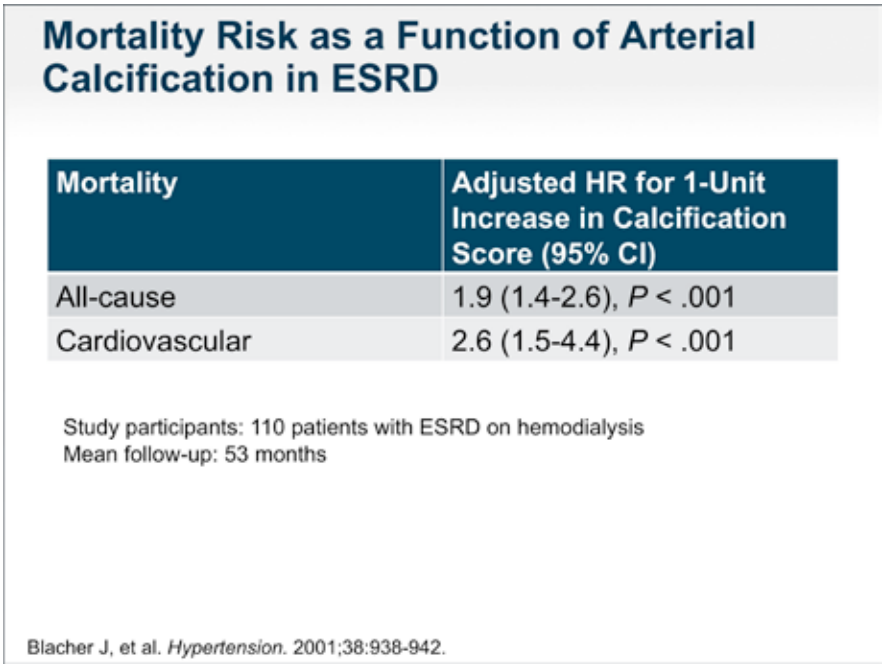
Slide 5.

A number of risk factors are involved: the traditional ones, such as diabetes, hypertension, smoking, left ventricular hypertrophy, hyperlipidemia, and the sedentary lifestyle that accompanies chronic illness. Then, over the years we've realized that a number of novel factors also contribute to cardiovascular risk, such as an inflammatory state or oxidative stress, endothelial dysfunction, alterations of proteins, and perhaps sympathetic activation.[4,5]

We should also consider CKD itself because there seem to be other factors in CKD that also contribute to increased cardiovascular risks. A number of those factors are associated with decreased kidney function. Some novel factors have arisen from this too, such as hyperparathyroidism; phosphate retention; and volume overload, which may be chronic; and a variety of unknown renal toxins.[4,5] Among the more interesting of these risk factors is vascular calcification, which may be linked with abnormal bone turnover.

This is an important issue because vascular calcification is extremely common in patients with CKD and can even occur in very young patients.[6]

This pointed the way to the question: What is it about CKD that can contribute to vascular calcification? Clearly, the worse the vascular calcification is, the higher the probability of mortality and other unfavorable outcomes.[7-9]

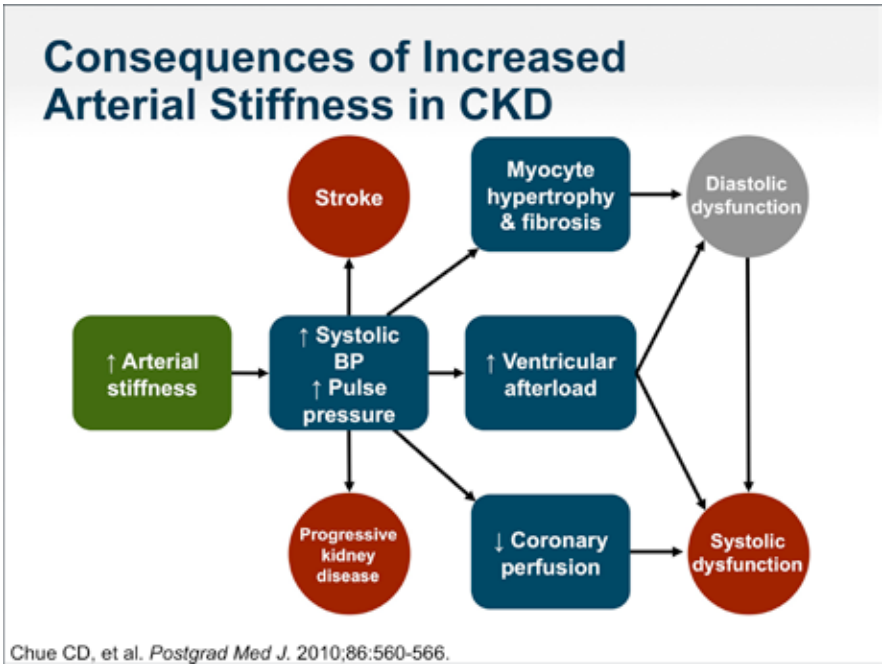


Slide 6.

Of particular interest is this apparent relationship between the skeleton and bone turnover there and the vascular calcification.

I'd like to ask Dr. Block to review the pathophysiology and see whether we can learn some things that may be relevant to therapy.

Geoffrey A. Block, MD: Kevin, you hit the nail on the head with regard to the fact that there are risk factors associated with CKD. I noticed the term "uremia" is on the list of risk factors. In fact, what we're learning is that abnormalities start to occur long before a uremic state occurs. Abnormalities that affect cardiovascular risk develop very early in the pathophysiology of decreased renal function.



Slide 7.

