(PLEASE NOTE: Transcribed automatically by Vimeo, mistakes are possible/likely. Our apologies.)

TRANSCRIPT - GR 02 18 22 " Updates in Heart Failure Management: The Evolving SGLT2i Story" ***Steve Philips, MD PhD,*** **from the University of Virginia**

UVA Chiefs

00:16:32So today we are very excited to extend a warm welcome for very own Dr Stephen Phillips, an expert in advanced heart failure, with special expertise and Cardio oncology.

- 00:16:43Dr Phillips started his training at the University of Michigan Ann arbor where he also obtained a PhD in cell and molecular biology.
- 00:16:51He then moved on to continuous training at the University of Texas Southwestern and Dallas where he served as an internal medicine, she President in 2015 to 2016.
- 00:17:01And also completed fellowship training and cardiovascular disease and an advanced heart failure and transplant cardiology.
- 00:17:09He said leading educator in the field and is presented at multiple national and international conferences on these topics, but he is also.
- 00:17:16One over the heart of the residency programs since, coming as faculty and the past several years we're very grateful to benefit benefited from his expertise.
- 00:17:25expertise and dedication to bedside education and today we're very excited to learn more about updates in heart failure and St lt today Thank you so much, Dr Phillips.

Steven Philips

00:17:36Thank you very much for that invitation and thank you for inviting me to speak today.

- 00:17:40You know, I was tasked with talking about updates in heart failure and the big topic.
- 00:17:46So I have nothing to disclose during my talk today I'd like to begin with just acknowledging that this is the.
- 00:17:52we're coming towards the end of heart failure Awareness Week, this is an important week in my world.
- 00:17:57Both for educating my patients and educating other practitioners about heart failure, how to recognize it, how to manage risk factors.
- 00:18:05Just to remind everybody in the audience you're all aware of the burden of heart failure in the United States there are over 6 million Americans that have this diagnosis.
- 00:18:14And it's important to recognize that almost a million new cases are diagnosed annually, more than half of which are women, I think the tendency is to think that this is a disease of men, but the reality is more than 50% of new diagnoses occur and women.
- 00:18:28So, as I was planning grand rounds, I again I was tasked with updates and heart failure, and there have been a lot of updates and heart failure in the past few years, a lot of.
- 00:18:37kind of things that have hit the news some of the ones that are pretty exciting are the recent expansion of the FDA indication for the use of.

- 00:18:47Tsukuba travail certain are in trust-o in that population, this is a very difficult to treat population, as you all know and the first FDA approved medication for this population is really important.
- 00:19:00there's not a clinic day that goes by that I don't get asked by my patients about myocarditis associated with either coven itself or the coven vaccine so that that was a huge topic and something I have spent a lot of time talking about.
- 00:19:14Interesting to me is what this pandemic has actually done to heart failure care.
- 00:19:18There has been a real robust expansion of Tele health and, for that matter, remote patient monitoring technologies that I think potentially has.
- 00:19:29can have an impact, going on beyond this pandemic and then something that I find fascinating.
- 00:19:35This the first ever successful hopefully long term successful pig to human heart transplant hearts, you know transplant was performed just up the road at the University of Maryland just a few weeks ago months ago.
- 00:19:48But as I thought about topics and did some reading really it dawned on me that all roads in heart failure are leading to one topic and that topic is sgt two inhibitors.
- 00:19:59there's not a day that goes by that I don't talk about it with my patients that I'm not asked questions about it, so I find that it's now's a good time to kind of review what we know.
- 00:20:09here are my learning objectives which were provided to you all beforehand so I'm going to skip that and briefly go over my outline for today so we're going to start.
- 00:20:18With a little segue on universal definition of heart failure I'm going to try my best to quickly summarize heart failure pathophysiology and the existing therapeutics that we have.
- 00:20:28And then we'll segue into diabetes specifically diabetic drug trials and how sgt two inhibitors have fit into that story and then lastly we'll talk a little bit about some of the putative mechanisms of these novel therapies.
- 00:20:41So let's begin the universal definition of heart failure so a really.
- 00:20:46broad international group of heart failure societies.
- 00:20:51did what I find was a really epic assignment of trying to come up with a universal definition and classification scheme for this very common diagnosis.
- 00:20:59Sometimes we find that communicating with the lean practice is difficult, so having this document is important to turn back to So this was published last year in the journal of cardiac failure.
- 00:21:08three simple questions that they asked and answered what his heart failure we know this we've learned this in Medical School but it bears reminding that heart failure is really a clinical diagnosis.
- 00:21:18The hallmarks are classic signs and symptoms, we all know, these orthotic nia bend up near.
- 00:21:25Paris Paris is more nocturnal just nia lower extremity swelling those are the signs and symptoms that we all are aware of.
- 00:21:32Importantly, they should be accompanied by objective evidence of structural or functional cardiac abnormalities that could be by ECHO by MRI by invasive team dynamics and corroborated by elevated natural peptides or some other objective evidence of congestion.
- 00:21:49next question they asked is, what are the stages of heart failure, I think we're all familiar with the traditional a B, C D classification scheme.

