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TRANSCRIPT - GR 01 27 23 "Contrast-Associated Acute Kidney Injury: Fact or Fiction?"
Paul Palevsky, MD, from the University of Pittsburg School of Medicine

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UVA Medicine Grand Rounds

- Well, Good afternoon, everyone, and welcome to medical grand rounds today. It's a real honor to introduce our
- our lecture. Dr. Paul Polevsky and I introduce everyone to Dr. Klein Bolton. As you know, this is the W. Klein Bolton lectureship, and it's a real pleasure to host. This medical ran rounds before I go into this I'd like to say that I'll say a few words about Dr. Bolton, and then Dr. Conkle will then introduce our guest speaker.
- So when you talk about pioneers in nephrology you have to include Dr. Bolton. Dr. Bolton is a physician, physician, scientist, and he's a leading authority in the area of Rpg. N. And good Pastor Syndrome.
- and through his investigative work he is been the one who definitively showed that cell mediated immunity alone, without antibodies, caused glomarol and arthritis, and he was the first to show that intra and intermolecular epitope spreading, occurred during experimental glomerial and arthritis.
- and much as it does in autoimmune diseases.
- He also described and disseminated the use of pulse, methyl prednis alone therapy for Rpg. N.
- Dr. Bolton went to Washington and Lee for his undergraduate degree, and then medical school at Uba. He then received a Residency training in internal medicine
- and nephology training at Harvard, followed by research training at the University of Chicago.
- He was an integral member of a number of different committees. Nationally he's a member of the Ascii, and a number of Nih panels. He was well funded by Nih throughout his tenure at Uba.
- but beyond his contributions to the field of nephrology, he was instrumental in establishing the foundation for the current Uva Division and nephrology
- for his great vision, and along with Medical the Medical Center he created one of the largest academic dialysis programs in the country. He has served to build the current academic division and anthropology through his work with the Dialysis program.
- and for me personally, Dr. Bolton hired me and shepherded me through the challenges of being a physician scientist, and he was a mentor when I first joined the division, and he continues to serve as my mentor.
- So we are truly grateful, and we are incredibly pleased to recognize Dr. Bolton through this endowed professorship.

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Thank you, Dr. Ausa. Thank you, Dr. Bolton, for being here in person. So it's my honor today to present our speaker, Dr. Paul Pelevsky. Dr. Pelosi, is a professor of medicine and clinical and translational science at the University of Pittsburgh.

- He is the chief of the Kidney Medicine section at the Va. Pittsburgh Health Care System and Deputy Executive Director of the Department of veterans affairs, Kitty Medicine program.
- So Dr. Pelosi completed his undergraduate and medical education at Northwestern University, followed by his internship and residency and fellowship training in Nephology at the University of Pennsylvania.
- he became a member and Fac, a member of the faculty at the University of Pittsburgh. Shortly after finishing his training in 1,989, and is internationally recognized and as an expert in acute kidney injury and critical care nephology.
- And this helped lead multiple clinical trials focus on the management of kidney dials of acute dialysis, prevention of acute kidney injury and slowing. The progression of diabetes related kidney disease.
- I mentioned one of the big trials. He was a part of this year talking about the timing of HD. And critically ill patients. That was a start, Aki trial. He was one of the contributing members to that trial.
- He's published well over 300 or so articles, reviews, books, chapters, and has held multiple impressive editorial positions. He's received numerous awards for his commitment to research and clinical excellence, and is most recently the most recent past president of the National Kidney Foundation.
- So I asked him to speak today via Dr. Okusa, on the concept of contrast, induce nephropathy. It's a topic that spurs a lot of frequent, and sometimes heated debate both within medicine and across division lines. So please enjoy this talk. Please welcome Dr. Paul Levsky.
- Thank you for that kind introduction. It is a true honor for me to be here today for this lecture in that lecture, and Dr. Bolton's name. I have known Dr. Bolton for many decades, and even before I
- knew him personally. His contributions with regard to glomerular disease, and particularly anti gpm disease, were legendary. When I was a of
- a fellow I was in particular, all of one of my co- fellows who had done his Residency training here at Uva because he came, and he actually had a publication with Dr. Bolton as a co-author, and that was a particularly impressive accomplishment in my very naive view as a second year fellow.
- So in any case, let me go on with the topic at, and which is contrast associated? Aki. Is this a real condition? Is it a fiction?
- Let's see. Are we advancing?
- Then you should be able to advance. There we go before I start. I have the obligatory disclosures. I've done some consulting recently for Jansen, R. Nd. That have nothing to do with the topic of this talk but
- necessary disclosure. So let me begin with a, a case a 63 year old woman, with a history of diabetes, hypertension, coronary artery, disease, C. K. D. Who's being evaluated for a new on set of exertional chest Pain and Dysmia Her serum creatnin is elevated at 1.8 9, which corresponds to an E. Gfr. Of 29
- and she has an elevated urine, album, and excretion of 932 micrograms per milligram creating.

