**Rajit Basu, MD: Targeting AKI Using Biomarker Combinations**

Speaker 1 (00:00):

We have now Rajit Basu speaking about targeting AKI Using Biomarker Combinations. Thank you Dr Ronco and Dr Goldstein and thank you Dr Mehta for the invitation to speak. I'm very excited and honored to be here as always, just to have a few minor disclosures and then a relatively major one. I guess that I'm neither an adult doctor nor a nephrologist. So please forgive me those things. I also am a witness to Dr. Mehta's extraordinary mid iron game. So if anyone wants to discuss this can be discussed later during the ping pong tournament. So I was asked to talk about targeting AKI using biomarker combinations and I kind of wanted to take a dumbed down approach to this because in the field of critical care, as many of you know, we have very crude therapies for very crude disease processes. And the traditional paradigm is very simple. We operate in the construct that's very black or white.

Speaker 2 (01:03):

Either have something or you don't, you have a marker that is denoted as positive or not. It's this very binary classification system that leads to a all or nothing approach, whether it be from the beginning, middle, or end process. And as we add more markers to the system, we don't complexify our thinking. All we do is merge them into this idea of a diagnosis still being positive or negative. And that dictates whether we quote, instituted therapy or we don't. The classic example for this is respiratory failure. So allow me to indulge in a couple of things. And many people would assume are good markers of respiratory distress, whether they come from a blood gas or they come from actually examining a patient or suctioning a patient out. You could agree with me that these are the markers that we would use to detect if a patient has some form of respiratory distress, and this leads to the very kind of binary process of you either need nothing or you buy yourself a plastic cigar.

Speaker 2 (02:04):

Now it's not that simple, but in cases that all these markers are aligned, it does become that simple, right? Because it doesn't take a very sophisticated approach to say all these things are bad. So guess what? You're ending up on the ventilator. Now this makes sense. And we can pat ourselves on the back and say, this is a very targeted approach. We combine these markers and they all agree, what we

do with it is we hopefully sedate somebody and put a breathing tube in, but in reality, our picture looks different. There's a lot of discordance between the markers, no matter how sophisticated they get. And what ends up happening is we have a very Doc of the day approach to something that theoretically shouldn't be that way, But yet we rely on this. And why would a blood gas be so useful? It's ubiquitous.

Speaker 2 (02:53):

It's something that we rely on all the time and we get without care for how much it costs, because it's dynamic, it changes, it's responsive to injury, it's timely. And each element tells us something. We believe that they're different, but related and synergistically, they turn data points into information. So if you don't believe me, take this gas, just a generic gas on someone tells us different things. You can believe that there's a marker of homeostasis, that there's a marker of an epithelial function CO2 clearance. There's a marker that tells us about the health of the alveolar capillary interface. There's a marker that tells us how much reserve is in the system to deal with respiratory distress or what that quantification is and what the stress on the system. Because ultimately what we do with this is we personalize, we believe our approach to therapy.

Speaker 2 (03:47):

Now this is important because without this you just have a bunch of data and as the Parachute study taught us very clearly, data sometime isn't really data. So if you randomized 25 adults to getting a parachute to jump out of a plane, you may not actually find any difference in survival if you don't think about it the right way. And I promise to include, this paper and every one of my talks, but is this possible for us? Can we do it using our constructs? Now, the previous speakers did an incredible job of illuminating us with the pathophysiology, the biology that that readily exists in different models of AKI. We don't have as many clinical sophisticated adjuncts to guide our process, This is the paradigm that we live in, that we have one ubiquitous marker that tells us generically speaking about everything.

Speaker 2 (04:37):

We don't even have this idea of a blood gas for the kidney. But the problem isn't that creatinine maybe a problem, but it's not the only problem. It's our approach to things, because if you take our approach to sepsis associated AKI, we have a

learned helplessness approach. So the patient has has sepsis and if you don't ignore them and leave them in the hallway and you actually pay attention to give them antibiotics, some of them do better. And if they don't do better, they develop some form of AKI. And if they don't do better with what you're trying to support them with, they ended up landing on CRRT. This is the traditional paradigm. You would argue that we in 2019 should be able to be a little more sophisticated than we were in 1979 to say, okay, can't we risk stratify patients?

