Episode 12 – Solutes, Scaling, Sex: Are we getting the dosing of dialysis, right?

Guest: John T Daugirdas, MD, FACP, FASN

Peter Kotanko

In today's episode of Frontiers in Kidney Medicine, and Biology, we discuss aspects around dialysis patient prescription. My guest is the nephrologist Dr. Daugirdas, Clinical Professor of Medicine at the University of Illinois School of Medicine in Chicago. In the dialysis world, he's a household name and one of the leading figures in the field. He has published about 300 papers and developed methods of dialysis dosing that they used widely today. I remember very well when I moved into nephrology and was rounding in dialysis facilities. I had his book, a sort of Bible, the “Handbook of Dialysis” in my pocket. It wasn't only me -- every nephrologist that I was working with, every nephrologist, I was training in the many years to come, had this book in his or her pocket. So, he has contributed tremendously to the progress in the field, to education, and I think his contributions cannot be overstated. So welcome, John. It's a great pleasure having you with us.

John T Daugirdas

Thanks, Peter. I think it's a wonderful program you have and I'm very happy to be part of it.

Peter Kotanko

Thank you, John. When I went to PubMed and would type in “Daugirdas- J,” I saw that your work really dates to the 1970s. This is quite remarkable. And I'm wondering, John, what have been the major advances in dialysis in the past 30 to 40 years? Is it technology? Is it processes? Is it drugs? Or a combination of those? How do you see thing from your vantage point? I mean, you have a long view here.

John T Daugirdas

I passed my nephrology boards in 1981. And before that I was a nephrology fellow and starting out in research. At that time, coil dialyzers had just stopped being used. And we were still dialyzing with plate dialyzers Cuprophan (cellulose). The membranes were arranged in a series of parallel plates. Hollow-fiber dialyzers were just beginning to be manufactured. People were looking at new membranes. They were looking at synthetic membranes for the first time -- membranes that would allow a high flux -- passage of larger molecules through their pores, specifically polyacryonitrile (PAN).

In terms of the dialysis procedure, not that much has changed in the last 40 or so years. Membranes have been improved. There are many more high flux membranes available now that are good.

The dialyzer membranes at the time were made out of cellulose. And cellulose, on contact with the blood would activate complement. This would cause some inflammation, such that 30 minutes into dialysis, there used to be a large fall of the blood neutrophil count, sometimes as much as 70, or 80%, which subsequently would go back up. Sometimes this was associated with chest pain and back pain.

There was a time when hollow fibers dialyzers were being sterilizing with ethylene oxide. This would soak into the potting compound, (potting compound is the goop at the ends of the dialyzer that anchors the hollow fibers) and leach out during dialysis and cause anaphylactic reactions. This has now been taken care of. But really, dialysis has not really changed that much. In fact, in a way it's gone backwards, because when I started out, there was an emphasis on home hemodialysis. We had a large number of home hemodialysis patients at the VA hospital where I trained. Initially, people were talking about longer dialysis treatment times, three times a week, and some people were dialyzing using daily dialysis. John DePalma in California was advocating daily dialysis, and this was back in the 70s and 80s.

There have been some advances in terms of the machines. The main advantage has been in controlling precisely how much fluid is removed during dialysis. In the early machines, you had to guess the pressures across the membrane and adjust the transmembrane pressures, which then would determine how much fluid was removed. Now they have volumetric modules for removing fluid with which you can precisely dial in either no fluid removal, removal of one liter per hour, or removal of a half-liter per hour, whatever you like. But the basic dialysis procedure really hasn't changed.

Now there are some new membranes available when you dialyze patients. The normal kidney removes molecules up to molecular weight of 40,000 to 50,000. So-called “low flux” dialyzer membranes remove very few molecules in the higher molecular weight range. One of the things that we measure is beta-2 microglobulin. And with low flux dialyzers, with their low flux membrane, no beta-2 microglobulin is removed, almost. But even with high flux membranes, you don't remove many molecules in the 20 to 40 kilodalton range. And so now we have these

membranes called Medium Cut-Off (MCO) membranes, that remove these higher weight molecules, these larger molecules. But in terms of the dialysis procedure, not that much has changed.