- 00:21:57And I think that the problem with that nomenclature, is that it isn't really informative on its face and patients have a hard time understanding.
- 00:22:05What this class B heart failure mean when a stage be heart failure mean so they really rewarded things so stage a is now going to be called at risk for heart failure.
- 00:22:14These are patients who have no subjective symptoms of heart failure physical exam findings of heart failure or structural abnormalities, but they do have one or more of the known risk factors cardiovascular atherosclerotic disease, diabetes, obesity.
- 00:22:30stage be heart failure is now going to be called pre heart failure, and this is important from a patient perspective because it aligns with what we talked about when we talk about diabetes and hypertension.
- 00:22:40This is before the disease manifests, but there are certainly objective markers on either.
- 00:22:47echocardiogram findings or other laboratory abnormalities to suggest that the patient is going to potentially move on to heart failure.
- 00:22:54Stage C is going to be called heart failure, this is what we all know, the classic clinical syndrome and accompanying corroborating evidence.
- 00:23:01And then stage D will be named advanced heart failure, this is where I practice, most of my time.
- 00:23:06This is patients who are refractory to standard of care and potentially need Advanced therapy so just transplant a mechanical support.
- 00:23:13An important distinction that was made in the stage see staging system was the explicit mention of two terms heart failure in remission.
- 00:23:22The they expand on this by saying that these are patients with prior heart failure, who, with appropriate therapies and modification of their risk factors, no longer have the clinical syndrome of heart failure.
- 00:23:36You know this is important because heart failure is never a disease that is cured, we know from the tread hf trial.
- 00:23:42That withdrawal of standard therapies in this population has really terrible outcomes so heart failure in remission kind of to align with their oncology colleagues.
- 00:23:51And then persistent heart failure, this is a term that was introduced to replace chronic heart failure.
- 00:23:56The implication here is that chronic heart failure is a disease that we can forget about we don't need to do anything else because the diseases chronic persistent heart failure disease that requires active management, both by the patient and by providers.
- 00:24:10How does ejection fraction fit into this, we are all very familiar with ejection fractions they I will say this is an area of debate, even within the world of Cardiology the role of ef in.
- 00:24:21classifying heart failure, but nevertheless it remains an important tool and the main reason for that is the.
- 00:24:28evidence base the existing evidence base for therapeutics seems to stratify based on ef that is normal versus abnormal so quickly the definitions heart failure with reduced E, F is those patients with an E, F less than 40.
- 00:24:41heart failure with mildly reduced E, F is an ef less than 41 to 49 that wording is very specific it's not mid-range it's mildly reduced the implication is that this patient population behave more like a reduced def population.

- 00:24:56heart failure with preserve the F is greater than 50 and then this is probably the most difficult one to wrap our heads around heart failure with improved yes.
- 00:25:04This is patients who at one point in time, had an ejection fraction less than 40 but made a game, either with therapies or.
- 00:25:11kind of changing their respective profile by at least 10 points up to a second measurement above 40.
- 00:25:17You can imagine that if you had a patient with an F of 44, for example, you could technically classified them either in the mildly reduced or improve def.
- 00:25:25Depending on the existing data that you had so it's always important to look back at old data to decide if a patient is in the improved def category or the mild he reduced yes.
- 00:25:35So the take home messages from that document, which is very dense and I don't expect you all to read that.
- 00:25:40But heart failure is a clinical diagnosis, but it is very important to recognize that we need a piece of corroborating evidence.
- 00:25:46staging is very, very important both for deciding about therapies and deciding when to refer to specialists and ef remains relevant for therapeutic decision making, but that field is evolving a little bit.
- 00:25:59So now I'm going to do my best to try to summarize heart failure pathophysiology and then we'll talk a little bit about therapeutics so.
- 00:26:08When I speak with medical students or interns about heart failure pathophysiology that the way I described it is homeostasis that's gone wrong.
- 00:26:19heart failure usually starts with some sort of index event that index event could be something like a large EMI.
- 00:26:24or it could be the accumulation of long standing uncontrolled risk factors like diabetes or hypertension.
- 00:26:30But that index event leads to secondary damage and the body activates many different pathways in an attempt to correct the situation.
- 00:26:40Those homeostatic mechanisms go already and we are left with progression of kind of dilation of the ventricle and progression to symptomatic heart failure.
- 00:26:51Some of the pathways that kind of are the cornerstone of heart failure at the pathophysiology or the.
- 00:26:56imbalance between sympathetic activation and parasympathetic inactivation the so called simpatico vehicle imbalance.
- 00:27:03This is caused by Barrow receptors which sense the transient decrease in cardiac output and reflexively clamp down increased heart rate to try to accommodate for that.
- 00:27:14This simpatico Vegas imbalance directly activities rena which feeds into the renal angiotensin aldosterone system.
- 00:27:20And activation of that system, leading to sodium retention in the kidneys activation of stress hormones and maladaptive homeostasis fibrosis in the heart.
- 00:27:30myocardial necrosis remodeling of the ventricle itself, more recently, a lot of interesting science and discoveries have been made about the endogenous natural peptide system.