- She has a prior history of an Mi, and previously had a drug alluded Stent placed for a 95 mid l a D. Stenosis. She is a history of congestive heart failure, with a modestly decreased left ventricular ejection fraction
- over the past 3 weeks she's developed new exertional chest pain with progressively lesser degrees of exertion. A nuclear scan was positive for Ischemia, and she's referred for coronary and geography. Her medications include furosamide license April and lodapine isosaur by dinitrate, Simvestad and baby aspirin.
- So a fairly typical
- patient with coronary artery, disease, and C Kd.
- The path is performed. She has a 90% seclusion of her proximal circ, which is successfully stented with another drug alluding St.
- And this is all done as an outpatient for
- 4 days post procedure. She complains of worsening just me on exertion. She's found to have rawls halfway up her long fields bilaterally an increase to lower extremity. Edema she has no skin lesions, her serum creat, and is increased to 2.6, and progressively rises over the next 3 days to 5, point 6 before beginning to recover, and 2 weeks after the procedure, her serum creat, and in his 2 points one.

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So this is the typical description of a patient that we would consider to be contrast Associated Aki

- High-risk patient receives a procedure with die
- creatin and goes up starting several day, starting several days after the procedure peaks about a week out, and then slowly recovers from that point. Although
- she has a through this disease, Catheter has been run up and down her vessels. Maybe she had some degree of atheroambolic disease. We didn't biop see her kidney, so we don't know what's there, but she doesn't have any skin lesions
- so contrast associated nephropathy contrast. Nephropathy has been around for a long time.
- This is what I can find, as the first published report, although the wording of this says, it's the second report.
- This is a case report of Fuck Aki after an Ivp in a patient with multiple myeloma, a report from the early 19 fifties
- obviously back. Then contrast Theropathy associated with Ct. Scans didn't exist because Ct. Scanners didn't exist. This case report from Jama, published in 1978
- is the earliest report that I can find of Aki associated with contrast and hands. Ct. Scans. So
- you know, we're talking decades of experience with contrast associated kidney disease. In fact, in classic studies of the epidemiology of hospital associated Aki
- Contrast Media associated Aki.
- This, the third most common ideology of Aki. This is from a classic study, published in 1983, where it was 12.4, and then a follow up study done by the some of the same investigators, although having moved to a different institution. In this follow up study 2 decades later.

- The contrast associated disease was still the third most common ideology representing greater than 11% of all hospital associated. A AI. So no. it existed.
- But now we see hosting such as this from Aj. K d blog contrast induced nephropathy doesn't really exist.
- This Twitter post stop making fun of older kids who still believe in Santa Claus. There are grown doctors who still believe in contrast, induce nephrop a thing.
- and this posting from Medscape nephropathy contrast to associated Aki is a meaningless endpoint.
- So how have we gone
- from contrast to associated Aki being the third most common ideology
- to being a figment of our imagination.
- Well.
- the data that has been used to suggest that it doesn't exist. Our epidemiologic studies, comparing patients who have had contrast
- enhanced Ct. Scans with non contrast in hand. Ct. Scans, and looking at
- the rates of Aki. Now these are very different populations. So the investigators have generated propensity, scores to try to match the patients, so that we're comparing
- at least
- 2 varieties of apples to each other, and not apples and oranges. So this study from the Mayo Clinic of over
- 20,000 patients, 10,673 in each of these 2 groups.
- after propensity matching
- well-matched in terms of age sex. But I will point out there is this slight, not statistically significant but slight difference in a baseline Korean, and what is seen
- is
- comparable rates. But though numerically slightly higher rate of Aki in the non contrast, arm and rates of dialysis of point 2 and point 3.
- So the conclusion
- contrast is not that for toxic
- slightly different analysis from the group at the University of Michigan by Davenport and colleagues to analyses that they've done the first one
- also a propensity matched analysis looking at the odds of con post-contrast a ki based on serum kiakin, so that's shown here and then on this side shown, analyze, based on the Egfr. And what you can see is that there is an increase in the rate of

Unknown Speaker

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Aki in patience as they're creating, and goes up comparing contrast to non contrast studies. And if you look at this in terms of the Gfr. At a egfr of

- 30 to 44, the odds ratio with 1.4. The lower bound of the 95% confidence interval is 1 point. Oh, so it just misses statistical significance. And when you look at the patients with even worse

kidney function in the Gfr. Of less than 30, the odds ratio is approximately 3, and this is statistically significant.