The other two parts of your question had to do with drugs and process, and I think with drugs, there have been major advances. The first one was erythropoietin. When I started out in dialysis in the 80s, it was very common to have people with hematocrits in the 20s and people required transfusions all the time. Erythropoietin really changed the ballgame in terms of of treating anemia of dialysis.

Many people in the past were taking phosphorus binders containing aluminum. Aluminum poisoning was prevalent in the 70s and 80s because of ingestion of these aluminum containing phosphorus binders. This was reflected by bone disease and problems with dialysis dementia. Today aluminum containing binders are very rarely used. Then the next issue was use of calcium-containing phosphate binders, even though calcium containing binders can be safely used and some are widely used. Calcium carbonate contains 40% calcium, and to get the required amount of phosphorus binding, you had to be giving patients an equivalent dose of two grams of calcium a day -- this was too high and was associated with vascular calcification, especially calcification of the coronary arteries. Today we have better phosphate binders. We have binders that are more effective and binders that contain no calcium. So that problem has been solved.

Most recently we have binding drugs (like sodium zirconium cyclosilicate developed by ZS Pharma and patiromer) that bind potassium and so can help us control potassium. So, I do believe that in terms of drugs, there have been major advances made. And now we better understand which antihypertensive drugs lower cardiovascular risk in dialysis patients -- specifically, thanks to Dr. Rajiv Agarwal and his work with the beta blockers. So, I think that in terms of drugs we've made major advances.

Probably the biggest advance in dialysis is process. When we were doing dialysis in the early 80s, there really wasn't this concept of quality improvement or quality management, and especially, of gathering patient feedback or patient reported outcomes. Emphasis on this has been very good. Getting information from patients, I think, should be done much more frequently; currently now the quality outcomes are measured in patients only once a year with a long questionnaire. I think the future will be to assess responses to just a few simple questions

regarding how patients are doing and doing this multiple times, perhaps even every day. One can ask five or six simple questions about how patients are doing and get an answer every day. There's some very interesting work showing that if you follow patient reports of how they feel and follow this every day, you can pick up a change (in a patient's condition) very early, and often this will predict an adverse change in their health, and perhaps you can intervene. One area has been, for example, vascular access. By just asking patients every day how their vascular access is doing may can give you better warning of a potentially failing vascular access than the results of fancy tests.

Another process improvement that has taken place in the United States, is, and it's still ongoing, has to do with limiting the use of venous catheters for vascular access. And perhaps also grafts, resulting in an increase in the use of arteriovenous fistulas. There are questions about whether there's a limitation to this (AV fistula use), especially in the elderly patients. Probably part of the benefits in survival and hospitalizations that have been noted in the recent past have been due to the area of emphasizing putting in AV fistulas.

I presume your authors, your audience will know what an AV (arteriovenous) fistula is. When you do dialysis, obviously, you need to have some access to the blood. The safest access is to hook up an artery and vein surgically under the skin. Nothing sticks out from the skin, there's no portal for infection, and then when you dialyze…, then you put one needle into the upstream part of the access and another into the downstream part of the access. And then there's a whole other dimension in terms of perhaps using a single-needle access. You can do dialysis from a single needle with periodic reversal of flow.

And one final aspect of processes: people are realizing that one of the major problems that dialysis patients face is not only removal of uremic waste products, but control of salt and water and fluid balance. The big question is, can we somehow measure and optimize fluid balance in our dialysis patients? Dialysis patients will take in 7 to 11 liters of fluid a week, a little bit more than a liter a day. If you dialyze the patients three times a week, on Monday to Wednesday, you have to remove two liters, and over the long weekend, you'll have to remove three liters. And this sawtooth pattern of fluid gain and removal is harmful to patients. Some are fluid overload all the time, even at the end of dialysis, but also, accumulation of fluid during the intradialytic interval can cause cardiovascular problems -- accelerated left ventricular hypertrophy and vascular damage. One problem is you want to avoid this fluctuation. And how do you avoid it? Well, you can avoid it on the intake side. The amount of fluid dialysis patients