Speaker 2 (05:28):

Can't we come up with something more? That is a precise approach, more of a phenotype driven approach, more of a targeted therapeutic approach to something like this that we see all the time. Because what we would love to do is to match all the things that the previous speakers have spoken of in the disrupted biology. Match that up to a signal that's apparent that we could actually match up one to one or maybe three to one and have that be specific for a target because ultimately that is what will lead to targetable therapy. How do we do that? Well, the first thing is to to think about what is disrupted in the homeostasis. Now ADQI 13 a couple of years ago did a wonderful job of getting together the experts and saying, what do we know? What needs to be known? And some of this has been reported already in the first hour of the session.

Speaker 2 (06:26):

The group split into five different kind of micro groups and thought about, okay, how do we approach the animal to human model of AKI and are there targets we can think of, now if you'll allow a pediatric intensivist to indulge a little bit in, in histopathology and such, we know that no matter if we find individual targets after remote ischemic preconditioning or if we look at the inflamma-zone, there's market heterogeneity in the kidney and so in reperfusion models whether they be in my certain rats, we know that heterogeneity masks our ability to really identify consistently efficacious targets in human dynamic appearances of AKI, but there are models that are found and you're not supposed to highlight all of them. We've talked about some of the bioenergetic failures specifically with fatty acid oxidation and how you can disrupt the electron transport chain and if you can actually intervene in these mitochondrial targets, you get improvements in oxidative damage, you get improvements in renal function.

Speaker 2 (07:26):

Generically speaking, you get improvements in oxidative kind of reactive oxygen species in the kidney itself. But taking another step back, when we think about the processes, what I would tell you as a pause is we are way behind in identifying targets that match up to those individual pathophysiologic processes. What we can potentially say is what is happening in the kidney as a response. So one of the papers that came out of this group talked about the idea of the repair processes that are triggered in the kidney regardless of the stress. So there are three main paradigms, and this is how I kind of simplified this for myself, that there's an injury and you can have a repair process, which seems to be immediate. It's dependent upon the microenvironment. You can have an adaptive response or a maladaptive response. Those three kind of major repair directions, and then you end up with two possible outcomes.

Speaker 2 (08:28):

Either have recovery, which is durable or you don't, which leads to long lasting change. This seems to be something that if you had markers which told you, okay, this is the repair process that are going on or not going on, or what's happening in the kidney in response to ischemia or in response to contrast or in response to cardiac surgery is that you're having a maladaptive process. Go on. That seems to me to be a target that these are the patients that would be most helpful to target in our therapeutic window because the theory would be that if you looked at different markers, either in isolation or together, there would be different thresholds for those markers being elevated or not depending upon your repair process. Now, this doesn't really get at the pathophysiology or the biology of the disease. This gets into what can we do at the bedside to detect after this patient's already been injured?

Speaker 2 (09:27):

Absent the model of cardiopulmonary bypass, what can we do? What can we do to say this patient's actually having a repair process that will have full recovery versus not? Because if you could, if you could target the endogenous repair pathways, if you knew that the arrow in the white was headed toward recovery or not, that is more of a contemporary approach. It's not really contemporary, but it's more of one than just being reactive to destruction because I'm not sure that we have these detectable signals that match up to the pathobiology. Dr Goldstein asked a question that we don't have TLR4 knockout humans walking around and similarly we don't have TLR4 knockout A's detectable in the urine yet in everyone,

right. We have to have some marker that tells us that in this process there's maladaption going on and that be specific.

Speaker 2 (10:27):

Now this isn't new. Combining biomarkers isn't new and what I wanted to talk about isn't something that it's just a couple people discussing. This has been discussed for many years. The problem is that the approach is relatively traditional. What is being predicted is simply just severity of injury, combinations include creatinine and damage markers, but the methodology is a little bit of TOWS and the population is very selected out. It is only primarily those patients fall in cardiopulmonary bypass and looking at discrimination. I picked this paper not to pick on the colleagues in New York and Philadelphia who did this, but just to show you that as an intensivist, I'm not sure that this logistic regression equation that includes NAG, NGAL KIM-1 into some formula that would not readily be computable at three in the morning is going to be helping you at the bedside.