With regard to vascular calcification and cardiovascular events, we are dealing with a coming together of both atherosclerotic disease risk factors and arteriosclerotic disease risk factors. Nephrologists and perhaps many other physicians don't commonly think about the arteriosclerotic aspect of the illness – the hardening and stiffening of the arteries.

From a pathophysiologic perspective, we've learned that very early in the course of CKD, patients have a mismatch between their calcium phosphorus intake and their calcium phosphorus excretion. It almost certainly relates to their skeleton. The skeleton is paramount in regulating calcium homeostasis and, it turns out, in regulating phosphorus homeostasis through a variety of mechanisms.

We now know that abnormalities in calcium and phosphorus lead to phenotypic changes in the arteriovascular endothelium cells, which start behaving like bone cells, turning on proteins that tell the environment to calcify. The result is this combination of a hardened, stiffened artery and the underlying atherosclerotic disease that is present because of other risk factors.[10]

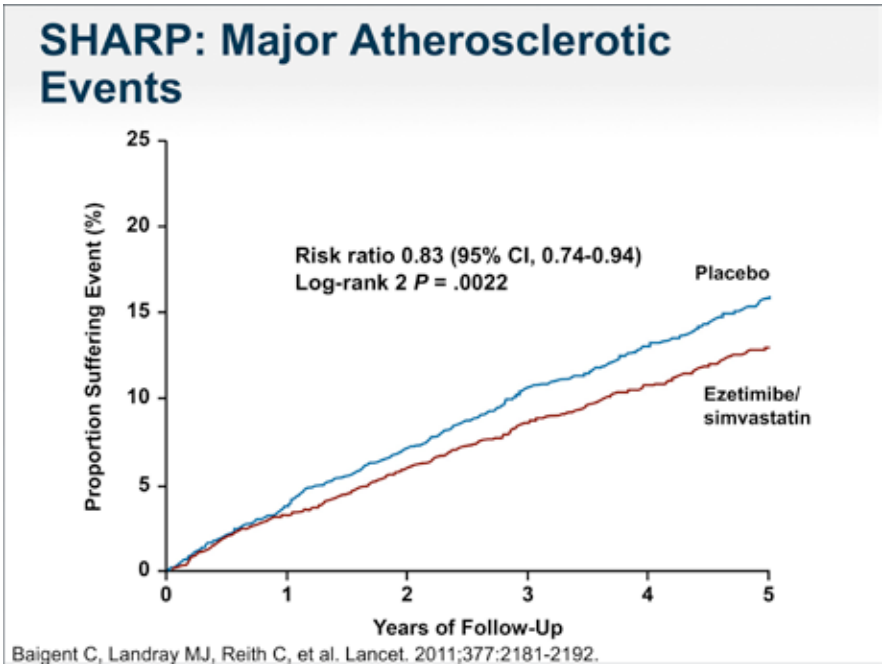
In patients with atherosclerotic disease – in particular, coronary atherosclerosis -- the addition of arterial stiffness manifest by aortic stiffness causes a mismatch in the coronary demand and availability. You can probably say that better than I, Matt [Dr. Budoff]. The stiffness causes this abnormal coronary perfusion, and it produces left ventricular hypertrophy and progressive hardening and stiffening of the artery.

We know that the vitamin D pathway is involved in this and that the phosphorus homeostasis hormones are involved. All of these variables seem to follow from an early reduction in kidney function.

Dr. Martin: That puts the field of nephrology back into the realm of cardiology where the tradition has been to try to understand the risk factors and begin to intervene early on. In this environment, we have to consider all of the traditional risk factors as well as some of these other factors that might also be involved. Let me ask Dr. Budoff: Where do we stand in terms of achieving cardiovascular risk reduction in patients with CKD? Are the traditional risk factors the most important here, or do they take a secondary role to some of these other issues?

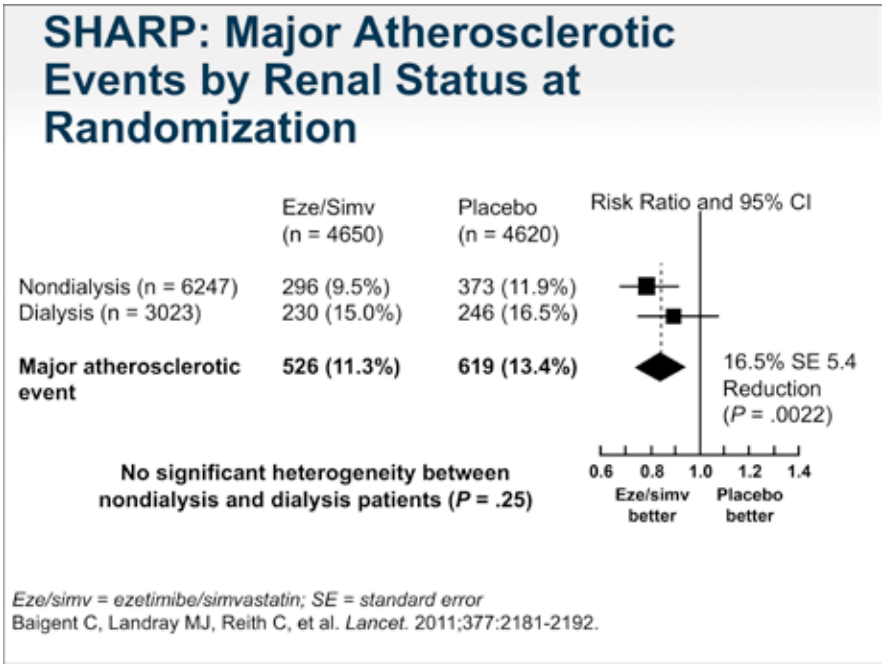
Matthew J. Budoff, MD: There's a huge interplay between the two. Hypertension is one of the leading causes of renal insufficiency and, of course, renal insufficiency begets hypertension. Renin-angiotensin control is very important. Statins are now being shown to play a role in reducing cardiovascular risk in chronic renal insufficiency and perhaps in end-stage renal disease (ESRD). The Treating to New Targets study found a renal subgroup that showed benefit with high-dose atorvastatin.[11]

Reducing Cardiovascular Risks



Slide 8.