- 00:27:43And how it acts to counterbalance the activation of these two maladaptive processes, we have taken advantage of this natural peptide system to develop new therapies, such as interesting.
- 00:27:55When I look back at the history of heart failure therapies in my mind the way I think about it is three different buckets the first bucket.
- 00:28:02This is back in ancient times when we realize that heart failure was a disease of fluid overload.
- 00:28:08Was this is a volume problem, we need to treat it with volume reduction so diabetics were one of the earliest therapies that were studied in heart failure, and while they do have some.
- 00:28:17You know, quality of life benefits they've never been proven to improve hard morbidity outcomes or, for that matter, mortality outcomes, the real shift in heart failure therapies came with an understanding of chemo dynamics and that.
- 00:28:31That potentially we could use therapies that were a little bit counterintuitive like phase of directors.
- 00:28:36And unless counterintuitive I know troops to improve the human dynamic situation both the pump and the pipes, so the heart squeeze itself and the vascular resistance that contributes.
- 00:28:46And in the last 40 years a lot of work has gone into understanding neuro hormonal blockade and therapies that have been born of this era, our beta blockers Ras inhibitors nipper licensed in addition to name a few.
- 00:29:00So we we have done a very good job in identifying sort of the cornerstone of heart failure pathophysiology and, though, and the way we know that is that we have therapies that work very well.
- 00:29:11This is kind of a cascade plot showing relative risk reduction in all cause mortality in real world populations, this is not trial data.
- 00:29:21of standard optimal medical therapy for heart failure So you see aces and arms traditional Ras inhibitors have a 15 to 20% reduction relative risk reduction.
- 00:29:30In trust-o has greater than 30% relative risk reduction from baseline so I don't want to make it sound like we haven't come anywhere, you know we certainly have very good therapies.
- 00:29:40But we also know that heart failure or means of really large clinical problem after a diagnosis of de Novo diagnosis of heart failure.
- 00:29:49The median survival, this is data from the UK, the median survival is less than five years you know that's heart failure within without.
- 00:29:56With reduced and preserve ejection fraction but nevertheless there's a significant reduction in mortality.
- 00:30:01And for those of us who care for patients in the hospital, we see this every day heart failure hospitalizations are.
- 00:30:07Probably more of a burden that we are able to kind of grab wrap your hands around there are over 1 million hospital stays every year in this country.
- 00:30:16For what's called to compensated heart failure at a cost north of $10 billion, a direct cost of North and $10 billion to the US healthcare system, the indirect costs of these hospitalizations is sort of unmeasurable last work time, etc.

- 00:30:32So now I’m going to pivot to diabetes, because I think.
- 00:30:36understanding that heart failure remains a large problem there's obviously a lot of people who have devoted their lives and careers to trying to find new frontiers for our player therapeutics and diabetes has emerged.
- 00:30:45As one of those frontiers and the reason behind that actually makes a lot of sense both diabetes and heart failure, have a lot of overlapping risk factors, we know that age.
- 00:30:56African American race male gender hypertension obesity are all shared risk factors for both of these two diseases.
- 00:31:03But more than that, we know that diabetes contributes to atherosclerotic disease and this contributes directly to heart failure progression in the scheme of patients.
- 00:31:10And both diseases contribute equally to renal progression so there's clearly these diseases, diabetes and heart failure are tied at the hip.
- 00:31:18So, potentially, we can use heart failure diabetic therapies to treat heart failure patients more direct evidence of the link here, this is UK PDS data, looking at the.
- 00:31:29The hazard ratio for incident heart failure depending on baseline hemoglobin a one see in an observational cohort study.
- 00:31:38And you can see it's a pretty linear relationship with every 1% increase in hemoglobin do and see there's a 16% increase relative risk for developing heart failure.
- 00:31:47So we know that insulin resistance leads to hypoglycemia hypoglycemia through various mechanisms, some of them atherosclerotic some of them non atherosclerotic lead to heart failure.
- 00:31:58What we've learned in the past few years is that heart failure actually also begets insulin resistance there's some really interesting.
- 00:32:06basic science work to show this, but the most convincing evidence to me is that when we cure patients of their heart failure, with an l bed.
- 00:32:14And i've seen this anecdote luckily in my practice, we see a dramatic reduction in their insulin resistance and then petitions can potentially be cured of their diabetes after we address their heart failure.
- 00:32:25So, certainly the link between heart failure and insulin resistance diabetes is real.
- 00:32:31I want to take a few moments to talk about diabetes and I will preface this by saying, I am not an endocrinologist I take care of patients with diabetes I didn't go into cardiology thinking that I would be.
- 00:32:42Focusing so much of my time and effort on that, but it really the overlap, the line between diabetes, heart failure is becoming blurred as we move forward.
- 00:32:50So let's step back in time to the early 2000s when diabetes drugs were first being developed, you know, think about goes back much longer than that but.
- 00:32:59Oral anti hypocrites glycemic drugs in the early 2000s were really tested in small trials by today's standards small trials with primary endpoints that focused on.
- 00:33:11laboratory data how loaded the glucose get was there was there hypoglycemia and usually a primary endpoint that had to do with hemoglobin a one see reduction.
- 00:33:21Then in 2007 after some signals for harm Stephen this and Catherine Polsky published a Meta analysis in the New England journal.
- 00:33:31That looked at rosiglitazone trials, you know there were 1314 small trials that they looked at.