take in relates to how much salt they take in, because sodium tends to drive thirst and thirst tends to drive fluid intake. However, sodium also drives food intake. Once you start to impose any kind of food restriction in dialysis patients, you tend to restrict their food intake, which is bad. And, you complicate the relationship with their family and caregivers. Because if you want to put dialysis patients on a very low sodium diet, sometimes if food is prepared in the family, the family cook or other people in the family don't want to be forced onto such a low sodium diet. Some dialysis patients eat largely in restaurants; their only access to food may be food that they get from fast food places and restaurants. So it's very difficult to restrict sodium intake in dialysis patients but it is necessary. And when sodium restriction is followed, it does limit the amount of fluid gained during the dialysis treatment.

Whatever fluid that you gained during the intradialytic interval, which is that period between the time you got off dialysis, and the time you get on dialysis, has to be removed over four hours. If you gain three liters of fluid, say over the long weekend, and then you are dialyzed for four hours, you have to remove 800 mL per hour of fluid during the dialysis procedure. The patient's blood volume might be around five liters, and plasma volume, maybe three liters, so you have to remove the entire plasma volume in a course of a four-hour interval. The only way you can do this is because as you remove fluid from the blood space, you get what's called refilling. Fluid migrates from tissues around the blood vessels back into the vascular compartment. Because of refilling, you don't totally deplete the blood volume during the time that you that you have your dialysis treatment. However, this still causes hypotension in a number of cases and low tissue perfusion. And now we know that dialysis that's associated with rapid fluid removal is associated with damage to organs and stunning. One of the key organs that people have been looking is the heart and they've performed fancy imaging tests of the heart during dialysis procedures. And they show that ventricular wall motion abnormalities are present, suggesting that the myocardium is not getting enough blood during dialysis.

There's also stunning in the brain, evidence of ischemic damage to the brain in dialysis patients, and this has been associated with low perfusion. And when people look at the microcirculation during dialysis, they find that regardless of the blood pressure, there are also changes in the microcirculation -- blood doesn't flow well through very small capillaries for whatever reason during the dialysis procedure.

The problem is that it’s very not that easy to figure out how much excess fluid a patient has. Sometimes you can examine a patient, and typically, in a non-uremic patient, as medical school

students are taught, if you have fluid overload, it tends to back up in the veins, and you have jugular venous distension. You can see pulsation in the neck veins, you can you get edema of the legs, you can edema elsewhere -- presacral edema. And the problem is, sometimes a dialysis patient can be markedly fluid overloaded, but there can be few signs of fluid overload. Of course, if you listen to the lungs, sometimes you can hear rales. But even so, physical exam is not that useful.

There are multiple technologies that now are just starting to be looked at, that might help us. Even as a medical student and resident, I always had trouble. It's not that easy to tell, sometimes, to what degree a patient is fluid overloaded. And so, technology can help.

There are a number of new technologies. One is bioimpedance, which looks at the resistance to electrical current going through the body. This can give some idea to what degree a patient is fluid overloaded. Other technology looks at the lungs. You can do an ultrasound of the lungs. What's more important than fluid overload somewhere in the legs is how much extra fluid you have in the lungs and the central circulation. And a good test of that is to do lung ultrasound. You can see these vertical lines that appear. And you can count those, and that gives you some idea of to what extent the lungs are fluid overloaded. There are some high-tech jackets that are being tested in heart failure patients that also give a measurement of lung water.

So, whereas the basic technology for dialysis has not improved very much, certainly, drugs have improved, and processes have improved, as has technology with regard to fluid overload. Some of this is fairly exciting and I do think that that's something to look forward to.