Speaker 2 (11:21):

So this group looked at a hundred patients and combined the markers in these logistic equations to point out that the performance was pathetic individually and slightly less pathetic in combination. Not sure that that's all that helpful, but in 10 years since that time, there have been lots of papers discussing this from a number of different groups and almost all of them show some increase in the AUC or sensitivity. And the takeaway is unclear to me unless we think about how we tailor the approach is really how do we increase the probability of who's at risk, who's not at risk. This is a small paper, but I like the approach of the classification and in Russian tree, and some of you probably know this already, but CART analysis is a little more of an objective way to eliminate the big miss. As a golfer, I can tell you the big miss is to hit a ball where you can't play it next, it's easier, it's better to hit it in the sand or somewhere where you can find it, right?

Speaker 2 (12:17):

So CART does that with your biomarkers or your markers of illness. And what this group did was identified terminal nodes of risk. So on the right side you'll see that the different population cohorts were stratified out by combination of NGAL and creatanine and hepcidin and PI GST to identify a low risk group and intermediate risk group and a high risk group. That's actually useful. Now in this idea of

identifying probabilities, a Bayesian model could be helpful and Bayesian model really just use weighted averages to eye to enrich population. And so the TRIBE AKI group looked at what the effect could be if you actually enriched a population based on this repair process. And looked at, well if you had a therapy going toward adaptive processes, you wouldn't need to test it as many patients if you use this enriched algorithm.

Speaker 2 (13:14):

Dr Koyner and colleagues looked at the furosemide stress test in the idea of looking in a year functional response and comparing it to biomarkers. And they went to great lengths to point out that the functional response of the kidney was way better than any biomarker. And when you added biomarkers and they still weren't as great as the FST, the conclusion being and the discussion, timing was influenced. The FST is better, not sure that's a complete idea because I think when we think about the biomarkers, what I wanted to think about is what's a feasible target? What are the things that as an intensivist and not a epidemiologist, I might be able to influence. And I found this editorial fascinating, so this was two years ago. This is every house officer's nightmare. If you're an adult house officer, there's three things you get called about it in the wee hours of the morning.

Speaker 2 (14:03):

Pain, tachycardia and low urine output. If you're a pediatric practitioner. You get called about a parent being upset, a baby crying and low urine output. What do you do? Low urine output either needs more fluid or a diuretic or vasopressor. All three are different. It's the same readout. You're not really sure what to do. What if we could be more theragnosis minded with using combination biomarkers. So instead of sitting on our hands, which is actually the best thing to do, most of the time, we can identify who needs nothing or who would respond to diuretics. And if fluid overload is bad as we believe it is, can it be predicted who could come off CRRT and stay off CRRT? And if you answer those, maybe you can target. Now there's two background things. One is that as you know, we don't look at these things in static process.

Speaker 2 (14:52):

We don't look at them in isolation. I don't take one blood gas. If I told my fellow who's sitting there that your patient is a lactate of 5.2 her correct answer would

be, well, what was it what the patient look like? What's the context that we use? We don't manage things with one point in time, so right away we have a combination. We use the same marker twice and also we need to be thinking about AKI as the outcome because as ADQI 16 pointed out AKI before day three may not be the one we should be looking at and we should look at it after that or creating an elevation after that. If you just had creatinine. Sheldon Chen showed us very clearly that the rate of change of creatinine as it translates into the rate of change in GFR matters, the person that's exponentially increasing continues to have a decrease in GFR as opposed to the person on the left who isn't increasing creatinine but improving kidney function.