- Mike Rudnick and Colleagues, in a Meta analysis.
- have summarized all of these propensity. Score adjusted analyses. The details may be difficult to see. But I want to point out a couple of things. The first is that there are really only 3 groups of authors who have published these. We have the University of Michigan Group from Davenport. We have a lot of papers from the Mcdonald's, a husband and wife team at the Mayo Clinic and we have a study from Hinson and colleagues, and certainly in patients with preserved kidney function. The risk of a Ki is very low with contrast, and there's some diff differences between the analyses in terms of whether there's an increased risk scene in patients with Low E. Gfr. However, the numbers of patients in those categories are rather low. One conclusion that you can draw from this is that if you have advanced kidney disease and you need a Ct. Scan with contrast, you probably want to go to Rochester, Minnesota.
- Now this is another analysis that was done by Glen Chertaz group at Stanford, where he took a slightly different approach, where he did an analysis of hospitalized patients using the Medicare Hospital Survey, and looked at the incidents of a Ki in patients who received contrast didn't receive contrast, developed a propensity adjusted model as well. And what you can see in this propensity adjusted model is that not only was the risk.
- No, not favoring, you know, a risk of contrast. In fact, the risk of Aki seem to be less than one, and statistically significant with contrast exposure.
- and that this was the case when you, str stratified by co-orbidities in patients, with relatively low Co. Morbidity only when the co-orbidity score was at the highest level. Was it there an appearance of an increased risk of AI with contrast exposure?
- Now, I I can't envision any way in which contrast administration is going to be nephro protective. And yet this suggests as co-orbidity score of 0 that there's a greater than 40% reduction in the risk of a K. I.
- This raises in my mind the question.
- Are the statistical models misleading us? And in the discussion in this paper.
- right even sophisticated analyses may fail to detect the full effect of patient selection on their results, and in that case may erroneously conclude that there is no real risk to patients. Even those previously believed to be high risks, such as patients with C. Kd. Or diabetes.
- And the bottom line is these statistical analyses are subject to residual confounding.
- But we need to concede that in patients with reasonably preserved kidney function the risks of
- contrast associated Aki are low and we may be overestimating the risks even in those who are higher risk patients.
- So what's it? Is there evidence to support the fact that there is a risk?
- Well we have data that suggests that there's a dose response. So here are data from a mere 1.3 million patients undergoing angiography with the intra-arterial contrast to recognizes a difference here between inter arterial and intravenous. But you can see that as the volume of contrast increases, the risk of a Ki goes up.
- Now, the counter argument. Looking at this data is well. The reason that it requires
- all larger contrast. Load is that these were more complicated procedures, and maybe there's something else from the procedure. Besides, the contrast that's driving the increased risk.
- True.

- what are risk factors that we have accepted as risks for contrast, Associated Aki
- well pre pre-existing renal insufficiency. And this is something that we can say for virtually any etiology of a ki. If you have underlying kidney disease, you're more likely to develop a complication, and it's a client and kidney function from something that that
- is that for toxic underlying diabetes melodies.
- the presence of proteinuria. And it may well be that the mechanism of the increased risk with diabetes is associated with the protein area, because in a diabetic who doesn't have pro mural kidney disease, the risk is similar to that in the general population volume. Depletion, decreased cardiac output and concomitant net for toxin administration, particularly non steroidal anti inflammatory drugs.
- We also have procedure related complicated risk. Factors increased dose of contrast
- having multiple procedures within a relatively short period of time. Intra arterial is compared to intravenous is thought to be an increased risk factor, although there is the question is this because we're having patients who have a throat andbolic disease are being interpreted as die associated, and finally the type of radio contrast. And we'll come back to that.
- I just want to point out a problem when we because we'd like risk adjusting patients and predicting risk there of a number of risk scores that have been developed, most of them focused on the risk of Aki following Pci.

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The most recent yeah, are scores published by Roxanna Moran and colleagues.

- So this is the most current score that it was an older score that had been criticized because it included the volume of die, that the it's hard to predict how much volume is going to need to be given. So I want to point out what the key risk factors here, whether the indication for the procedure is a stable engineer, unstable engine, a non st elevation, am I? Or an St. Elevation. Mi: so we're seeing increasing risk based on the severity of the cardiac disease which raises the question as to whether Aki associated here is being driven by the contrast, or is related to the underlying cardiovascular disease. Severity of kidney disease decreased Lv. Function
- Diabetes anemia which may be a marker for other comorbidities. We don't quite understand how hemoglobin is mediating the Aki Glycemic control uncontrolled heart failure and increased age recognizing that the older you are at any given level of serum creating. The Gfr. Is going to be lower factors into that. But these risk scores, all of the risk scores that have been published are really very problematic because the vast majority of patients are low risk.
- So in this risk score here's the progressive risk, as score goes up. But here are the number of patients at each risk score, and there are very few patients in this very high risk category. In fact, in the derivation cohort.
- There were more patients who developed a Ki in the low and moderate risk. Categories then developed a Ki in the high risk categories, even though the rates of Aki were very low, so one of the of a another takeaway from this is that we have very few high-risk patients or very few very,

very high risk patients, and in low risk populations. Aki is a rare event, but because there are so many patients, we see these episodes of Aki.

