Evaluating Changes in Serum Creatinine While Getting BP Controlled: A Nephrologists' View

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EVALUATING CHANGES IN SERUM CREATININE WHILE GETTING BP CONTROLLED:

A NEPHROLOGIST'S VIEW

DR. GEORGE BAKRIS: Okay. Now I think we are ready to hear about something very important that a lot of clinicians really struggle with in spite of all of the two decades, plus, of literature that exists on this. So let me try to put it all together for you from a nephrologist's standpoint, to see, kind of what our thinking is about these patients, and then how we move forward. It is critically important—this is very unimportant, as far as I'm concerned, but I have to show it to you, so here you are.

So let's talk about ACEi inhibitors and ARBs. Now, all of you know that they are kind of bread-and-butter for diabetic kidney disease. But this is the trend from the ESRDs, that data bank that keeps all records of all patients going on to dialysis. And you can see here, especially if you look, just to help you with the nomenclature here, the dark brown that you are looking at is stage three in A and B CKD. And 4 and 5 represent this line. And look what happens as you approach dialysis. The use of ACE inhibitors and ARBs dramatically drops off. So, in fact, it almost drops off by 50%. So, this is typical. We see this all the time. Hyperkalemia is one of the major reasons for this. But, what are the consequences of this? This is an analysis that was done that actually looked at people with and without kidney disease, with and without diabetes, heart failure. And then, pretty much everybody over the age of 65. And it asked a simple question. If you stayed on maximal dose RAASi, did you do better than if the dose was cut in half, or, if you didn't get it at all. And it turns out, when you look at this, this is a percentage of people who died. So this is deaths on the Y axis. And you can see here that if you stayed on the drug, which is represented in blue as maximal dose, it didn't matter what your condition was, you did far, far better than if the dose was cut in half. This was subtherapeutic doses. These are, for those of you out there, the lisinopril 5 mg., or enalapril 2.5 mg. This is what you are doing. You are not helping anybody. So, you've either got to be on maximal dose, as is seen in all the clinical trials, or you are really not helping the patient. And, of course, stopping the drug ultimately takes you a little bit further in terms of not helping the patient. So, this is in 92,000+ people, so this is not some small data analysis. So I think it's important for you to understand that maximally tolerated doses of ACEs and ARBs are what need to be given. I am going to show you a little later in this talk that when that is given, these data are true. You can say, well, this is epidemiology, it is retrospective, and all that. And this is data garnered from ten years ago. I will show you data that was just published in JAMA Internal Medicine that actually supports this data. So, this is an important concept that I want you to keep in mind. Don't back off on ACEs and ARBs.

Now let's start off with a case, and see how you do with this. A 58-year-old African American male comes to you, states he hasn't been feeling well, and he has had periodic headaches. And he was told that he was hypertensive a few years earlier, and was given treatment, but, eh, you know, didn't really take it. He had adherence issues, and whatever. He now comes because he figures that he does have a blood pressure problem because he checked it, and it was elevated. His review of systems is negative. And in the office his blood pressure is 182/92, with a heart rate of 84. He does have an S4 on the heart exam, and he does have 1+ pedal edema.

As far as his labs go, his potassium is 3.4, creatinine 1.4, and a spot albumin creatinine was checked by a very astute clinician, because most of the time that is not checked, and it should be to properly stage somebody with kidney disease, it's 423 mg./g. So the patient was educated on a low salt diet. We inquired about sleep, and sleep apnea. He said that he feels very good. He doesn't snore. He sleeps

well. So he was started on a combination of chlorthalidone 25 mg./D, and amlodipine-olmesartan as a single pill combination, and most insurances will pay for that, by the way, 5/40 mg./D. And he was also told to get an OMRON device, specifically, because they are all validated, and to check his blood pressure at least three times a week when waking up in the morning, and checking it three times each time he checks it. So, very important point. Kind of the sprint method of checking it. And told him to come back in five weeks. Told him to call if there was a problem.

So he comes back in a month. His BP is now 146/90 mmHg, better. Heart rate is 76. He has no pedal edema. His labs—his K is now 3.6, his creatinine has gone up to 1.72, and his albuminuria has dropped to 184 mg./D. His home BPs, he states, are 138-146 mmHg systolic, and he feels much better, and his headaches are gone. What would you do now? You examine him. And, by the way, his edema is dramatically better, as noted above.

What would you do now? Well, what we did, was we added spironolactone 12.5 mg/D. Why? Because he is not at blood pressure goal of <130/80. So we added spironolactone, which is the guidance recommended for hypertension, 2018, December issue, consensus report on resistant hypertension. And we told him to come back in a month.