That was followed by a very large trial, the SHARP [Study of Heart and Renal Protection] trial, the results of which were recently published.[12] This study included more than 8000 patients and showed significant benefit – about a 20% risk reduction – among dialysis patients, as well as those with renal insufficiency, by putting them on simvastatin/ezetimibe vs placebo.



Slide 9.

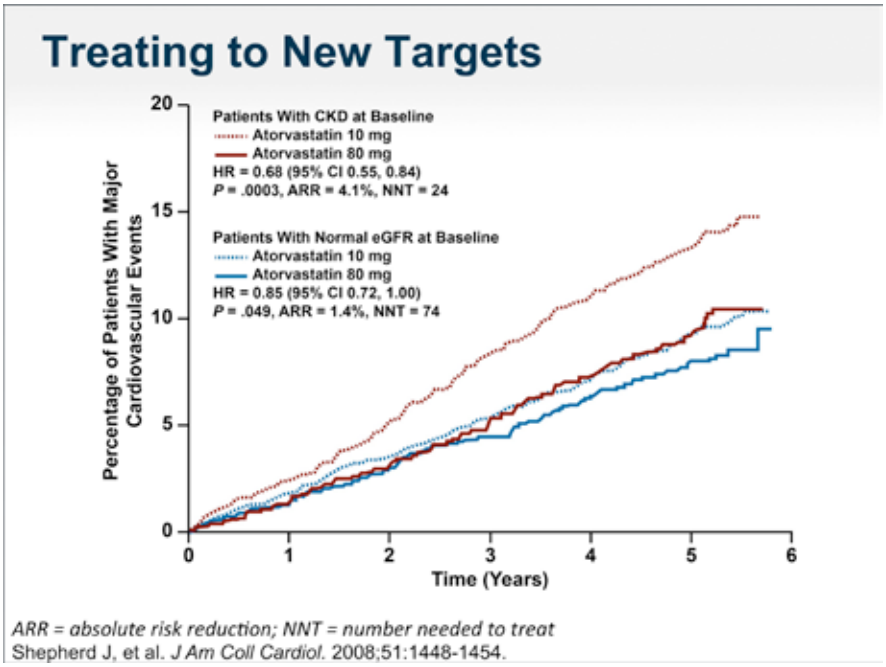
The goals of lipid control and blood pressure control – the traditional things that we do in cardiology – are very important in this population. I don't want to downplay the need for renin-angiotensin blockers and tight blood pressure control. That is very well established, and I think it's something that we are a little too [lenient with], at least in cardiology. This may be true in primary care

as well. Patients come in with excuses: I didn't take my pills today; I had too much salt last night; I had Chinese food. We don't really get the tight blood pressure control that the patients deserve.

Dr. Martin: These are important issues. In CKD, we probably need to begin risk reduction interventions early in the course if we're to avoid some of the [problems that we have discussed], such as the consequences of hyperlipidemia and calcification. In nephrology, it has not been in the mainstream to aggressively approach these issues early on. There is more of a precedent for [addressing] the traditional risk factors, and some of these newer ones are more difficult.

Dr. Block, should we begin to tackle these nontraditional risk factors early in the course of kidney disease, or is it sufficient to wait until the patient is approaching dialysis?

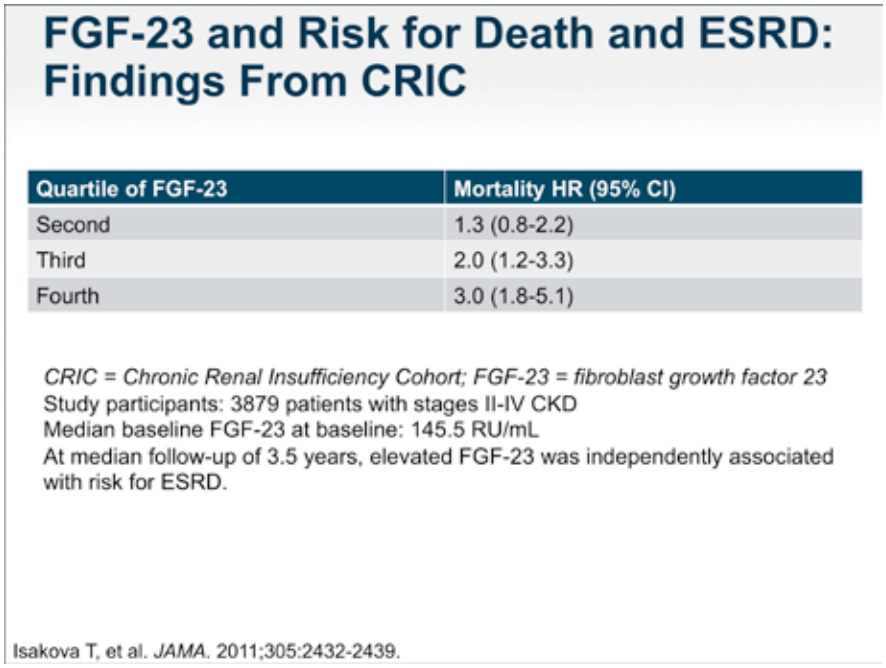
Dr. Block: First, I want to ask Matt a question: With regard to the SHARP trial and the positive outcomes, such as the reduction in atherosclerotic events, there's been a lot of debate within the nephrology circle. Is lipid lowering any less important in people with CKD than it is in those without it? My own take is that SHARP demonstrates that LDL [low-density lipoprotein] or lipid lowering is absolutely an important cardiovascular risk reduction strategy that we should be paying attention to.