- the mechanism of contrast associated with a Ki and I'm. Not going to go through all of the studies showing me the mechanisms, but there are effects both direct cellular toxicity.
- There's toxicity due to an increase in the viscosity of the tubular fluid. From the contrast media leading to tubular obstruction or increased risk of tubular obstruction, and there are changes in hemodynamics. There's Renal vaser constriction that occurs as a result of the contrast, administration and change in flow that is described, increasing the risk of aschemia within the Megalo Cortico medullary junction.
- So all of these mechanisms are thought to contribute to the toxicity, and there are animal models of contrast Associated Aki. Now, admittedly, the animal models are
- difficult models.
- I. Animals need to be volume depleted. And Many of the models require pre-treatment of the animals with non steroidles in order to generate a Ki. Although I would point out
- that models of my globe and Eurek Aki also require volume depletion; and if you infuse pure myoglobin, which we recognize as an effort toxin into otherwise healthy rats, it's hard to generate Aki.
- Now, one of the arguments against the fact that contrast theropathy exists is data that that has come from the preserved trial that I was a co-investigator on where we collected biomarkers
- we had we collected samples prior to calf and 2 to 4 h postcath looking to see if biomarkers could identify who were the patients at risk or patients developing a Ki, and we found no difference in biomarker levels in patients with or without a K. I. Without in blue, with
- in red. And here we have the absolute change in biomarker level. And here the relative change compared to baseline.
- But one of the problems with this data was that we could only collect the samples 2 to 4 h post
- die. Administration, which may have been likely was the wrong time point for looking. There actually had been data before we did this that said, You need to be looking 8 to 12 h later, after contrast, exposure that 2 to 4 h was too early. But since most of our patients had their procedures as an outpatient. We couldn't keep them around for the time points that we wanted to collect them at. So, while this may be a weak argument for a against contrast, nephropathy existing. I think that this is fundamentally flawed data for that argument, and I think I have a particular right to criticize it, since it's my data from our own study.
- So why has the incidence of contrast associated? Aki apparently decreased? Because that
- does seem to be the case, particularly when it's intravenously administrated, Die?
- Well, the first is our contrast. Agents our iodinated contrast agents have evolved.
- They've changed and they're less never toxic than what we had in the 19 eighties and 19 nineties. So just to point out that the iodinated contrast media are derivatives of try ayoto benzoic acid shown here, so varying in the side chains on the molecule. So we started out
- in the 19 seventies, 19 eighties, using what we're referred to as high as molality agents. These are agents that have osmalities of 1,400 to 2,200 milliasms per kilogram.
- Then in the 19 eighties we saw the introduction of low o's molality agents, that came in 2 flavors, Ionic agents that were dimeric derivatives of triado-benzoic acid or Monomeric non-ionic derivatives and there was less enough for toxicity. Described. With these and then

- we saw the introduction of an iso osmolar agent which is a non-ionic dimer that is markedly more viscous, but has an optionality of 300 I should point out low as molality is a relative term with an osmolality of 500 to 800 milliasms per kilogram. So they're not low. They're just low compared to the altar agents and each of these classes. Is so, it appears to be associated with the less toxicity than the original agents.
- The second is the volume of contrast that's used so for Ct. Scans. I can remember when I was a medical student and a resident, that Ct. Scans required 200 5,300 Ml. Of contrast now 70 to 150 ml. Of contrast.
- If there's a dose, respond dose relationship, we've moved the dose down. Why has the volume of contrast that we need for ct scans decreased very simply. The Ct scanners have gotten better
- rather than single channel. Scanners we have multi-channel scanners with a rays of 32 detectors as, or even 64 detectors, as compared to the single channel. Ct. Scanners of the Ninth, the original scanners from the 19 seventies. So we've seen in advance in technology.
- And we're also using preventative strategies.
- And we've stopped using some preventative strategies that were harmful.
- So when I was a resident, I was taught that when the patient was on their way to the Cath lab we should have 10% man atole in Saline to give a manitol infusion, because man at all was beneficial.
- And then we had a ran, had randomized control trials that showed Manitol, isn't beneficial man at all, is actually associated with an increased risk of post-
- So we're doing a better job caring for the patients.
- Think the bottom line is this is a syndrome that still exists but that has become less common, and in a patient with well preserved kidney function is very, you know the risk is very low. When I needed a Ct. Scan with contrast. I didn't think twice about my risk of a Ki.
- There's a flip side also and that is that our fear of a Ki leads us to not do appropriate diagnostic studies, and this is a term that was called realism that was coined by Dr. Chertau in 2,000, and 4,
- the failure to perform, appropriate diagnostic, or therapeutic, and interventions in patients with C Kd. Due to concern about the risk of AI, and in analysis he did then he observed, in a nearly 60,000 patient cohort, that patients presenting with St. Segment, elevation, Mi. So patients who, we would agree are appropriate for and geographic intervention you were about half as likely to undergo and geography.
- If you had C. Kd. As compared to not having C. Kd.
- Mortality in the patients with Ckd. Was about double the mortality at one year in those without C. K. D. And in a propensity score adjusted analysis among the patients with C. Kd.
- If you had undergone and geography, your odds of death were reduced nearly 40%.
- So you know, there seems to be a real cost to not doing these procedures?
- Has it gone away?
- And the answer is No. Here's an analysis published in 2,018. The blue line, No. C. Kd.
- The green line is Ckd on dialysis, the red line Ckd: without dialysis.
- These are all coronary and geography. These are pci. These are patients with non sd segment, elevation, am I? And what you can see is over time. There's been an overall increase in interventions but consistently less likely to have an intervention than absence of c.