- 00:33:37They combine all of that data and showed that there was a signal for harm, with increased risk of myocardial infarctions and patients taking rosie or Avandia.
- 00:33:46This drug was already on the market to the FDA was pushed into a corner on this and less than 12 months later, called a special advisory meeting.
- 00:33:56And at the end of that meeting by a 14 to to vote, they mandated that all new diabetic drugs had to show cardiovascular safety data before they would be approved.
- 00:34:06In addition to that they placed rosiglitazone on my rams Program.
- 00:34:10Since then we've seen really the birth of the diabetes, cardiovascular outcome mega trials, these are trials with thousands of patients, they take years and years to complete and.
- 00:34:22Millions hundreds of millions of dollars to complete usually the bill being funded by the pharmaceutical company up front.
- 00:34:29I say up front, because the reality is that cost is passed on to consumers eventually and we're seeing that nowadays, with some of these expensive diabetic drugs that we're trying to use.
- 00:34:39Since 2008, this is the last 10 years I don't expect you to read all of this, but really This is just showing you, the number of cardiovascular safety trials that have been done.
- 00:34:51All of these were done based on that FDA 2008 regulation, showing that we must go below a hazard ratio of 1.8 and then 1.3 and post clinical data.
- 00:35:01The serendipitous finding that we have here is that, while all these trials were designed to prove cardiovascular safety not only were they showing safety, some of them were actually showing a cardiovascular benefit and that's where we'll transition our story into the inhibitors.
- 00:35:17Just a reminder sodium glucose co transporter the system is there's two receptors sgt to one and sgt to.
- 00:35:29These are trans membrane receptors located on the luminous aspect of the proximal convoluted to be on.
- 00:35:37And they are responsible for the reabsorption of nearly all the glucose that is filtered across the globe Mary was in states have high hypoglycemia.
- 00:35:47glucose is built into the urine and it's this system that's primarily responsible for the reabsorption sgt to does 90% of the work sgt one does 10% of the work.
- 00:35:59So inhibitors of slt one and two were clear targets for diabetes medications and, in fact, as early as 1835 this compound flow horizon.
- 00:36:11which was isolated from the tree bark of apple trees was used to treat diabetes, this is back in the day when we tasted urine to know whether we were effectively causing glucose Syria.
- 00:36:22So in the pre insulin era fluoride in a root bark was used this.
- 00:36:26You know it's not really clinically relevant nowadays for horizon is broken down immediately in the stomach so a glucose side analog of horizon called glyphs closings was discovered in the mid-1980s.
- 00:36:39There are now on the market in the United States at least three lift closings in Europe there's even more, but these are all really bioavailable and leukocyte analogs of horizon which work to inhibit the sgt to some due to some do both one and two.
- 00:36:57So getting back to our FDA regulations we have this drug, we think it may help for treating diabetes, we have to prove that they're safe.

- 00:37:03In terms of cardiovascular outcome so there's many large trials that have been conducted I highlighted the four earliest ones here.
- 00:37:10and break outcome looking at an impact with losing canvas looking at capital flows and declare timmy 58 wouldn't get the panel flows in.
- 00:37:18And then I marked it a little bit differently, but credence looking at canal flows and, and the reason I marked that differently as a slightly different.
- 00:37:24Inclusion criteria and primary endpoint.
- 00:37:27All of these patients had diabetes That was really the only principal inclusion criteria here we'll talk about cardiovascular baseline cardiovascular risk in a second, but that was not part of the inclusion criteria, as I mentioned the credence trials enriched for a Reno population.
- 00:37:42For the three pure diabetes trials, the primary endpoint was what we traditionally use and sort of athletic atherosclerosis type.
- 00:37:50cardiovascular trials, which is a composite of three point major adverse cardiovascular events.
- 00:37:56These are separately adjudicated events, so this is one of the large advantages of a large outcomes trial versus smaller trials, is that we can independently adjudicate these events.
- 00:38:05But the three point mesas made up of CV death nonfatal EMI and non-fatal ischemic stroke interest interestingly, the declare timmy investigators included an efficacy endpoint which, as part of the it's composite included hospitalization for heart failure.
- 00:38:22These patients were not yet yes, they were all diabetic but there was pretty important differences in their baseline cardiovascular risk Emperor REG specifically recruited.
- 00:38:31Almost all of their patients had to have some baseline cardiovascular disease, this includes things as serious as.
- 00:38:37coronary artery disease and am I peripheral arterial disease and some heart failure.
- 00:38:41declare timmy and canvas have less of a requirement for that baseline cardiovascular disease, but the real point I wanted to make here and relevant to this talk and my experience is the.
- 00:38:51baseline heart failure diagnosis so prevalent heart failure was only present in maybe 10 to 15% of the patients in all of these trials.
- 00:39:01So, what was the finding the punch line is that these drugs were safe, there was no signal for harm.
- 00:39:07For increased atherosclerotic risk, as measured by three point mace in any of the trials and, in fact, there was a clear reduction in three point mace in all of the trials reaching significance in Emperor REG and credence.
- 00:39:20But much more interesting to that at least to me as a heart failure practitioner was what was found in the secondary endpoints and that was a very robust.
- 00:39:28very consistent reduction in the risk of heart failure hospitalization across all four trials again with slightly varying baseline risk profiles.
- 00:39:39You can see that the relative risk reduction between all four trials it's the blue arrows here is on the order of 30% across the trials and that's a really impressive reduction in risk.
- 00:39:51You might ask yourself was that risk driven by the patients with prevalent heart failure so.