Slide 10.

Dr. Budoff: Right. A better trial to look at that exact question is the Treating to New Targets trial.[11] About 1500 patients with renal insufficiency were randomly assigned to high-dose atorvastatin and another 1500 to low-dose atorvastatin. There was more benefit among those 3000 patients than in the 7000 patients who had normal renal function. The benefit was double. You can argue that on the basis of that substudy – a 3000-person substudy is pretty significant – the benefit is twice as important among patients with CKD as in patients with normal renal function.

Dr. Block: I think that's so important. I'm sorry to digress. Let me address the question that you asked, Kevin, which is about nontraditional risk factors. This is absolutely an area in which nephrologists need to change what they're doing. Unfortunately, our national guidelines and even our international guidelines recommend that the first point of intervention with regard to phosphate homeostasis is after the development of overt hyperphosphatemia. Many of us now recognize that that occurs very late in the course of CKD. People are essentially at the end of stage IV before that happens, and the downstream effects related to phosphorus occur probably at GFRs [glomerular filtration rates] of 60 mL/min/1.73 m^2.



Slide 11.

Data from CRIC, the Chronic Renal Insufficiency Cohort, that were just published this year show that approximately 25% of people with GFR of 60 mL/min/1.73 m^2 have elevated levels of FGF-23 [fibroblast growth factor 23], telling us that the phosphate homeostasis is already disturbed.[13] A very simple intervention that you've recommended, and I think we need to adopt, is taking a look at the fractional excretion of phosphorus early in the course of kidney disease. If it is elevated and/or increasing, we need to intervene early.

One of the large epidemiologic studies, ARIC [Atherosclerosis in Communities], which followed 13,000 people for nearly 15 years, showed that as the phosphorus level goes above 4 mg/dL, the relative risk for death goes significantly up – and this is in normal community-dwelling people.[14] By the time nephrologists start intervening, the relative risk hazard is doubled at least. Clearly, we should be intervening in that regard much earlier.

We've learned that vitamin D deficiency is important in this process, whether it directly affects arterial health or not. It's probably a consequence of abnormal phosphorus [via FGF-23] affecting vitamin D biology. I think we can manage the vitamin D issues if we intervene earlier.

Slide 12.

Dr. Budoff: From CRIC, we saw a graded relationship between renal insufficiency, starting with stage I and II disease, and calcification.[13] Phosphorus was a major predictor of calcification, even in the earlier stages. We have to start looking earlier, as you suggested, for the phosphorus imbalance that we see among patients even with mild renal insufficiency.

Dr. Block: It's remarkable. One study that I'm aware of looked at risk factors for rapid progression of calcification in people with kidney disease. The only 2 studies that I'm aware of both found that the phosphorus level predicts rapid progression, and this is a phosphorus level at which we don't even recommend intervention: 4.2 mg/dL.

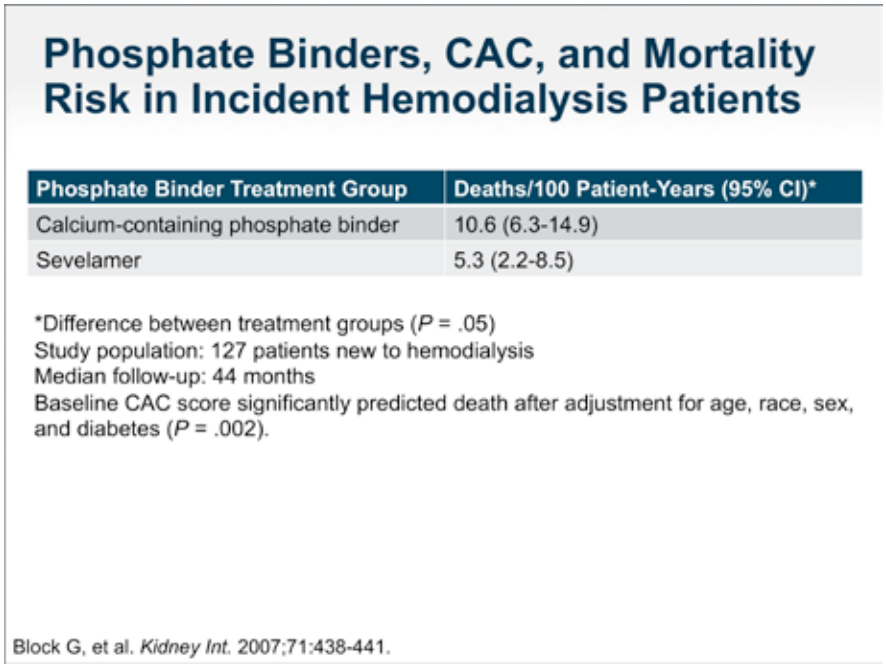
Dr. Budoff: I think we're going to find that the cutpoints were set high and perhaps were set conservatively. We're going to see more stringent targets for phosphorus as we learn more from these observational studies showing that patients have more cardiovascular events at what was considered a normal phosphorus level for renal insufficiency.

Dr. Martin: These are important issues because our methods of addressing phosphate retention with phosphate binders and with our dietary maneuvers are difficult in our current environment. None of the phosphate binders are approved for this purpose. We clearly need more intervention data to assess outcomes.