Peter Kotanko

Thank you, John, really for sharing your view on this on this question. As you say, the fundamentals of dialysis, meaning the removal of solutes following a concentration gradient has not changed much, the physics haven't changed, but many of the components involved have changed and have been improved. In both technologies and processes. And of course, also drugs now. When I was for the first time exposed to dialysis, I believe it must have been as a medical student, dialysis was called as a quote unquote, “artificial kidney.” And, first of all, I was impressed that dialysis was an artificial kidney. But then I felt it was a huge overstatement because, in the kidney, in the glomerulus you have a filter that, for example, lets large molecules pass. In the kidney we have a delicate highly developed system like the proximal tubule, Henle’s loop, the distal tubule, the countercurrent system etc., etc. where most of the substances that

have been filtered are regained. But this is not the case in dialysis -- there is no regaining of substances -- at least not in the way that we know dialysis today. So, what's your view on that? This talk of creating membranes that look like the glomerulus. How effective is this, when you consider that you don't have this this intricate, highly effective system of regaining molecules, proteins and other substances?

John T Daugirdas

It's a very good question Peter. The kidney basically is a filter connected in series with the reabsorber. So, what happens is, that you filter 180 liters a day, an ultrafiltrate from the plasma that contains dissolved solutes, but then you only excrete 1.5 liters of that. So, you reabsorb 178.5 liters during the day. The kidney is very smart and it can selectively alter what it reabsorbs. It's sort of like a smart machine. So, the kidney can reabsorb more acid. It can reabsorb more base. It can change the amount of sodium that it reabsorbs, change the amount of potassium. It can reabsorb protons, as I mentioned.

I know, when I was in medical school, people were saying, well, why do you want to be in nephrologist instead of a cardiologist? Cardiologists basically treat just a stupid muscle, it just pumps and that's all it does. The kidney's really a very, very sophisticated computer, device, and machine. And that's not even talking about the other metabolic functions of the kidney. You have manufacture of erythropoietin. You have 1-hydroxylation of 25-hydroxyvitamin D. You have gluconeogenesis and metabolism of certain amino acids. Some people are trying to mimic the role of the kidney by seeding the fibers of hollow fiber dialyzers with kidney cells in an effort to replicate some of that smart functionality. So, it is very simplistic to say what the kidney does is that it just filters and removes molecules.

Albumin has a molecular weight of about 60,000. And, of course, albumin is held back by the kidney --. part of that is because of its negative charge -- by the glomerular basement membrane. But the kidney will filter many compounds that are in the 20 to 30 or 40 kilodalton range. If you enlarge the membrane pores of a dialyzer, if you make them too big, then you start losing albumin, which is considered a bad thing, because, of course, serum albumin level is probably the single best marker of survival in patients. So, you don't want to lower the serum albumin levels, and you don't want to make the holes in the membrane too large -- otherwise, you'll start spilling albumin.

Now, there is one theory out there that losing some albumin may be good. You have one class of uremic toxins that are tightly bound to albumin called protein-bound uremic toxins, and you can't get rid of those by normal means…. Normally, they're stripped from albumin in the kidney in the distal tubules. One idea was, that if you lose a little bit of albumin, such as happens during peritoneal dialysis, maybe that's a way of removing some of these proteins bound uremic toxins. But in general, you don't want to have make the holes in your dialyzer membrane so large that you start spilling albumin, although you do want to start getting rid of some of these (higher molecular weight) compounds.

Beta-2 microglobulin has a molecular weight of 11 kilodaltons. You have this range from 11 to 40 kilodaltons, where you have substances that accumulate in uremia that are associated with inflammation. And the idea or question is, if you could make a membrane that gets rid of these compounds, will you improve the situation? And the problem with some of this is, if you look at drugs, you have a sigmoidal dose response curve, right? Pharmacologists teach that first you have very low quantities of a drug that do nothing, then at a certain concentration, the drug starts to become active. And as you increase drug concentration further, if you're on a steep part of that sigmoidal dose response curve, changing the concentration of that drug will make a big difference in terms of the efficacy of that drug. But then once you get above a certain concentration, giving more drug doesn't have any effect as you get onto the flat upper part of that S-curve.