- 00:39:57A sub study of declared timmy published in circulation, a few years ago, looked at that, and they stratified patients, based on their underlying.
- 00:40:05Either absence of a diagnosis of heart failure or heart failure with and without reduced ejection fraction.
- 00:40:11And while the curve is very low down here the patients without for heart failure.
- 00:40:17did have a statistically significant reduction in the incidence of heart failure hospitalizations the implication here is that this is prevention of new onset heart failure in this at risk population.
- 00:40:29In a small number not small number in the small fraction of patients in these trials that did have heart failure, there was a very significant reduction in heart failure hospitalizations as you might expect.
- 00:40:40So what do we learn from these diabetes trials closings we learned that in patients with diabetes and either increased cardiovascular risk.
- 00:40:48or underlying cardiovascular disease, there was no increase in the risk of three point major adverse cardiovascular events and there was a very consistent signal for heart failure risk reduction on the order of 30% across all the trials, so the FDA has approved.
- 00:41:05Many of the glyphs closings for treatment of diabetes, and in fact the endocrinology associations have upgraded the glow flows ins to.
- 00:41:16sort of first line therapy is I don't want to talk to the diabetes well too much here, but basically what we've learned is that this drug works in diabetes.
- 00:41:25I didn't show data about the renal trials, but that is an entirely very, very important results of some of these trials and others.
- 00:41:33That the blood flows ins in patients with renal disease, independent of diabetes status had an improvement in their heartbeat outcomes progression to end stage renal or dialysis or transplantation.
- 00:41:46So when I was a fellow and I started seeing these trials coming out what I was interested in was this really robust heart failure signal.
- 00:41:54And to me the idea that we could be preventing heart failure and an at risk population was fascinating, but it really begs the question could these drugs have utility in preventing or sort of secondary prevention in a population with heart failure already diagnosed.
- 00:42:09As we talked about in the universal definition section of the talk heart failure with reduced ef and preserve the F are really different diseases.
- 00:42:18They liked the share common signaling pathways and pathophysiology pathophysiology mechanisms, but.
- 00:42:24The response to different therapies shows that they are different, so I think testing this question requires different trials for her for half and half path.
- 00:42:32So we'll start with the ref trials glue flows in heart failure, there are two very large trials double blinded randomized control trials.
- 00:42:42You all have hopefully heard about these by now dapper hf which test is packed with those in single dose 10 milligrams and nearly 5000 patients and Emperor reduced which tested impact lives in 10 milligrams in nearly 4000 patients.
- 00:42:56Different inclusion criteria here, these patients all had reduced, yes, so when you have less than or equal to 40%.

- 00:43:03Importantly, there was no pre specification for diabetes these patients, there were some who are diabetic some who are not.
- 00:43:10It was pre-specified to include a certain baseline a diabetic population to answer that question, but nevertheless was not part of the requirement slightly different outcome, rather than our atherosclerosis sort of.
- 00:43:23Safety outcomes we're looking at an efficacy heart failure outcome, and what we looked at here was a composite of CV death or hospitalization for heart failure, this is a common composite endpoint for heart failure trials.
- 00:43:36Whenever we look whenever I look at heart failure trials, I always try to understand what the populations baseline level of health was.
- 00:43:42And what I would say is that both in depth hf and Emperor reduce this is a relatively stable heart failure population.
- 00:43:48I say that because you know 65 to 75% of the patients were classified as myth, a class to So these are ambulatory patients and, as I mentioned, about half of them had diabetes.
- 00:43:59background medical therapy is very important in interpreting the additive benefit of a new heart failure therapy, so we have.
- 00:44:09As of the time of these trials three essentially pillars of what we now call guideline directed medical therapy.
- 00:44:16And you can look at these bar graphs and see the blue is the depth hf trial, the Red is the number just trial excellent usage of beta Blocker.
- 00:44:25really good usage of Ras inhibition as well as kind of above observational real world danger use of morale quarter card receptor antagonist.
- 00:44:34neverland inhibition use was low remember these trials recruiting early afternoon per license hit the market, so this is not surprising, nevertheless, that that has to be taken into interpreted interpreting this data.
- 00:44:47So the punch line both of these trials met their primary endpoint deputy Jeff had a point estimate of 0.7 for that was statistically significant.
- 00:44:56Emperor reduced had a point estimate of 0.75 that was also statistically significant.
- 00:45:02Look, for a moment at these numbers and think back to any two trials that have tested similar drugs in your world and tell me if there's any trial that's ever been as consistent.
- 00:45:13The findings here are almost shocking how equal these results were for two drugs with the same mechanism of action.
- 00:45:22Looking at the raw data, we see that the absolute risk reduction was on the order of 5% which gives us a number needed to treat in both trials around 20.
- 00:45:33A very important question that was asked, from both trials was the effect modified by baseline diabetes status, so this is data from the depth hf trial.
- 00:45:41which was kind of published in a sister publication in JAMA with pre-specified stratification of diabetes or diabetes.
- 00:45:48You see that in the diabetics, which is the top two solid lines that hazard ratio for the composite end point 0.75 which was statistically significant.
- 00:45:57In non diabetics the overall risk of the endpoint is lower, as we would expect, but hazard ratio for reduction in risk remains almost exactly the same.
- 00:46:06And the p value for the interaction between these two populations was non-significant, so the punch line here is that diabetes is not modify the effect.