He comes back in a month. His blood pressure is now 128/80. He feels great. His creatinine now is 1.8. It has gone up a little bit more. In fact, here is a summary of his blood pressures, and his serum creatinine. So you can see what the trends were over time. And what happened to his creatinine. This is very common in many people that have poorly controlled blood pressure for years, and then, all of a sudden, it gets controlled. So you did not cause acute kidney injury. You did not cause any damage to the kidney. And I am about to show you a truckload of data as to how I can defend that statement. But, believe me, I'll tell you now, and I'll tell you again periodically through the talk, >30% increase in serum creatinine, assuming the BP has gotten controlled, in someone with a history of poor BP control, or longstanding diabetes, poorly controlled. This is typical, not surprising, and it's not uncommon for me to tell patients that have this kind of history, you've got more advanced kidney disease than you think. You just don't know it, and we are going to show it once we get you to the levels that you need to be. Very important for the patient to know that, and very important that you communicate that and not have a conniption fit yourself.

Now, this is a study that we did in the 1980s. This was when lisinopril first came out, by the way, for those of you unanointed, lisinopril is the enantiomer of enalapril. And they found that lisinopril was longer-acting. All of a sudden, forget the enalapril, we're going to go with lisinopril. What we did here is we took patients with Type 2 diabetes, and we wanted to explore whether we were really damaging the kidney, and what is really going on here with this change in GFR.

So we took people with diabetes. We put them on lisinopril, maximal dose, 40 mg. And we checked real GFR. We did technetium-99 DTPA measurements in these patients, and that is what you see on the right. And on the left, you see blood pressure. And this is office blood pressure. And you can see here, a nice reduction in the blood pressure. But look what happened to the GFR. It dropped from the 80s to the 70s. Pretty significant. It didn't keep dropping. It leveled off. But it dropped. And that is in the first month. And then we continued to follow these patients. We saw them every four months. I abbreviated the data for you because it would really be crazy. But, going out about 5.5 years, you can see the GFR dropped a little bit more, as did the blood pressure, because we got it better controlled. But

then we said, look, we can't go on forever like this. We need to see whether this has really caused any injury. Has this really caused any harm. Or is this hemodynamic resetting.

So we stopped the ACE inhibitor, and we substituted clonidine. Why clonidine? Because it is totally renal hemodynamically neutral. That's why. So we put it on board, and you can see what happened to the blood pressure—nothing—kept it about where it was. But look what happened, on the right, to the GFR. It went back up. Now you could say, now wait a minute, it went back up but it didn't go back up to 85. Well, of course not. Let's remember that six years have elapsed. The average rate of loss in GFR is a little <1 ml/min/year. So you would expect the GFR here to be, on average, 5-6 ml/min less than where it was when you started. And you started at 84, you're at 79, that's about where you should be. So, we concluded that there was no loss in kidney function, that this is a pure hemodynamic effect. And we have the reference there for you. And it is 22 years old right now. So this is not news.

Okay. That's one study, you're going to say. Alright. At the same time, unbeknownst to me, at the same time we were doing this, there was a simultaneous similar study going on in Copenhagen, Denmark. This was predominantly on type 2 diabetes, as well. They were also looking at lisinopril. And, what you see on the left are the changes in GFR. The initial changes in the first four months, and then long-term changes. And what you see on the right is the actual systolic blood pressure at the end of the trial. And what you notice is that we had, on the left, a huge drop in GFR initially, but then, overall it was down to about 4 ml/min/year. Whereas with the Danish study, they barely had a drop in GFR, but look at their long-term GFR drop. It was 7.5 ml/min/year. Well, what's the difference? Well, our mean BP was 137. Their mean BP was 152. And so it is not just the ACE inhibitor, but it's the level of blood pressure you achieve that also contributes to the change that you see in the GFR. This was in the same paper.

And there is a big literature on this. This is not everything by any stretch of the imagination, but it is just papers since then that cover the issue, all of them saying, including guidelines, that a mild rise in creatinine is not AKI. It is to be expected in diabetic kidneys, and in fact maybe portends a better prognosis. So, just keep that in mind.