If you look at the plasma concentrations of some of these very large molecular weight substances, for example, beta-2-microglobulin, the normal concentration is 1.0 to 2.0 mg/L. In a dialysis patient being dialyzed with the membrane that doesn't pass any beta-2-microglobulin who has no residual kidney function, the beta-2-microglobulin level be around 30 mg/L. So, more than 10 times the normal value. With a high flux membrane, you can reduce this level down to about 25 to 24 mg/L. And then if you jump through a lot of additional hoops, you can make get it down to range of 19 to 20. But the question is, if you're lowering the concentration of some substance, and you're reducing it from, say, 30 times normal to 20 times normal, are you still on that upper flat part of the sigmoidal dose response curve, such that you're not really making a big difference. Maybe to make a big difference, you might have to reduce B2M concentration down below 10 mg/L, or below 5, which is what you have when you have with substantial residual kidney function. So, I think the jury's still out. These MCO membranes can show a (predialysis) concentration decline sometimes up to 20 to 30% (of high-molecular-

weight uremic toxins), but the question is, are you making clinical difference -- does the patient's survival or quality of life improve?

Peter Kotanko
My concern is also that we may lose beneficial substances, we may lose binding proteins for hormones, certain coagulation factors, factors that are relevant to the immune system. As you said, the jury is still out. Now, let me change gears a little bit here. Almost like a drug, dialysis has to be dosed, in a way, right? And so, the question is, how is dosing of dialysis accomplished and what is the dialysis dose?

John T Daugirdas
The story of dosing starts back before when I became a nephrologist. People would look at two substances in the blood that accumulate in dialysis patients: one was urea, and the other was creatinine. Urea by itself is not a very toxic substance. Urea is the way that the body detoxifies ammonia, and urea is manufactured by the liver. You have you have carbohydrates, you have fats, and you have proteins. Carbohydrates and fats contain no nitrogen, but proteins and proteinaceous substances do. You have to do something with this nitrogen – to excrete the excess nitrogen. Of course, you can recycle it, but somehow the excess nitrogen from proteins in the body has to be excreted. The liver takes ammonia and makes it into urea. As you know, when treating patients with alcoholic cirrhosis, you can get ammonium toxicity if they're not making urea. So, urea is a good thing, not a bad thing, in terms of a relative toxicity scale. Although there is some new recent evidence that urea itself might be relatively toxic.

Normal urea concentrations depend on how you measure them, but the way we measure it in the United State, normal levels are 5-20 mg/dL. In dialysis patients, it's common to have pre-dialysis urea nitrogen concentration of 40 to 60. Back in the old days, you would often see uremic patients with urea nitrogen concentrations (we measure urea nitrogen, not urea), of 100 mg/dL or higher. So, one early idea was, that you could just look at dialysis patients' level of blood urea (nitrogen). And if the level of blood urea nitrogen was high, it would be bad; if the level was low from dialysis, this would be better. And then they found out to their surprise, that sometimes patients with lower blood urea concentrations had a worse outcome compared to those with higher urea nitrogen concentrations.

And at first, they were scratching their head, but then they figured it out – the more protein you eat, the more urea nitrogen you generate. Patients with a low blood urea nitrogen levels had low

levels because they had stopped eating, as they were sick and feeling terrible. And this is why they had a bad outcome. So, people quickly realized that just looking at the blood level of urea nitrogen was not a good measure of the adequacy of dialysis.