- And it's not just co- morbidities, because patients on dialysis are going to have more co-orbidities than patients, not on dialysis. So the fact that the red line is below the green line suggests that it's fear
- of Aki.
- and then an analysis that we just published. Steve we's Board as the lead author on this project, where we interrogated the Va. Database, identify
- over 80,000 patients with Acs eliminated patients where there were either end stage disease, stage 5 Ckd. Or contr indications
- to an intervention, and then use natural language processing to read the records for these patients, and generate what's known as a grace score.
- which is a a score identifying the appropriateness of, and geographic intervention in 22,000
- 900 and nearly 23,000 patients, with C Kd. And nearly 42,000 patients without C. Kd. And what we saw when we stratify this, based on
- quartiles of the grace score at any level of serum creat, and then at any level of the grace score as serum creating and goes up.
- you are less likely
- to undergo
- what is considered appropriate invasive care.
- So this is still a problem. We don't
- take it, treat our patients with Ckd. Appropriately, because we are scared
- of Aki, even though
- the risk of Aki has decreased.

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So let me turn now to talking about how we can prevent the development of a Ki in a patient who is at high risk.

Unknown Speaker

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I already talked about the contrast agents, and we're not the ones who control what contract agents is chosen. And, in fact, the high risk agents. The original first generation, high as molality agents are not available in the United States anymore.

- Volume administration.
- This is the core aspect of what we can do. Is it necessary.
- There have been some studies that have tried to assess this. This is a study that's really 2 decades old, now done by Harry Prasad, Travidian colleagues, where patients undergoing and geography were randomized either to Iv fluids or no fluids, and the study was stopped very early on by the safety monitor, because the rate of Aki was 3.7% in the group receiving Iv Fluids Iv

sailing and almost 35% in the group that received all my oral fluids and I actually thought that would be the last time we'd ever see a study like this. But about 5 years ago the amazing trial was published which looked at the question of oral fluid versus Iv fluid again in a non inferiority analysis, and concluded that oral fluids were non inferior.

- However need to recognize this was not a very high risk population, so most of the patients had a Gfr. Of greater than 45 Most of the patients received Iv. Rather than intro arterial contrast.
- Most of the patients had non-interventional procedures, and the overall rate of a was very low. It was less than 3% you're not going to demonstrate a benefit in a study of 600 patients looking at a low risk population.
- This was an under-powered study in the wrong population. To answer the question in population with a risk of 3%.
- You probably don't need to do very much for prevention of a other data have shown different results. So this is a study of patients presenting with St. Segment elevation. Am I undergoing primary Pci? They come in. They're rushed to the path lab they don't get any fluids precedure. And this was looking at those who received fluids versus those who didn't receive iv. Sailing post procedure and stratifying, based on low risk, moderate risk, and very high risk patients, and you can see that there was a reduction in the rate of Aki associated with post procedure, saline administration particularly in the higher risk patients.
- The Poseidon trial was a study humorously named, looking at 2 strategies for fluid administration in patients undergoing Cardiac cap either giving all of the patients the same fixed amount of fluid, or giving larger amounts of fluid in patient based on the left, ventricular and diastolic pressure during the cardiac app, and what was seen was the Lvdp guided Fluid administration was associated with a lower risk of a Ki.
- The and what's shown here are various definitions of Aki, so that as you go from a less stringent to a more stringent definition, you move from a statistically significant benefit to a non significant difference. It was underpowered, using the more stringent definition.
- There's also an approach of forced saline diaries that's been used. There's a device that essentially is a a links, a flow meter on a fully catheter with the Iv pump, so that you can match the saline administration to the urine output and the protocol. Use the patients get a bolus of saline, they get a bolus of furosomide. The urine output is matched with the fluid administration to maintain volume, status, and when the urine volume exceeds 300 milliliters an hour, the patients then go to the calf lab, and there is a reduction in the risk of a. K. I. Using this very high volume, Saline Administration.
- So it does look like Volume has a may have a benefit.
- One of the questions that came up, is what fluid to use sailing or bicarbonate containing fluid, and the interest in this was peaked by this study, published in Jama in 2,004, a study that was stopped halfway through intended enrollment because the rate of a ki in the bicarbonate arm was markedly lower than the rate in the saline arm, although by strict rules it did not meet criteria for stopping.
- In fact, what it did. Trigger was what I've described as a cottage in industry of trials. Looking at Bicarb versus sailing. This is a Meta analysis that was done in 2,016 that demonstrated that
- overall the results suggested a benefit. But they then did something known as a sequential trial analysis, where they treated each trial as if it were an interim analysis of a large randomize control trial and asked the question: Did it reach