One important issue is to consider the population that's being studied. For example, the vascular calcification that is aggravated by calcium intake was brought to the forefront in patients on dialysis or prevalent patients. When studies looked at calcium-containing phosphate binders vs non-calcium-containing binders, the results were somewhat disappointing, with no really convincing outcome data. That makes us question the initial premise. Does that mean that calcium is not a factor, or is it possible that the experiment was wrong because the population was wrong?

Maybe I should ask Geoff to comment on his studies where he took incident [hemodialysis] patients and asked the same question.[15] Perhaps you can summarize the outcomes of that. There may be a fundamental issue that's a problem in terms of gathering data.

Dr. Block: This is clearly an area of controversy in our world – nephrology. Actually, now it's broadened to the large population of patients receiving osteoporotic treatment. There's a raging debate now whether calcium supplementation affects cardiovascular risk in elderly women with osteoporosis.



Slide 13.

No offense to any of the other investigators, but I'm pretty convinced that our study was quite conclusive in what it showed. We randomly assigned 129 new dialysis patients to get a calcium-based [phosphate] binder or sevelamer-based binder.[15] We followed them for 18 months with serial CT imaging of their heart, and then followed them for close to 5 years for outcomes. We found a significant difference in progressive calcification of the coronary arteries and a significant effect on survival.

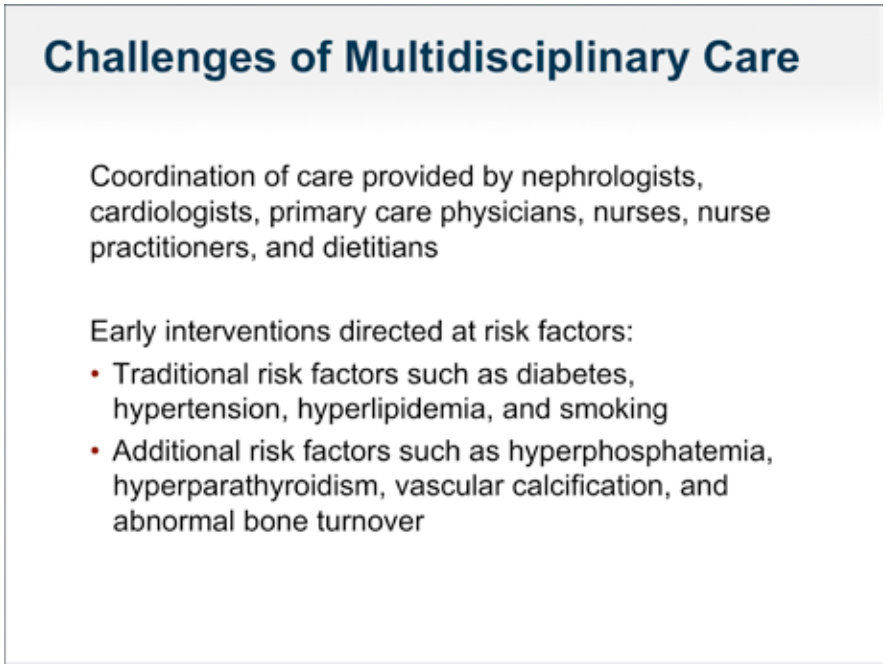
In the literature on this issue, there are about 10 trials, 9 of which suggest that there is risk associated with excess calcium load in this population. In the early CKD population, we don't have a lot of data. The data that we do have seem to confirm or at least support that same hypothesis, so we have to be a little concerned. I agree with you that we clearly need some outcome trials.

I'd like to make another comment about early intervention and phosphate binders. Our world overlaps with cardiology quite a bit. The data on niacin affecting serum phosphorus, affecting the intestinal transport of phosphorus, and potentially affecting outcome are interesting. [I would also like to mention] the very important issue of phosphate additives to food. It's going to be very difficult to conduct an outcome trial with phosphorus intervention if we have almost no idea of how much phosphorus is in the food that we eat. It's going to be challenging.

Dr. Budoff: To revisit Kevin's earlier comment: We have outcome data from a study that Kalantar was the lead investigator for – an NIH [National Institutes of Health]-funded study that followed about 200 patients.[16] About half of them happened to be on calcium and half were on sevelamer. There's clearly a long-term survival benefit in the patients taking sevelamer. [It isn't clear] whether the earlier trials were too short and the curves hadn't fully diverged yet or whether there was overcontrol from what we do in clinical practice in a clinical trial setting. Observational data continue to come out, but there may be some difference in binder approaches.

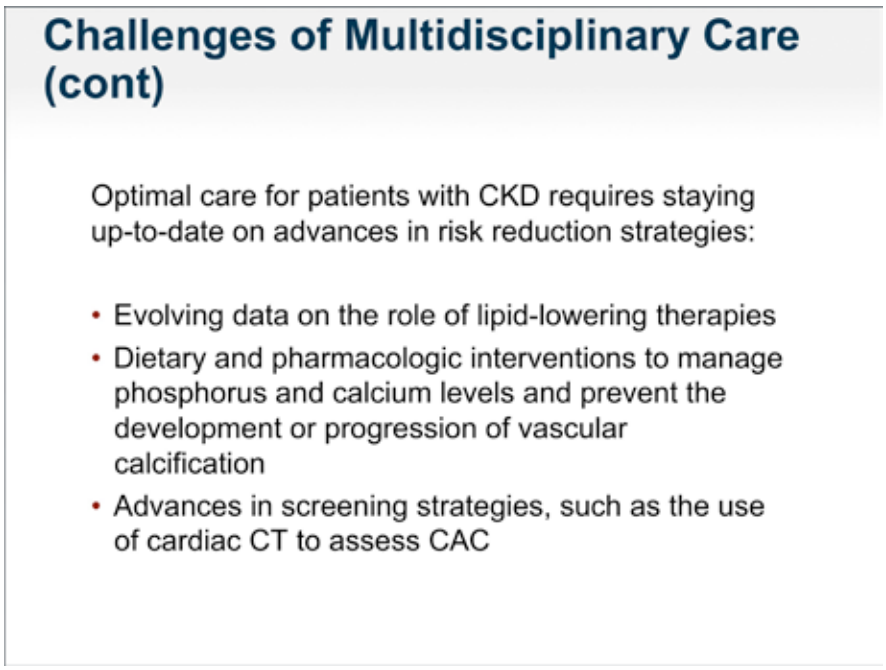
Dr. Martin: It also raises the issue of the timing of intervention. Intervening earlier in the course of CKD would involve a lot of healthcare delivery issues.