There was a major randomized trial done called the National Cooperative Dialysis Study, which was designed to look at the levels of urea, a higher level and a lower level of urea. And then the people who looked at this study reanalyzed it. They considered the blood urea level before a dialysis treatment and after a dialysis treatment. And they looked at the percent reduction of urea. And they thought, well, what's important is not what the blood urea level is, per se. But what's more important, and what gives us a better idea of survival, is how much the urea is reduced in a typical dialysis treatment. And what they found is, that in those dialysis treatments where the reduction in urea was very low, there was a poor outcome. There was a high incidence of treatment failure; but when the percent urea reduction was high, there was a much better outcome. And the dividing line was around 60% reduction of urea. So, above a 60% reduction of urea, the outcome was okay. If the percent reduction was much lower than 60% (these were patients being dialyzed, three times a week) the outcome was a lot poorer. And then this was translated mathematically in terms of fractional excretion of urea. And this whole concept was called KT/V, where the clearance of urea (K) was multiplied by time (T) and divided by the volume of distribution of urea (V). Clearance in nephrology is abbreviated as K. I was wondering about this, because K is usually a symbol for a mathematical constant and, and you would think that they would abbreviate clearance as C, but the reason it is called K is, because back in the early-to-mid-20th century, much of the important physiology was done in Germany and other German speaking countries, where the word for clearance is “Klärung.” So, that's why clearances are abbreviated as K. This urea reduction ratio of about 63% to 60% translates into a KT/V of about 1.0. And so that's where this concept came out that we can just look at the reduction of urea in a given dialysis treatment, and that this will give us our measure of dialysis adequacy. When people looked at large databases and looked at survival as a function of urea reduction ratio, or KT/V, they got a nice sort of a curve where the mortality rate was markedly increased when the urea reduction ratio was less than, say, 60% to 65%, or the KT/V fell below 1.0. As a result of this NCDS study, the initial guidance was, that we need to keep a KT/V of at least 1.2, or a urea reduction ratio of at least 65% to get minimally adequate dialysis.

There were a number of issues that this system of dialysis dosing engendered. And one of these problems was, that in a small patient you could get a high KT/V, and you could reduce urea by more than 65% very quickly, in a couple of hours, because the patient was small, while

the clearance of the urea in the dialyzer could be very large. So, in small patients and women, you could get a 65% urea reduction in, say, two hours. And the question was, is this, okay? Because the problem in dialysis is not only associated with removal of urea. Urea is very quickly dialyzable, as it has a molecular weight of only 60 daltons. Remember that blood only spends about 15 seconds in the dialyzer. Normally, the dialyzer has a blood volume of 100 mL, and blood flow rate is 400 ml/min. So, your blood is rushing through the dialyzer in 15 seconds. And substances like urea dialyze out like crazy. The dialyzer can clean out the urea not only from the plasma, but also from the red cells in those 15 seconds spent in the dialyzer. But urea is not at all typical of how other solutes behave, how larger molecules behave. So, the question that came up was, if you can dialyze smaller patients with a high efficiency dialyzer and can get this urea reduction ratio of 65% or higher in two hours… is this good?

And the other issue had to do with fluid removal, as we just talked about: you're going to gain three liters of fluid over the weekend. And if you remove that over four hours, then you have to remove 800 mLs and change each hour. But now if you're only going to dialyze for two hours, then you have to remove 1.5 liters per hour. Can you do this? When you shorten dialysis time, you have to achieve a much more rapid removal of fluid, which may cause severe adverse effects.

Another issue is, that for large molecular weight substances, and even for phosphorus, and substances like vitamin B12 that are not very large (beta-2-microglobulin is in the 11 kilodalton range, but substances like vitamin B12, as a marker, have a molecular weight of about one 1 kilodalton (MW 1355)), you wind up not removing adequate amounts. So, there was a sort of a realization that perhaps this KT/V measure was not the best measure of dialysis adequacy.

Another issue explains why the HEMO trial was done. -- When one looked at mortality curves vs. KT/V or urea reduction percentage, it was found that if you went above a KT/V of 1.3, if you went up to 1.7, which is equivalent to a urea reduction ratio about 75% or so, that you got a further improvement in mortality risk. So that's why the HEMO study was done. And they compared a urea reduction ratio of 65% with about 75%, corresponding to single pool Kt/V levels of 1.3 vs. 1.7, to see if additional removal of waste products would give you a better benefit. And they found out that there was no additional benefit overall for additional removal of these small molecular weight substances. So, those were the first sources of data.