Speaker 2 (15:44):

This is only possible using a combination approach to combining creatinine with each other. We thought about that patient who shows up postop in the morning following cardiac surgery, 350 kids. Some of them all have a bump in their creatinine, which is normal. What if you had a negative damage biomarker with a positive creatinine. In that situation that identifies a functional, reversible AKI. That patient probably just needs nothing. Observation is Dr Zarbock pointed out in the PrevAKI study randomization to a bundle. When you identify stress using a biomarker can actually help you so that intervention using that combination approach can actually help you, whether it be cardiac surgery or whether it be general surgery. In a big P AKI study, we had an experience that we reported using a bedside biomarker and this is a 6 year old girl who with pseudomonas and sepsis who came in the color of the wall here at . Her baseline creatinine was about 0.5 she looked terrible. She got fluids, resuscitation, and day 1 to 2 her creatinine had doubled or tripled. Her NGAL was close to 7,000 which many people would say, that's high,

Speaker 2 (16:58):

but the second day or NGAL had gone down or creatinine goes up, but she was not making much urine. This is a classic situation. What do you do? Do you add more vasopressors ? Do you use diuretics? Do you give fluid? In this case, the decreasing NGAL said to me, why don't we try diuretics hinting a tubular recovery and she peed. She got better. Now, I wanted to go back to this because the interpretation for this was, okay. FST is better than biomarkers. Timing was different, but if you look at the AUCs, maybe they're unique pieces of the injury puzzle. The FST tells you one thing. The biomarkers tell you something else in

combination, you get a more rich picture of the phenotype. That's what I draw from this. As powerful as the FST is, which I believe it is together, they tell you something more.

Speaker 2 (17:48):

Now, I'm going to show you recent patients from our institution. This is a nearly 20 year old with down syndrome who came in with pneumonia, was terrible, ended up on VV ECMO. You could see his creatinine and purple there, vacillating in in the initial stages in between 1 and 2 got put on ECMO. CRRT creatinine went down. He started making little urine. We started measuring NGAL and you can't see the numbers, but they're up in the thousands and what happened was after he got separated, his creatinine went up, continued to go up after he got separated from ECMO and back on conventional therapy came off CRRT, but the creatinine went up and NGAL went down, urine output went up. This was actually kind of a test for the providers never really used this combination approach to say, can we just stay off even though you're an output is marginal and the creatinine is going up.

Speaker 2 (18:39):

Yeah, stay up. If fluid overload is bad, what if you could predict it earlier? This is 150 kids mapping out 2 NGALS at 12 and 24 hours and really side by side comparison. The dots represent different percent fluid overload achieved in the first week. Now most patients fit into this window of low values because most of them don't have AKI, but every patient who ended up on renal replacement therapy who was outside that window of 24 hours, and I'll tell you what, in pediatrics, most 6 year olds do not get an 11 and a half French triple lumen catheter down there, right IJ at 24 hours, and

Speaker 2 (19:20):

it was pretty telling phenomenon to see that happen. Here's a 25 year old with abdominal sepsis. Hurler's parents had gone through the DNR process numerous times, came to us extubated after an ex lap, huffing like a stuck pig, not making any urine. His creatInine rapidly went on the rise shown in red from in between 1 and 2 up to 8 .NGAL was 15370 and then on a Sunday wasn't measured on Monday because he's a fiberoptic airway and he looked so poor. We had convinced the parents to go back to the OR get a catheter in place, go cross that Rubicon again. The nurse sampled the NGAL because it was ordered. The NGAL

came back low and this Dr Goldstein in a very Tiananmen Square fashion stopped the bed from going to the OR. The OR trip was a avoided and we were able to avoid some serious interventions because the biomarker combination told us there was some recovery. Here's a teenager who took a bunch of Tylenol after she got into a fight with her boyfriend creating exponentially increasing urine output was pretty minimal NGAL went up, came down, she tried some Lasix, not much of response, got some more Lasix, not much of a response. She left the ICU on this day. The NGAL had dropped by 25% her creatinine was on the rise. We didn't get to manage her. I kept, I was kind of eavesdropping on the nephrologist conversation. What ended up happening was she got a biopsy

Speaker 3 (20:50):

with nothing.