Multidisciplinary Care



Slide 14.

Many patients who are seen by nephrologists are also seen by primary care physicians. They're also seen by cardiologists because of the attendant cardiac issues. We have a reluctance of one discipline to interfere with what may be the turf of the other. Primary care physicians may be unwilling or reticent to change a patient's vitamin D regimen or initiate a phosphate binder and would leave that to the nephrologist. Nephrologists don't want to change the lipid-lowering regimen because they think that the cardiologists will do it. Then we have patients who are seen in the CKD clinic, perhaps by nurses or nurse practitioners, and they want prescriptions renewed. They might be told "the cardiologist will refill that one for you" or "the primary care physician will do that."

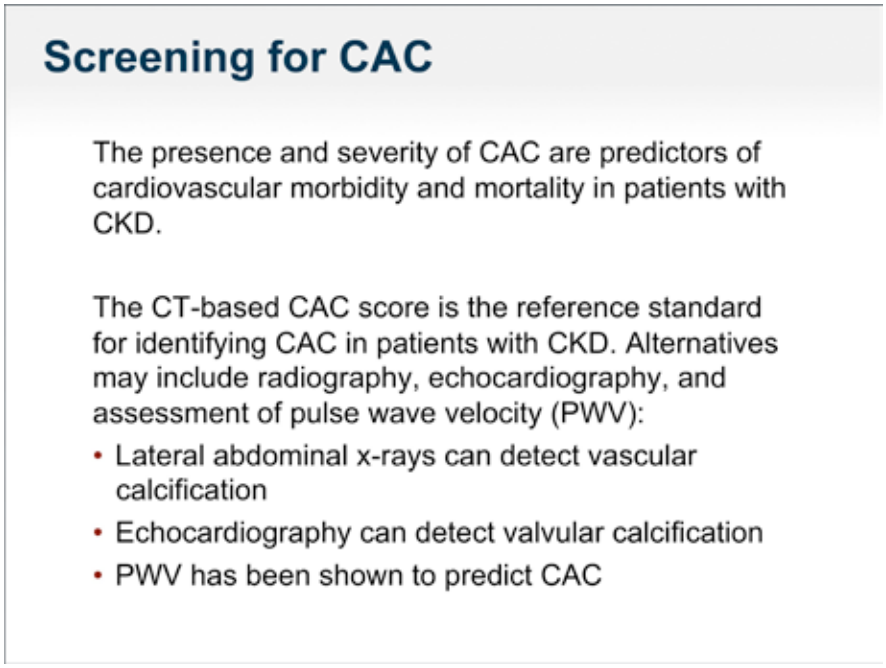


Slide 15.

In terms of healthcare delivery, we face enormous challenges of trying to coordinate care. And whose responsibility is it? We have to begin to communicate better between the various disciplines if we're going to have a coordinated approach to this. [This also includes] dietary issues. If we are to have a true CKD clinic, we will need input from all of the disciplines, including dietitians and nurses, [to address the] anemia, blood pressure control, lipid lowering, and all of the other variables that occur in this patient population.

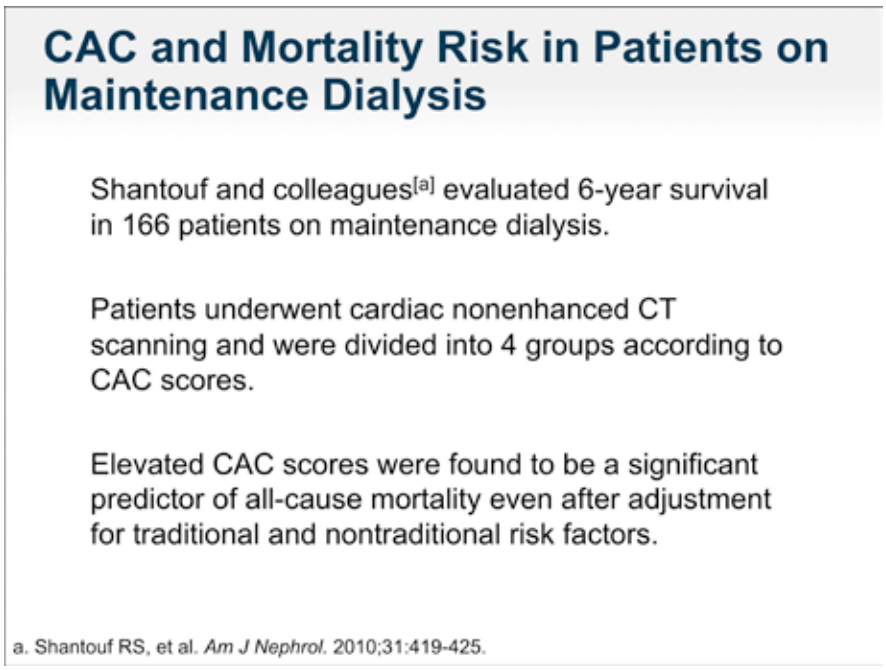
Dr. Budoff: There's a huge referral bias too. Nephrology takes care of everybody with stage IV or V CKD, but many patients with mild-to-moderate disease do not see nephrologists. It may be perceived that statins are not needed and that internists and primary care physicians can deal with the blood pressure issues. There also can be a treatment gap: where there's only one provider who may not be up-to-date on all of the newer aspects of phosphate control and calcium or phosphate binders or the earlier use of statins.