- the point that the trial should have been stopped?
- Was there enough evidence? And the conclusion was. No, it did not reach the stopping boundaries.
- So in that environment we did the preserved trial, which was a randomized control tri comparing, sailing to sodium by carpet and an acetal cysteine to a placebo in a 2. By 2 factorial design we had a targeted enrollment of close to 8,000 patients.
- We were stopped by the Dsmb. When we and had enrolled a little over 5,000 patients we stopped because of utility and I think the sponsor wanted to conserve research dollars. We had about just under 5,000 patients with the a valuable data. There were some patients who were randomized to them were excluded from the analysis, because they never underwent, and geography. The first step in the analysis was to see whether there was an interaction between sailing and bicarbonate there wasn't so we could analyze and that between bicarbonate and an acetal system there wasn't. So we could then analyze the data, looking at bicarbonate versus saline independent of the analysis of an acetal Cysteine and placebo, and what we observed was no benefit for by carbonate. The primary endpoint from the study was an outcome at 90 days of death need for dialysis or a persistent decline in kidney function.
- Aki, at 3 to 5 days post procedure was a secondary outcome. There was no benefit with regard to the primary endpoint, and, in fact, the trend was to lack of benefit for Aki. It was a higher risk of Aki, although not statistically significant, associated with bicarbonate administration.
- We've also looked at the relationship between volume of fluid that was given, and the outcomes dividing fluid administration based on quartiles.
- And what we've seen is that once you're into quartile, too, there is no added benefit to higher volumes of fluid, so that the benefit seems to be giving at least of around 900, and to you know, a more than 900 Ml. Of fluids. Perry procedurally pharmacologic therapy. The greatest interest to seems to have been an acetal. Cysteine, triggered by this study, published by Teppel and colleagues in the New England Journal in 2,000 that demonstrated a reduction in the risk of Aki Us. With administration of 600 milligrams bid of an acetal cysteine on the day of in the day following this with ct scans, I want to point out one thing we'll come back to, which is what the Serum kiatnin was 48 h after contrast administration it went down by point 4 in the antecedal system Group went up by point, 2 in the control group, and also note the number of patients. There were total of 83 patients in this trial again triggering lots of further studies, most of them very small studies.
- This is a Meta analysis, also published in 2,016 again, showing a benefit of the odds. Ratio is Point 7. So, and the preserve trial. When we analyze the patients looking at the An acetal Cysteine versus placebo, as with bicarbonate, No benefit at the 90 day endpoint and no benefit in fact, the direction pointing away from benefit in contrast to associated Aki 9 point, one within an acetal system, 8.7% with the placebo.
- Now, a an interesting Meta analysis that was recently published, looked at all of the studies, and concluded a 101 studies, including preserve.
- and either with a fixed effect or a random effect analysis. It's showing a benefit associated with an acetal system.
- But what they observed was that this was driven entirely by these small studies.
- because it was almost entirely small studies. There were only 3 trials with more than 500 patients, and they were neutral.

- There's probably publication bias. If you did a small study that was didn't show a benefit.
- It was hard to publish that, because it was underpowered. But if you showed a small study that showed a benefit well, what showed a benefit. It must be an adequately powered study.
- So this just illustrates the problem of underpowered studies, possibly giving us misinformation.
- Now there's been interest in statins for prevention of contrast on the foropathy after angiography to back to back studies published in Jack in 2,014, showing a reduction in risk associated with the acute statin administration, although I would suggest that any patient who is undergoing and geography probably is supposed to be on a statin so I'm not sure that this is an added benefit, and we'll come back to another problem with it in a minute.
- The interest in time, I'm going to skip that remote ischemic preconditioning is an interesting approach. The idea here is that causing aschemia somewhere else
- results in the release of danger molecules that trigger the kid. This epithelial cells and the kidney to go into a transient cell cycle arrest where they are relatively protected from the potential net for toxic injury, and there have been a variety of small studies that have suggested that the remote a scheme preconditioning is beneficial in contrast prevention of contrast associated Aki. There has not been a benefit, a scene with Ct. Surgery associated. Aki, and I would just suggest that the number of patients here is much too small to draw any definitive conclusions, and I think this has to be considered a an experimental procedure. What about hemodialysis and hemophiltration?
- There have been Meta analyses done of the studies suggesting that not only is he a dialysis, not a beneficial way of preventing toxicity, but it's actually associated with harm chemo filtration. On the other hand, let me show you the problem here.
- So here is a classic study from the New England Journal of Medicine.
- Patients come in. They're randomized to either receive hemophiltration, starting 12 h pre procedure serum creat, and then drops continuing for 12 h post procedure. And the outcome of this study is change in serum creatinin relative to baseline. Well, there's a problem the intervention lowered creating.
- So, of course, creatin, and is going to be lower. And in fact, if you look at the change in serum create, and from day one to discharge those are somewhat parallel lines. The interestingly they did a a follow up study where they had 3 arms either starting the Cvh 12 h prior to, and geography, and continuing if the 12 h post, or starting it post and geography, and providing it for 12 h, comparing it to control, and, interestingly, the posts, the the the the one that only received 12 h, had a smaller change in serum creating than the one that had the 24 h of Cvh. I think this is a dose effect of the Cvh. I I find that astonishing that this was actually published.
- What about avoidance of concomitant net for toxins, non steroidals? I I I mentioned that actually used in experimental models, but the question that comes up all the time is, what about rest, blockade?
- Should we continue it? Should we stop it? I can tell you that there are randomized control trials that show the cap to prol prevents contrast. Associated Aki.
- There are not great data. This is among the best of the studies, and it's a really small trial, but it illustrates a key point. So this was a study that took 220 patients on Ras blockade and randomized to continuation or discontinuation, but also looked at 63 patients who were ras naïve those that continued and ras naive had the same rate of aki the rate on the patients where

it was discontinued was lower not statistically significant. This is a horrendously underpowered study. But what happens when we start a patient on Ras blockers?