Now, let's go back to the 90s, and let's take a look at the African Americans that have kidney disease. This is non-diabetic kidney disease in people with advanced kidney disease who are African American, and they got there because of poor blood pressure control. And when you look at the changes, you can see that there are significant changes. We are going to get back to this in a little bit. But I want to make the point that the amlodipine arm here looks like it's going up, the GFR is going up. Everybody back then said, whoa, this is great. This is improving GFR. Well, if that is true, and if that's so good, why did the amlodipine arm get stopped early for adverse effects? Specifically, significant increases in albuminuria. It doesn't quite make sense. So, we'll get back to this. But, needless to say, amlodipine should never be given to people who have >300 mg. of albuminuria in the absence of an ACE - -.

This is another study, done by a single center nephrologist that has a lot of patients with diabetes, and he has asked the question about whether >30% increase in serum creatinine occurs, whether diabetes has an effect. You can see these are people with GFRs in their mid-30s. And you can also see that >90% are black. And, that they don't have large amounts of albuminuria. This is the so-called "old" terminology of microalbuminuria. And when you look at this, you can see that >90% were on ACEs or ARBs if they had a >30% change in their GFR. And even if they didn't have a significant change in GFR >30%, you are still noticing here that about 80+% were still on ACEs and ARBs. So, what happened? On

the left, this is everybody, in dark circles. And then the people with diabetes are the open circles. So you can see over time, and the numbers got really small here, so really, let's just go out to seven years, which is here. You can see that they pretty much travel together. So diabetes didn't really make an effect. But, now, over here, when we look at the people with >30% change in GFR, that's the dark circles, and then <30%, the open circles, you can see that initially, in that first year, things looked really bad for the people that had a big change, because there was a big drop. But if you stuck with it, which they did in this study, you can see that they reset to a lower level. But, by six years, they got back to the same place. And, after that, the decline was hard to say because there were very few patients. So, nevertheless, you are not causing harm. You are not making people go to dialysis faster. It is nothing like that.

Now, there are trials that have looked at this. This is a non-diabetic trial, people with nondiabetic kidney disease with a mean age of 45. This was done in China. But you can see here, benazepril was the ACE inhibitor used. And these are baseline creatinine levels. Baseline creatinine levels, and, of course, if you are on benazepril and your creatinine was 1.5-3 mg/dl, you did the best. You did second-best if you had a higher creatinine at 3.1-5 mg/dl. I mean, how many of you have ACEi being given to people with GFRs of 3.1-5, but here it is. This is the benefit over placebo. So this is really the money here. Advanced kidney disease and ACE inhibitors offer slowing of CKD progression, even in advanced kidney disease. These are people with GFRs in the teens.

Now, if we look at the adverse events here, what we found was interesting. Of course, there is more hyperkalemia, but not significantly different from the placebo. So, again, this is very high GFRs, but not that many events, given the total number of people that were involved.

The SolvD Trial is a cardiovascular trial. But this also looked at declines in kidney function and survival. And WRF is worsening renal function, then this was defined as a 20% drop in GFR, more conservative. But, if you look at the trends here, the top group here are the people on enalapril. And that compares to the bottom group, this is of people that were on enalapril. And then here you have the placebos; the dotted lines are the placebos for the respective groups.

So, long story short, even in this trial of cardiovascular disease, the ACE inhibitor was providing benefit to the kidney.

Now the Paradigm Trial is a more recent trial, a much larger trial with 8,400 people. And this is people with heart failure. So I want you to understand that it's with people with heart failure. And the trial was stopped for overwhelming benefit. And I think that's an important observation. The number needed to treat 35 – to prevent all-cause mortality. So this is an important study. I've highlighted the primary outcomes for you here, which, of course, are cardiovascular, and heart failure-related. But, if you look at the secondary outcomes, the decline in kidney function – this was not programmed to look at decline in kidney function – and, yet, the numbers don't look all that bad.

An analysis was done by one of the senior investigators, to actually look to see if there was a difference in people with or without diabetes, and what the effect was of the sacubitril/valsartan over just the enalapril. And the top group were the people without diabetes. The bottom group are the people with diabetes. And you can see across the board that, while there was no (I mean the standard air bars are huge, so hard to make an argument for significance). But the point here is there seems to be a trend

towards a better, or slower, decline in kidney function if you were on sacubitril/valsartan, regardless of your diabetes status.

Now, there's a certain element here, there's an argument, and I thought I'd put this in here, because the cardiologists now are trying to figure out the best way to assess kidney function decline because, now, the nephrologists have moved into looking at GFR slope. And total slope is what they are looking at. Why am I bringing this up? It is important in when you look at these changes in GFR that are acute. Here is the AASK Trial. Remember, I showed you this again? Well, this changes the linearity of the decline. So, here, and by the way, for you fans of beta blockers, this is the beta blocker. It also, because it is a renin inhibitor, also caused a decline in GFR. And there is the ACV arm. And then here is the increase with amlodipine, not good. So, here, you really need to look at total slope because this really detracts you from what the truth is.