- 00:46:15You know, two trials published within two years of each other testing basically two versions of the same mechanism of action.
- 00:46:22All of this data was dumped into a Meta analysis pretty quickly and what we find is a really consistent benefit both for CV death production and heart failure hospitalization reduction for the sgt two inhibitors.
- 00:46:36One thing that I think sometimes gets missed when we look at these dapper hf and Emperor reduced trials, is the separation of the event curves.
- 00:46:43So on the left is the Emperor reduced event curve and I put up just for comparison, a very zoomed in view.
- 00:46:50Of the paradigm trial so paradigm, just as a reminder was a trial published in 2014 that compared Tsukuba troll Val certain or interest oh.
- 00:47:01Actually, to an active competitors, with a few trials that had an active competitor of analysis, looking at the exact same composite endpoint CV death or heart failure hospitalization.
- 00:47:11And you'll notice that an emperor reduce the curve separate almost immediately.
- 00:47:16Within 90 days, obviously we can't get too granular here on kind of the data that's presented in the in the primary publication, but within 90 days these curves are separating.
- 00:47:25That is in stark contrast to the paradigm trial or, for that matter, any other heart failure trial that's been published, as far as the early separation of the curve.
- 00:47:36So we shown that sgt two inhibitors are efficacious and safe for diabetes and ck D and now with the publication of depth hf and Emperor reduced we have.
- 00:47:46Consistent statistically and likely clinically significant data showing that sgt two inhibitors work in heart failure with reduced tf to reduce CV death and reduce heart failure hospitalization.
- 00:47:58Now we're left with the big hole in the chart and this whole exists, all the time, with every job that's ever been studied for heart failure with reduced def were left wondering.
- 00:48:06Might this work for preserved df so Now the question is, does this work, last year, the Emperor preserved results were presented the European Society of Cardiology meeting.
- 00:48:17This is a sister trial tamper reduced which looked at a bangle office and 10 milligrams in a larger population 6000 participant trial.
- 00:48:25etfs above 40 slightly unusual ef cut off, in my opinion, but important and again patients with them without diabetes, the same composite endpoint of CB death or hospitalization for heart failure.
- 00:48:38kind of understanding the baseline risk of this population is more challenging it's less of a homogeneous population than half rough.
- 00:48:44But nevertheless Nevertheless, this is the ef breakdown in this population about a third each fell into these categories of VF 40 to 5050 to 60 and greater than 60.
- 00:48:54And they had sort of the typical flavor of a half path population compared to have.
- 00:49:00More hypertension higher degrees of obesity and more atrial fibrillation, this is what we're all familiar with one, taking care of patients FF.
- 00:49:09And the punch line is exciting and for a preserve didn't meet its primary endpoint again a composite endpoint of CV death.
- 00:49:18or heart failure hospitalization the hazard ratio 0.79 and statistically significant again the early separation of the curve should be noted.

- 00:49:27Of note there was when we look at these composite endpoints we want to look at the components of the composite.
- 00:49:32That composite was driven almost entirely by heart failure hospitalization and this trial there certainly was a trend towards improved CV mortality, but that was not significant in this trial.
- 00:49:43The number needed to treat the absolute risk reduction was closer to 3% of this trial giving an empty of 31.
- 00:49:51Again subgroup analysis prefix pre-specified subgroup analysis showed that baseline diabetes status did not have any impact on the event.
- 00:49:59But interestingly, there seemed to be attenuation of the benefits as the ef got above 60.
- 00:50:06This is something we see in all half half trials it's likely that these three groups of patients are actually.
- 00:50:12Different diseases, and you know the inclusion criteria for half path in trials is very hotly debated really E, F is probably not sufficient to make to make an accurate assessment, nevertheless, there was a clear benefit and E, F less than 16.
- 00:50:27So now we've closed the gap in addition to interest, though, which I mentioned very briefly at the beginning of the talk which.
- 00:50:33The paragon hf child showed might work, we now have at least impactful of losing data showing heart failure hospitalization reduction and a half bath population.
- 00:50:43The deliver trial is ongoing and will hopefully know the results soon, which will ask the question whether do Pagel flus and has the same effect in a similar population.
- 00:50:54A question that already I'll just ask themselves after these trials republished is what about acute heart failure, you know, this is a slightly different situation patients who are.
- 00:51:03You know, recently admitted for heart failure or who are congested and require IV diabetic therapy and is there a safety issue with using this.
- 00:51:13Basically diuretic in addition to this therapy so to answer that question the soloist worsening heart failure trial was started.
- 00:51:22This is a trial a randomized controlled trial of satirical frozen over 1000 patients.
- 00:51:27slightly different inclusion criteria here, these word diabetic patients who did have a recent heart failure hospitalization and this actually included patients with any yes.
- 00:51:35soloist worsening heart failure actually was going before Emperor preserved so this is actually the first F trial really.
- 00:51:42Unfortunately, the trial had to be stopped prematurely the sponsors ran out of funding, and I think this speaks to.
- 00:51:49The difficulty of these trials they're very expensive they take a long time and we're kind of left with the black box, we have this data.
- 00:51:56From the trial, which was published in the New England journal, but has to be interpreted with a grain of salt, because the trial did not reach its primary kind of event driven endpoint.
- 00:52:05Nevertheless, the curve, speak for themselves there's a clear separation with photographers improving heart failure hospitalizations and cardiovascular deaths.
- 00:52:13There were a few smaller trials of impact low flows in in the acute heart failure population.

- 00:52:18Emperor response hf a very small trial and then em pulse a slightly larger trial which the the results were presented at AJ last year we're still waiting, this data.
- 00:52:28So for what it's worth Meta analysis of unpublished data and incomplete trials, we it looks like it's efficacious and heart to heart failure population.
- 00:52:39I kind of glossed over the safety issues for all of these trials, just because there's a lot to talk about, but just take my word for it or we'll look at the data yourself.
- 00:52:46There was no real signal for harm with any of the slt to inhibitors in any of the heart failure population so hypoglycemia a KPI persistent aka I know, no real, significant difference between the treatment arms and the placebo arms.
- 00:53:01So, how does this translate into the real world so regulatory approval is important we can't prescribe drugs that are not approved so FDA and AMA the European equivalent of FDA in 2020 and 21 approved.
- 00:53:16and impact of losing with full approval for patients with heart failure and reduced ejection fraction independent of diabetes status.
- 00:53:24And, last year the FDA granted breakthrough designation for impact let's loosen for half path we're hoping for the deliver data soon and then maybe we can get full approval for me I'm sorry for EPA and DHA for.
- 00:53:39How the professional societies responded to this, so this is a tough position to be in I don't envy the guideline writers for.
- 00:53:47For for heart failure because the data is emerging so quickly and it's hard to keep up with this, but nevertheless the Europeans are a little bit ahead of us, they are on a five year cycle for writing their heart failure guidelines and they published last year there.
- 00:53:59update and they did upgrade to class one recommendation dapper and empathy for patients any patient with heart failure and a reduced ejection fraction.
- 00:54:09Specifically, to reduce hospitalizations and death.
- 00:54:12there's other blood flows ones that are available in Europe that we don't have access to Here are two blood flows in and sabbatical flows and are approved.
- 00:54:18For all diabetic patients to reduce the risk of heart failure hospitalization and in patients with both diabetes and half rough so tangled flows and was included with death by Tampa based on the results of soloists presumably.
- 00:54:32The American societies are we're awaiting the guideline update soon hopefully.
- 00:54:37But in the interim have published expert consensus decision pathways that gives strong recommendations for use of sgt two inhibitors generally speaking for heart failure with reduced ejection fraction they did not comment and heart failure with preserved ejection fraction.
- 00:54:51So we've done kind of a whirlwind of sgt tues in diabetes trials and then transitioning to Hartford trials for I hope I've convinced, you have the data.
- 00:55:00That these drugs do work they work on patients they're approved and they're recommended as class one.
- 00:55:06So now we're left asking how do they work, and this is a question I get a lot in clinic, how is it diabetes drug supposed to help me Doc I don't have diabetes.
- 00:55:15And my answer has evolved over time as i've thought about this more of my answer initially was i'm not really sure the data look like they work, we should we should do it.