- We expect up to a 30% increase in Serum Crean, and because of the hemodynamic effects. Well, what happens when you acutely stop a rest blocker the exact opposite. You expect Serum Creatin to decrease. So let's think about this for a moment.
- We give patience, contrast and we expect serum create, and to have some distribution of change. So this is the chain, the distribution of serum, creatin and relative. This line is the baseline, so some patients will have a decrease.
- Some patients will have an increase. We expect more patients to have an increase than a decrease and we call some threshold of Increase Aki.
- Now, if we do something that systematically shifts, the serum, creating and distribution like stopping a drug that we know increases the serum. We get this shift and the percentage of patients who appear to have a K. I.
- Decreases.
- Have we protected the kidney or are we looking at an epi phenomena?
- That may be what we see with Ras Blockers?
- Certainly is what we see with chemo filtration.
- The question is this: is giving a leader of saline enough sailing to actually lower the serum creatin, and so that we're seeing a ep of phenomena, or is it actually protective something to ponder?
- So what are my recommendations? Identify the very high risk? Patients who use lowers risk. Contrast in the high risk. Population volume expand with isotonic crystalloid. I can't tell you what the best protocol for volume administration is. There's no benefit to by carbon. It is compared to saline Don't. Give an acetal system. I think the role of staten is uncertain. So, but for patients undergoing cardiac app, they probably should be on them anyway.
- On the other hand, non-steroidal should be discontinued there's no need to discontinue ras block aid in my view.

Unknown Speaker

01:20:54

I also don't discontinue chronic diuretics.

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If our goal is to maintain your in volume, and you acutely discontinue with diuretic, you're going to increase sodium reabsorption and actually decrease tubular flow, distal tubular flow. So this is one of those situations that a patient is on diuretics, and I continue the diuretic. When I give. I now I want to conclude just pointing out a a a problem with this idea of looking at the longer term outcome.

- So Aki is associated with adverse outcomes.

- We're not all that concerned about small changes in serum creatin and in and of themselves.
- Our concern is that those small changes are linked to longer term bad outcomes, decline and kidney function.
- The problem.
- So the risk factors for Aki are also generally the risk factors for longer term app adverse outcomes.
- Our hope is that interventions to prevent contrast associated? Ak: I.
- Decrease the adverse outcomes mediated by a Ki, and therefore decrease these adverse outcomes.
- But as we learned from in the preserved trial. Lots of patients end up with intervening and events between the angiography and our 90 day outcome should come as no surprise that there is a substantial number of patients who ended up in the or on cardio pulmonary bypass, because they weren't good candidates for pci and that is associated with an increased risk of Aki and an increased risk of other adverse outcomes.
- So that leads to a bit of confounding. And, in fact, what we observed in preserve was that of the
- patients who developed a Ki.
- Only a small percentage of them went on to the primary outcome and the majority of the patients who developed the primary outcome. Never had a ki. So 12.3 of patients with Aki developed the primary outcome versus only 3 and a half percent of patients who didn't have Aki. So the odds ratio for developing the primary outcome, if you developed a Ki was substantially higher but only about less than 30% of the patients who developed the primary outcome
- had had preceding a. K. I.
- So the linkage is problematic.
- So where does this leave us?
- The incidence of contrast Associated Aki has been decreasing, but I don't think that it has actually disappeared. I think it is a real condition.
- However, the risk of AI following intravenous administration in patients with relatively preserved kidney function, is vanishingly low and I really don't worry about it in patients with an egfr of greater than 45 fear of a Ki should not preclude the performance of medically indicated procedures.
- So if you have a patient who you're worried has a dissecting thoracic aneurysm get the imaging
- because you need to know the answer.
- If they've got an St. Segment elevation, am I get the imaging? Do the intravenous? Do the pci and in a high-risk. Patients give fluids.
- Unless the patient is in florid part failure give fluids, and if they're in florid heart failure, then you have to balance, managing the heart failure and optimizing their cardiac status before proceeding with imaging versus the necessity for taking the patient to the Ohm, They're in florid art failure because they're going into cardiogenic shock from acute ischemia.
- Treat the, you know. Get the diagnostic imaging. Get them either a pci or to the or because that's what's going to keep them alive. So with that I thank you for your attention. I apologize for running a bit over and again it's been a true honor to give this talk in Dr. Bolton's honor.
- Thank you.

Unknown Speaker

01:26:31

I have the so thank you so much for you. This talk as a researcher. I know you like data. You did have the most amount of zoom attendance we had. So far we had a total of 80. At 1 point that was great. I did wonder about.