If you look at quality improvement standards, KT/V or urea reduction ratio is still the main quality improvement standard we look at. And it's a way for a payer or the federal government to look at you. You are telling them that "I'm providing dialysis, pay me for it." And they'll say, "Well, you have to show that the dialysis you're doing is effective, at least to a minimal certain minimal level." And I think there's nothing wrong with that.

Peter Kotanko

The question that occurred to me, and maybe you can back it into the answer you want to give to the first question. I mean, I was still thinking about the fact that the so-called artificial kidney lacks this whole reabsorption portion of machinery. So, this in my mind begs the question, is there something like over dialysis? Is there actually a range where dialysis is just so highly efficient in terms of urea removal? That, indeed, you also lose so many other beneficial substances that the survival may go down? Are there any data to that effect?

John Daugirdas

So, I think there are some actual clinical data. There was a movement afoot, and it started out largely in Canada, of doing dialysis overnight, for seven hours, sometimes even up to eight or nine hours every night, putting patients on the machine doing this. This is all done at home, of course. So doing dialysis at home, putting the patient on the machine in the late evening, until he or she wakes up in the early morning. And now some units are doing this, but they're not doing it every night. But anyway, in the Canadian approach, they're giving dialysis six nights a week. So, if you say that each dialysis treatment is say 8 hours, this translates to 48 hours of dialysis a week. There are 24 hours in a day. If you're dialyzing eight hours every day, you're spending about a third of your time on dialysis hooked up to a machine, just incredible. It's almost like having a kidney, kidney cleaning a third of the time that you're alive. And you would think that this is wonderful and that these patients would have very, very good outcomes. In fact, this was one of the treatments schedules studied in what's called the "FHN" or "Frequent Hemodialysis Network," trial, in this case, the Nocturnal Trial. And they didn't achieve such a high dialysis dose in everybody but in certain patients they did. And we were able to look at outcomes in those patients.

So, there are there were two adverse events that were identified. Perhaps, three. One was not really an adverse event; it's well known that if you dialyze patients to that degree, you will remove too much phosphorus, to the point that you will get hypophosphatemia. If you don't do something, these patients will have severe hyperphosphatemia and they can have

complications. When you start getting into the serum phosphorus levels below 1.5, you start getting cardiac and respiratory signs. It's something easy to fix by adding some phosphorus to the dialysate. Now it's an open question whether something else might be lost in terms of other substances. There was no evidence of an adverse effect on erythropoietin sensitivity. There was no evidence of increased infection rate. There was maybe some (very unclear) signal for perhaps a few more deaths, but there weren't any decreases in deaths in the FHN nocturnal trial arm.

One thing that was found was this: In those patients who started dialysis with this aggressive regimen who had substantial residual kidney function, when given nocturnal dialysis to that degree, once they got more than 24 hours of dialysis a week, the kidneys tended to shut down. And they lost residual kidney function at a more rapid rate than in patients who had a control amount of dialysis, which was three times a week for three and a half to four hours per week. So, there is some loss of residual kidney function.

Now the question is, why does this happen? Is it because you now are keeping people at a much lower fluid levels such that you are lowering the perfusion rate to end stage kidneys that cannot autoregulate their blood flow? Such kidneys may be more sensitive to ischemic damage by low blood pressure. Perhaps, when you spend this much time on dialysis, there's an adverse effect due to lower perfusion of the kidneys. The other thing is, kidney perfusion and GFR is driven by osmotic gradient, and urea participates in this. And we know, for example, even if you look at residual kidney function and measure during the post dialysis days, residual kidney function picks up on day 2 post dialysis versus day 1 and is even a little bit higher during the long weekend on day 3 versus day 2. Some of this may be volume related, some of this may be the fact that you have a higher osmotic load.