Screening



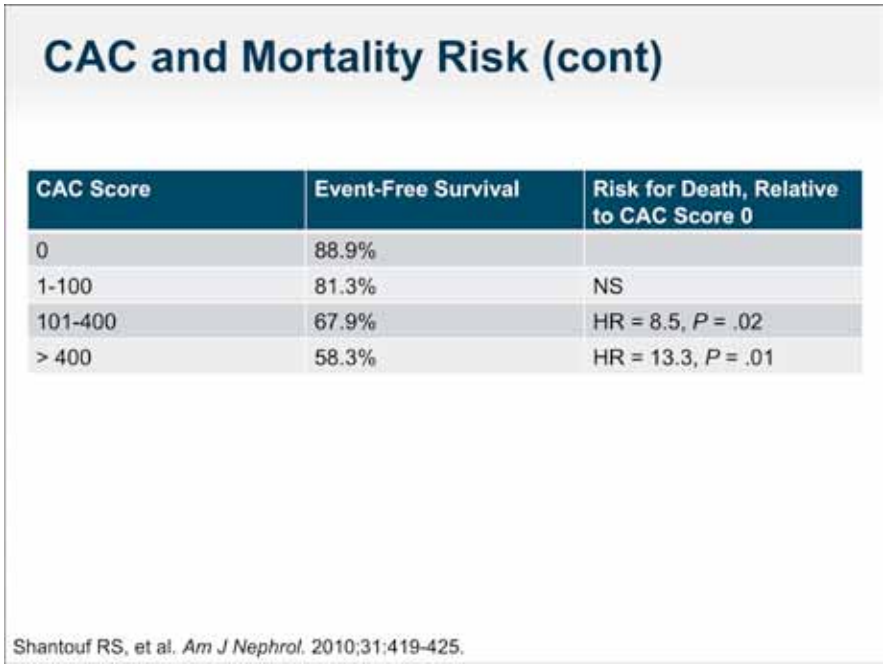
Slide 16.

Dr. Martin: Even in terms of practice guidelines, [there's a question about] how vigorous we should be in screening for some of these issues, such as vascular calcification or valvular calcification. Do you think that we're at the stage where we should be actively screening for that as a problem in patients with CKD?



Slide17.

Dr. Budoff: It's clear that CKD elevates risk, and you both addressed the issues behind that. There is increased risk from both medial and intimal calcification. CT calcium scoring is now advocated by the American College of Cardiology and the American Heart Association for intermediate-risk patients. [I hope there is consensus that] patients with any level of CKD are at least intermediate-risk patients. We have the KDOQI [Kidney Disease Outcomes Quality Initiative] guidelines and other guidelines.[17]



Slide 18.

Knowing the vascular calcification level – whether you detect it on echocardiogram or CT scan or even a plain film – is helpful because patients who have a lot of vascular calcification are at much greater risk in the short run than those with no or undetectable calcification.[7-9,16,18]

Dr. Block: Matt's done a tremendous body of work in this area. Screening is important not only for identifying people with the disease, but also for detecting a change in calcification, which tells us about outcome. Nephrologists tend to have a bit of therapeutic nihilism, meaning we're not entirely convinced that we can do an intervention that will affect outcome. But your [Dr. Budoff's] work has shown quite clearly that even if calcification is present, if you can stop the progression, patients will do much better than those who continue to progress. This is now being shown in patients with kidney disease. I think that's important.

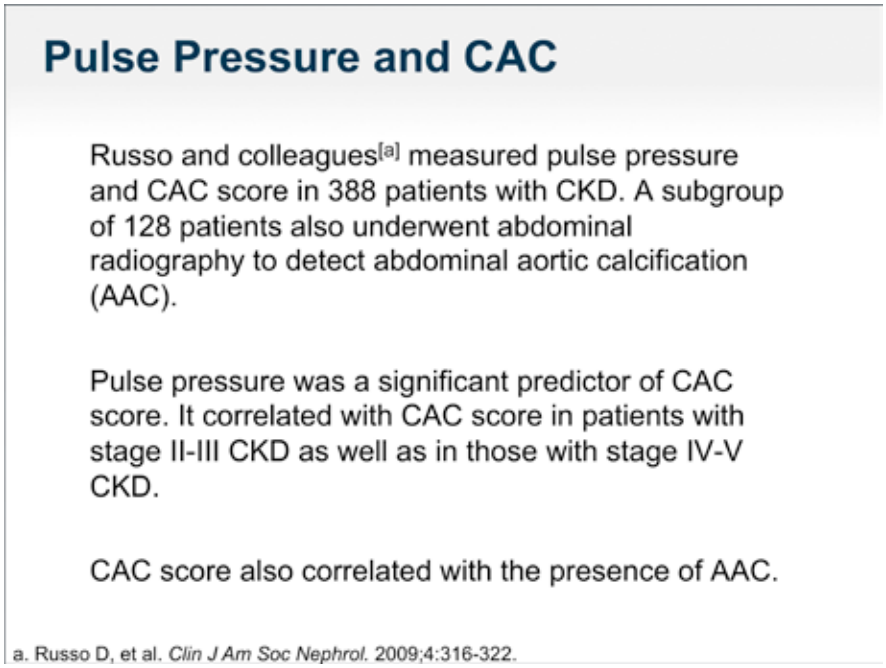
Dr. Budoff: CRIC will add to that literature because we're going to have rescans in all of the participants and follow them for future events. We'll have even more data in the renal-insufficient population. [The results may clarify] how important calcium progression is and what modulates it in renal-insufficient patients.