Here is data with SGLT2s. Guess what? SGLT2s also affect GFR. And you get an initial decline in GFR. Very important point. Here is finerenone, the new boy on the block. Nonsteroidal mineralocorticoid receptor antagonist (MRA), a different class of antihypertensive drug. And guess what? It also has an initial decline. So the commonality in all of these is this initial decline in GFR. The FDA has provided guidance that you need to look at total slope of decline. So this initial decline is a distraction, and really of no great significance because it is hemodynamic. That is the way you should view it when you see these changes at the bedside.

So, I just want to make the point that Sprint, which you have all probably heard about, it's a large blood pressure study, and it looked at a number of factors. But, if you take the data I just showed you from the AASK Trial, and I didn't show you these other trials, but, nevertheless, they did look at changes and they were all similar in terms of the initial effects. So with Sprint you had a very large separation of blood pressure. So you would expect to see some changes in creatinine with these large changes. And, you did. This was the prespecified outcome. They had a subgroup of people to look at. It wasn't powered for kidney outcomes, but they had a small subgroup of people that actually looked at changes in kidney function. And you can see here there was a huge overlap in terms of the outcome. And when you look at the number of events in terms of outcome, the intense versus the standard, there wasn't a huge difference. Not a huge difference. But when you then look at acute renal failure, acute renal failure defined as they defined it, you supposedly had more. And when you look at changes in potassium, those were also different. But let's take a look at acute renal failure.

This was acute kidney injury (AKI) that was looked at, and it certainly looks like the intensive group had a more AKI Or did they? That is what it was being called because there were just looking at the numbers.

Well it turns out that over 85% of the people that were accused of having AKI were all volume depleted. They were all volume depleted. And, in fact, over 85% of that resolved in three to six weeks without changing anything, just giving fluid back.

Now, if they really had AKI, they would have biomarkers that are well-established as markers of acute kidney injury. And what you see to the right are a whole group of biomarkers that were evaluated in this study associated with AKI. Unfortunately, none of them, none of them were positive. So, is this acute kidney injury? Absolutely not. It has nothing to do with acute kidney injury. It is hemodynamic. So, the conclusion of the Sprint analysis for acute kidney outcomes was that more intensive blood pressure lowering resulted in more frequent episodes of seemingly AKI. But these were all related to

pre-existing volume depletion, and restoring volume back to the patient resolved the issue. So, any time you are giving ACEs or ARBs to patients, make sure they understand that they can't be drinking half a quart of water a day, and they're done. They need to be drinking at least two quarts. Otherwise, the ACE or the ARB will become more powerful, and yes, they will get a change in serum creatinine.

I want to finish up by showing you this study, which is really powerful. This study took people from the Geisinger health plan, and you can see here, over 3,900 people. It was retrospective, but it was propensity-matched. And what they looked at here, they asked a simple question. If your GFR was <30, and your ACEi or ARB got stopped, did it matter as far as your outcome goes? So I am showing you first here, all caused mortality. And I think it is more powerful to look at the propensity-matched score. So I am going to go over here. And when you look at this, I mean, they are no different, as you can see them. But here, you can see that, if you continue, if you continue the ACEi or the ARB, you did better in black. You had better survival than you did if it was stopped. These are people with GFRs, by the way, averaging 23. And what about dialysis? What happened there? Surely there must be a difference. Well, there was, but it's not what you think. Again, if we go over here, you can see very clearly if you continue ACEi or ARB treatment, it took you longer to get to dialysis than if you didn't. So, there is no question there is a benefit here. If you have potassium issues that you are worried about, use a binder, not kayexalate, but the newer, better-tolerated binders.

What about spironolactone? Well, there are no long-term studies with spironolactone because of hyperkalemia. However, if you look at the initial drop concept, in this analysis that was published in 2013, those with the biggest initial drop in EGFR, post spironolactone initiation, had the best one year EGFR outcomes. So, even here, although the database is small, still got the same kind of effects.

So I want to finish with this slide. It is taken right out of our 2000 archived internal medicine paper, as to how to assess changes in GFR with ACEs or ARBs when you start. And how to go about it, and how to deal with potassium and fluids, etc. And I think it's important for you to understand what is happening in the kidney, how to deal with it, and how to prevent it, so that you don't freak out and have issues that are really because of lack of knowledge, and not because of anything else.

So I want to thank you for your time, and hope you got something out of this. Have a good day.