But there's another issue too. We tend to think that dialysis is harmless. I go back and think about the artificial heart. Back about, 20 years ago, they did the first total artificial heart implant in patients. And one of the big problems when you have a totally implanted artificial heart is you had activation of blood elements by the surfaces of the implant that blood flows through. So, designers spent a lot of time optimizing the flow dynamics of the implanted artificial heart to make sure there were no corners. These might activate blood elements and cause clotting or other problems. (By contrast), if you look at the dialysis blood circuit, it's quite primitive. If you think about an extracorporeal circuit, you have the needle then you have these blood lines. You have pressure sensors in the blood lines, you have a venous air trap. You have the dialyzer

membrane. And it's been shown that when you put patients on dialysis, even though you solved the complement activating problem by optimizing membranes, there's still a lot of platelet activation that takes place whenever you put patients on a dialyzer.

There's also another problem related to so-called microbubbles. There are some systems that are now looking at this and trying to optimize this. But it's very difficult to avoid microbubble injection into the blood; they get through the venous air trap and are typically not picked up by the air detector. And the problem is that these microbubbles get into the circulation. They can activate platelets; they can cause aggregation of platelets and neutrophils. If you listen to cardiologists, they'll talk about whether you should give one or two antiplatelet medicines to prevent, cardiac events. So, there are dialysis “maxis,” if you like. From cryptocurrency I learned this term called “maxi,” where maxis believe firmly that their thing is the best. And so, when we give a therapy as nephrologist, we are uncomfortable with the fact that the therapy might be doing some harm, because we want to help our patients. And so, this idea that the more dialysis the better – to give dialysis every day and give longer treatments to limit ultrafiltration rate, is OK, but we might still be doing some harm. And some of this may just be related to the fact that our extracorporeal circuits and the way we run blood through them and smash blood in the roller pump and doing this while spending a third of your life hooked up to this type of system may not really be that good for your health. And few people have looked at this.

If you look at the CRRT literature and you compare intermittent dialysis with continuous treatment, you will think that the best sort of removal to mimic the artificial kidney is to give dialysis continuously, instead of intermittently. And that's the CR in CRRT for you. But when outcome studies compared CRRT versus intermittent hemodialysis, people have not been able to show a major benefit. And that suggests one of two possibilities. One is that we're not removing the things we need to remove. And you’re pointing out that maybe we are removing some things we shouldn't be removing. But perhaps continuous exposure of the blood to an extracorporeal circuit causes some harms that offset any additional benefit of removing certain molecules, where we may already be way up in the toxic range. So, I think there's still a lot of a lot of unknowns about dialysis, dialysis adequacy, and you just have to approach it with an open mind.

Peter Kotanko

I think that what you just said is important guidance and advice for everyone who enters that field. Now, I see we are coming to the end of this conversation. I always feel one thing that we

shouldn't forget. That dialysis extends lives, saves lives, to the millions as we speak and looking at the past. Dialysis has certainly contributed to the survival of many millions of people globally. And there's always this area where improvements can be made, of course, and that's why I for example, entered the field, with this elusive wish that maybe there is a sort of renal - replacement therapy that can approach the functionality of the human kidney. John, as we are wrapping up maybe in very brief in 30 seconds or so what would be a key message you would want to bring across to the audience.

John Daugirdas
I think of a “Star Trek” episode where the crew go back from the future and Bones (the doctor) visits a hospital from 1970s. And he comments that these people are savages in terms of how they're treating patients. I would hope that dialysis is no longer practiced much 100 years from now or 50 years from now. I think we are doing a tremendous amount. There are patients who have lived for 30 to 40 years or more on dialysis and have done very well. And it's unquestionable that dialysis is a great therapy. And my hat's off to all the people who have continued to improve the therapy and the treatment. I think that there will be further improvements as we go.

Peter Kotanko
I'm truly honored for a conversation with someone who has contributed tremendously to the improvement of that therapy. So, on that note, and what you just said earlier, always keep an open mind. Be, be ready for surprises, think hard about the problems. I think that's something that eventually will move the field along and help us to improve patient outcomes. So, John, Dr. Daugirdas, thank you so much for this fascinating conversation. I very much appreciate that and have a good rest of the day.

John Daugirdas
Wonderful. Thank you, Peter.

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