- Do you think this is a research? Well, that is, run dry it. I think I think you did a good job convincing us that the data has been looked at, looked at pretty closely.
- Do you think there's room for further research here? And if there is where that might be.
- So I think. Let me first say that, as I pointed out, I think that doing small, poorly designed research studies as this area is peppered with does not advance our knowledge in a meaningful way.
- I do think that there are likely ways to make contrast administration even safer.
- and we need those studies to be pursued developing even safer, iodinated contrast. There are contrast agents that have been essentially packaged in lipid emulsions, so that they don't get into the kidney and which appear to be completely free of, or virtually completely free of net for toxicity developing those agents that would be great.
- But I think many of the you know, having techniques to minimize volume of contrast administered are important. I think, more studies for agents that can prevent contrast toxicity
- where the agent is expanding, let me choose an example. So there was a drug that was touted as protective Finol, Japan, dopaminergic agent.
- I could never figure out the rationale for using phenol to Pam, because the cost associated with it was so high You would need a if you were to have an agent that was going to be beneficial.
- It needs to be dirt cheap because you're going to need to treat hundreds of patients to prevent one episode of clinically meaningful. Aki I.
- The administrators at you. Pmc. Don't like me saying this, but up in the year before the randomized trial came out that showed Funlda Pam to be ineffective. They spent where you, Pmc. Spent 1.5 million dollars on Phenol, the Pam for prevention of contrast associated Aki. That is not a, you know. Multiply this across all the medical centers in the United States
- There was over a 1 billion dollars spent on, and an agent.
- The same thing costs now a dollar for a bag.
- That's about as much as we should be spending on an intervention.
- So I think that this is a well that we probably shouldn't be spending a lot of research dollars on.

Unknown Speaker

01:30:35

Thank you.

Unknown Speaker

01:30:43

Get you out of the

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01:30:49

Thank you, Paul, for that terrific talk. I do have a question about studies and contrast and foropathy, and we talked about prevention studies. But is there room for studies to look at, defining the high risk population better. I used Moran's risk score factor, and that was recently 2,017. Do we have other opportunities to identify that high risk? Population predictive approaches, possibly guided by markers that may indicate who is at higher risk rather than merely the clinical determinants that we have, you know, is this a an St. Elevation? Am I? Is this a patient with a markedly decreased heart function, or markedly decreased kidney function, I think all you know. And this is an issue in Con. And you know, risk of contrast, exposure, risk of Aki after cardiac surgery. We really need to be able to define who the high risk patients are in a much, much more precise way. I mean the problem, as I pointed out with the Moron score, is that the majority of the patients who develop a Ki are in the low risk category. We want to be able to identify in advance the majority of the patients who are going to develop a Ki, not just who's high risk, but who's going to actually develop the Aki? I think that that you know that should be what we strive for. Obviously, if we could predict the future there are a lot of things that would be different.

Unknown Speaker

01:32:58

Okay?

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01:32:59

Oh, that was actually, I very much enjoyed it, and I saw a great many things that Haven't changed and I have to admit that I still believe in Santa Claus. I have 2 questions: Number one.

- Would we better be better off using a different marker for Geo. Far than correct me because of the many perturbations that I'm. Subject to, and number 2.
- When will the day be coming out about the liquid associated? Contrast materials that will allow us to do? Even I number 2. I can't answer that question. I don't know that the manufacturers are pursuing it as aggressively as I would like to see. I can also tell you that the manufacturer, you know one of the things that we really would love is a randomized control trial of contrast versus no contrast that would settle the question G. Healthcare, which makes Ct. Scanners and makes contrast agents, was doing such a study. They couldn't enroll patients because practitioners were so scared of contrast associated Aki, that they didn't random, that that they wouldn't allow their

patients to be randomized to potentially get in contrast when the other choice was ct scan and the ultrasound. This was in follow up for evores so I don't know I can't comment at all on what industry is going to do in terms of the lipid emulsion. Contrast with regard to better markers of Gfr.

- The first better marker exists, and that's just that, and see it's not a perfect marker of Gfr. And the big problem there in increasing its use is that it is much more expensive. So, as a health care system. We really can't afford universal use of system, and see until we get to the point that the cost of the test comes down from 5 to $10 a test to 5 to 10 cents a test.
- But in the patient in whom we have reason to suspect that Korean is a poor marker, the patient who's coachctic, the patient who's markedly obese patients with neuro muscular disease, we should be increase spinal cord injury. Patients. We should be increasing our utilization of Sis Stat and see. But that's a whole. Another talk.
- But I I think that's a direction that we that we're going to need to move, and there are efforts that even additional markers. But you know, how often do we measure Beta trace protein? mean it's simply not something that is routinely measured at this point.
- Thank you so much, Sarah, for your talk. I did have one of the questions that we often face as residents is ordering a contrast included study in patients who have an acute kidney injury already, and in our inability to accurately assess the patients actual Gfr. Based on an acute kidney injury. It feels like risk. Assessment is much more difficult in that case, in cases where it's actually necessary to put on a medical procedure, I understand medical procedures should be performed, but it balancing the risk and benefits. Do you have any advice?
- It's a difficult question in the patient who has really, you know, severe Aki
- dialysis depended. Day K. I. The Oligo, and your patient.
- Probably the risk of further damage is minimal, because it's not the contrast Isn't going to get into the kidney to cause toxicity. The real question in my mind is the patient who has relatively
- Modest A. K. I. Where that's where I worry that another insult is going to be a major problem in terms of further decline in any function.