Dr. Martin: Should we include simple measurements like pulse pressure as a stimulus to get more formal screening?

Dr. Budoff: Pulse pressure is very important, especially in renal-insufficient patients.[19-21] You previously mentioned the stiffening of the arteries and medial calcification as another mechanism behind that. Pulse pressure is a simple, widely available test that would at least stimulate you to look further, whether you go on to formal endothelial function testing or a more formal calcification testing with a noncontrast CT scan. The radiation dose for calcium score is the same as a mammogram. Clearly, these patients, even the female patients, are at infinitely higher cardiac risk than breast cancer risk. If we're going to subject them to radiation in the form of annual or every-other-year mammograms, I think that a CT scan of the heart once every 5 years would be beneficial.

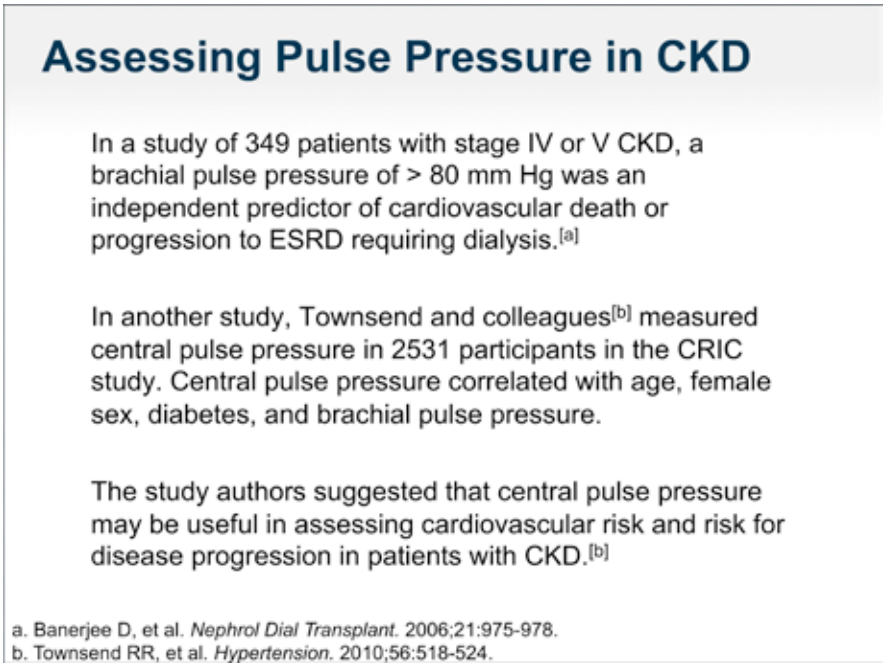
Dr. Block: Do you think that there will ever be a time when pulse wave velocity testing reaches the mainstream as a screening or monitoring tool?

Dr. Budoff: I would like it to. It's very simple and straightforward, and it's diagnostic. There have been some nice studies out of France that show that the survival curves are markedly different – a fast pulse wave velocity and stiff vessels vs a slower pulse wave velocity or normal compliant vessels. It's an elegant test. There's no radiation; it takes 10 minutes to perform, and it can be done by nurses or nurse practitioners. Billing [is an issue], but I think this test will be used more. I don't know whether it will ever be mainstream in that regard.



Slide 19.

Dr. Martin: In the general day-to-day practice of nephrology, one sees patients with CKD and in the problems list, there's hardly ever a specific mention of the pulse pressure. Sometimes the blood pressures are circled or annotated to say that patients did not take their medicines today, and 4 lines down, the same medications and "see in 2 months." There may be a credibility issue here in the perception of nephrologists that either they can't do anything about this as a risk factor or it's not important. That's something that probably should change in day-to-day practice.



Slide 20.

Dr. Block: Just writing the pulse pressure down [would be beneficial]. Making somebody stop and think about what the pulse pressure is and write it down so it can be seen serially over time – that would be an advance.

Dr. Budoff: It's a predictor in nonrenal patients as well as in the CKD population, so getting that message out to primary care would be very important.

Dr. Martin: It even extends to echocardiographic reports, in which sometimes calcification is not even mentioned, but if you specifically ask about it, then it's clear that the valve is calcified. When patients with CKD come for echocardiograms, perhaps the calcification should be specifically reported: Note that this patient has significant calcification of the mitral valve or aortic valve, for example.

Dr. Budoff: The same problem exists in the setting of CT screening for lung cancer. There can be tons of atherosclerotic calcification in the aorta or in the coronary arteries, but it's not reported because the primary intent of the CT scan was to look at the ung fields. Even going back to existing lung CT scans may – for free – give you some very important information about atherosclerotic risk.

Dr. Martin: That's a good point. What we've done today is focus on this issue of cardiovascular mortality in patients with kidney disease. We've discussed the risk factors and the need to intervene early in as many of these risks as possible to try to get better outcomes for patients. With the body of epidemiologic evidence that exists, there's ample plausibility that this would be a reasonable approach. We have to figure out the healthcare delivery issues of trying to get this broad landscape of issues into the CKD clinic to try to get better outcomes for patients.

Slide 21.

Thank you, Dr. Budoff and Dr. Block, for this interesting discussion today. I'd like to thank everyone for joining us for this Medscape panel discussion and ask you to take a moment to complete the post-test questions and the program evaluation.

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