Speaker 2 (20:52):

So this girl who tried to commit suicide got anesthesia and a biopsy. When you can argue there was recovery already going on and finally this matching patients seven year old and necrotizing pneumonia, si6 year old at sepsis, both had creatinine that were up and down. Both had urine output. That was pretty pathetic. Both were on CRRT. One of them had an NGAL. They both had very high NGAL in the tens of thousands. They came down, one of them stayed down. One of them went back up predicting two days later who was back on CRRT and who wasn't. So I believe that there's an opportunity we need to align the biology. We have these markers to tell us things about injury recovery, stress and damage adaption and maladaption because you can determine a phenotype if you combine them and Dr Goldstein is testing this theory as we speak in Cincinnati with the idea that you risk stratify, put someone through biomarker panel and FST and you randomize them or you don't randomize them but they get put into a protocol.

Speaker 2 (21:54):

So you can do this. You can combine these markers to target therapy. So this is the path pretty simple because I think we can combine therapy. If you doubt then think about this. We have markers that tell us these specific things. We're just not thinking about them in combination. We're trying to compare them to each other because if we combine them with each other, I think there's a rich amount of data that we can get from this. I'll finally am just by saying, as a pediatrician we do

these things and why do we do things like this? It's because we are preventative medicine specialists. We combine the markers that we have in our hands. We can do the same thing instead of looking at targets that are already past where they need to be. I'll stop there and I appreciate your time. Thank you very much.

Speaker 2 (22:49):

any question? Yes, Dr Kellum has a question.

Speaker 5 (22:57):

Great talk. And certainly I agree with the sentiment, there's going to be a couple of presentations at this meeting that are gonna make you very happy. and I'll plug them right now. So one is on Friday, at about noon or so. there's a new biomarker out for, exactly what you're looking for. And the second is we actually took your approach. because we have the same idea we looked at and there's going to be a poster on this. presented from our group. We looked at a variety of different biomarkers because I have the idea that it would be like cancer, right? If you are multiple biomarker positive, somehow that would be worse than you know, one biomarker positive. And it turns out, I guess relatively reassuringly, that there are very few times when you get a lot of discordance. Like, there are very rare situations for example, NephroCheck is elevated but KIM-1 is totally normal.

Speaker 5 (23:50):

You know, they're shades of gray and that's why there are different performances across the biomarkers. But it's not clear to me that you really get that much added benefit by pooling markers. And of course, you know, we looked at this in SAPPHIRE for example, where we looked at a whole bunch of biomarker combinations and we really couldn't find combinations that were that helpful, when they were added together. So I wonder whether your concept might work better if you're including things like a filtration marker and an injury marker and a stress marker rather than looking at maybe combining a lot of different injury markers

Speaker 2 (24:28):

because I don't know what you thought. I appreciate that and that's exactly the point. I mean there's two things to that. One is absolutely combination of a stress marker, a functional filtration marker, a tubular epithelial marker. Those things tell you different, give you different aspects of the puzzle. But I also think if you

take KIM-1 as an example, I would argue that if you followed that over time those patients with a persistent elevation, you may be able to identify who is actually progressing to chronic kidney disease, epithelium is a camel transition potentially if you looked at HIP1 adaptation, those things over time change. So I feel like you can tease out the patients over time using the combination and linear or longitudinal approach.

Speaker 6 (25:12):

Thank you. Great talk. I like to reinforce that the word that you just used in that is time, because each of these biomarkers has a profile as well. And so on the one hand, if you had an instantaneous measurement of either real-time GFR or damage, then everything would be valid. You might only need one biomarker. But in reality, the biomarker profiles change depending on how they're induced or whether they're in fact a preexisting biomarker sloughed into the urine or filtered as may well be the case for some of the NephroCheck markers. And in that scenario time is important and you need serial measurements or combinations of biomarkers, I think, which may include function, which may include other things. And that was the point that you made in your initial presentation that things change with time and you need to add those in to the mix.

Speaker 2 (26:08):

Yeah, absolutely totally agree. we need to test this in a way at places that have the ability to test multiple things at once and real-time GFR tracking percent fluid overload, NephroCheck, NGAL, KIM-1. All these things I think are added. So I will stop. I know. I'm over time. Everyone can play ping pong. Great. Thank you, Raj.

Speaker 4 (26:36):

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