- 00:55:23And then I moved on to well, it might have something with something to do with like reducing your risk of developing diabetes and the diabetic effective glucose area.
- 00:55:32But as i've read more about this and looked into the science i'm realizing that this is a true bedside to bench story and we're learning a lot about how.
- 00:55:41inhibitors might work do they fit into one of these three buckets that I described earlier, or is there some other mechanism that we have yet to understand.
- 00:55:49So really a true bedside adventure story there's a lot of putative mechanisms that have been proposed, I don't have time to go over all of them, I want to highlight a few.
- 00:55:58First and foremost, I want to address what I view is the elephant in the room is is the effects due to glucose reduction or blood pressure reduction.
- 00:56:06I really have glossed very much glossed over the kidney protective effects during my talk today apologies to my renal colleagues that's a grand rounds into itself, but the.
- 00:56:15Improvement in gold medal or hyper filtration that has seen with that sheltie two inhibitors is quite impressive and merits and indication for the drug by itself.
- 00:56:24But nevertheless this via the Cardio renal mechanisms that we're all familiar with probably improves cardiac health as well.
- 00:56:31The three mechanism, I want to briefly touch on today are down below cardiac remodeling the interstitial and cardiomyocytes biology so we'll start, first and foremost by addressing the glucose and blood pressure so.
- 00:56:44I think it goes I think it's pretty obvious that the slt to inhibitors work, independent of glucose reduction and we know that from both dap hf and Emperor reduced were.
- 00:56:53In non diabetics there was a clear reduction in heart failure risk, but if we look more closely at the diabetic populations.
- 00:56:59First of all these aren't the best anti diabetic drugs they actually only reduce hemoglobin anyone see in the trials on the order of point two 2.5% there are other drugs that were much better for.
- 00:57:11glycaemic reduction and then, when you plot baseline hemoglobin a one see as a continuous variable against the hazard ratio for the composite events.
- 00:57:21This is from the deputy Jeff trial, but the same has been shown for Emperor reduced.
- 00:57:25There is no significant change in the hazard ratio, so the implication here is that independent of glycaemic changes sgt two inhibitors are.
- 00:57:33Improving heart failure hospitalization and cardiovascular deaths, the same goes for blood pressure reduction, so those of you who have used these drugs.
- 00:57:41Especially in the hospital, where we will sometimes initiate them and can see this happen, there is a blood pressure reduction that happens pretty early on.
- 00:57:48On the order of two to three millimeters of mercury from the systolic blood pressure.
- 00:57:52I would point out that that reduction in blood pressure is variable depending on the baseline blood pressure so more hypertensive patients seem to have a more robust effect and patients borderline.
- 00:58:03kind of hovering on low blood pressure, tend to have less of an effect that's important in my world with advanced heart failure.
- 00:58:09But, overall, the average reduction in stop blood pressure was less than two millimeters mercury.

- 00:58:14And again when plotted as a continuous variable this is baseline systolic blood pressure, the hazard ratio did not very I didn't show this data, but in addition to his baseline blood pressure, the delta blood pressure, one part of the same way she has the same effect.
- 00:58:28So I hope i've convinced you that it's probably not the glucose it's probably not the blood pressure, it might be something else so let's talk a little bit about cardiac remodeling.
- 00:58:36We know that heart failure medications lead to changes and ventricular shape and size, and so the obvious question is what is what are sgt two inhibitors doing there.
- 00:58:46You know the big heart failure trials did not have robust imaging components to them it's hard to do in large trials, so this really.
- 00:58:54I love this clever name em but tropism randomized control trial was conducted to look at more nuanced imaging characteristics.
- 00:59:02This is obviously a small trial, but large by cardiac MRI standards at for patients with etfs less than 50%.
- 00:59:09Importantly, without diabetes or randomized to impact with losing 10 milligrams or placebo, and they had at entry into the trial at randomization a baseline cardiac MRI and then six months later, and other MRI.
- 00:59:21Six months is a pretty short time to expect to see cardiac remodeling and I applaud the investigators, for being able to wrap up this trial so quickly, I think they had some preclinical data to suggest that they might see a benefit this quickly.
- 00:59:33And the punch line here is that in Pangalos and within six months, showed a robust and clinically statistically significant reduction in LV and diastolic volume LV and systolic volume and more translatable to all of us.
- 00:59:48A six percentage point increase in left ventricular ejection fraction.
- 00:59:52Remember MRI is the gold standard for measuring Chamber sizes and ejection fraction so we believe this results.
- 00:59:59There was also interesting findings with a reduction in LV mass and a change and what's called the sphere city index.
- 01:00:06Remember, with dilated cardiomyopathy we go from a normal bullet shaped heart too short of a basketball shaped heart and that can be quantified with something called sphere city into index that did improve with impact.
- 01:00:17So MRI results are really interesting, we are seeing remodeling MRI is obviously an extremely powerful tool, much more so than Chamber sizes so.
- 01:00:26there's some more information we're going to get from the semper tropism study, but first I wanted to present this hypothesis that one of the reasons that diabetes and heart failure overlap, has to do with.
- 01:00:36inflammation and adipose tissue specifically systemic adipose tissue and EPA Cardio adipose tissue.
- 01:00:43We know that EPA Cardio adipose tissue on surgical specimens and in vitro will it has is very active, it has pair cranes secretions of cytokines so called adipose cytokines that act directly on the myocardial that they touch.
- 01:00:58So that's one potential putative mechanism for why EPA Cardio fat might be important in heart failure, the other is just that epic Cardio fat contributes to decrease distance ability of the ventricle and.

- 01:01:08and contributes presumably to diastolic dysfunction so what effect might sgt two inhibitors have on this system so.
- 01:01:17The tropism investigators looked at this with MRI data, where we can carefully delineate the EPA Cardio fat and quantify it.
- 01:01:26And what we see is a very robust reduction and statistically significant reduction in EPA Cardio adipose tissue in patients treated with agriculture, and this is really fascinating.
- 01:01:35We need to follow this up with a little bit more biological data to see if this pro inflammatory cytokines are also being decreased significantly and probably larger trials, but I find this very interesting.
- 01:01:47The next potential mechanism is has to do with the interstitial in heart failure doctors clinicians and scientists have thought about the interstitial for a long time, and the reason for that is, we know.
- 01:01:57That heart failure is at its core a sodium problem there's a aggressive sodium retention by the kidneys in response to the effective.
- 01:02:06Interpretation of low cardiac output and that leads to fluid expansion in all compartments intro vascular intracellular and muscles and tissue and then interstitial space, including potentially in the skin.
- 01:02:19And what we know is that our traditional way of reducing volume with loop diuretics.
- 01:02:24is very effective at lowering total body sodium it's very effective at lowering interstitial volume when used appropriately.
- 01:02:31But importantly it can pretty dangerously lower intro vascular volume, especially when we don't have kind of invasive monitoring of the investment your vascular volume status, and I think we've all taken care of these patients, we have.
- 01:02:44You know, over diaries their gsr reduces acutely they get hypertensive and that likely has to do with this intro vascular blood volume reduction effect from loop diuretics.
- 01:02:55It has been proposed that inhibitors because of their site and mechanism of action differing from loop diuretics these are proximal computed tubular diuretics have less of an impact and intro vascular volume expansion or reduction.
- 01:03:10This is a really fascinating hypothesis it's yet to be proven in heart failure population, but in a.
- 01:03:16Healthy control population, we do have some data, so this is healthy controls, who are exposed either to deepak liberalism or be met night.
- 01:03:25And had objective measurements of blood volume and interstitial volume and you can see that boom X and Pangalos in both reduce interstitial volume.
- 01:03:34And bulimics clearly reduces blood volume goes into effect is attenuated.
- 01:03:39How does that translate well remember with reductions and effective arterial circulating volume, we have activation of the region angiotensin system so it's a similar kind of small random my study of.
- 01:03:52Those in verses be met and I measured plasma reading activity in the same patients and they showed that after you Max dosing there's a significant increase in plasma reading activity that was not seen it all.
- 01:04:02flows, and so this is potentially a really important mechanism by which the slt to inhibitors work, this is a special kind of diuretic.

- 01:04:12Finally, I wanna spend the last few minutes talking about cardiomyocytes handling I on handling party my psychology in general I think in heart failure we tend to we so far historically have thought, upstream, you know.
- 01:04:25improve blood flow to the myocardial affect the heart rate when it's a problem treat the risk factors, diabetes and hypertension.
- 01:04:32But at its core cardiomyopathy is a problem with the cardiomyocytes.
- 01:04:36So again, a lot of really, really important basic science work has looked at cardiomyocytes biology and specifically heart failure according last night biology and come up with these four categories as.
- 01:04:47Potential mechanisms and areas for targeting one is mitochondrial dysfunction contract out dysfunction of the sacrum your unit itself and ophelia and vascular dysfunction and then timing and mechanisms cell death of the cardiomyocytes.
- 01:05:02So along those lines, I want to kind of segue a little bit away from St ott to something called the sodium hydrogen exchange system.
- 01:05:09This is, it has, for the past few decades, been characterized very well as a very important system in both cardiac and renal disease.
- 01:05:17This is a trans membrane receptors that's located in both the kidney and the heart that pumps sodium into the cell at the expense of a proton there are multiple forms of this.
- 01:05:28Exchange System, and he one is ubiquitously expressed, including in the heart and he three is isolated to gastrointestinal cells and the kidney.
- 01:05:38And there are two disease states which up regulate both of these systems those twos diseases are diabetes and heart failure in both cardiomyocytes and the kidney BC.
- 01:05:47Increased expression of these transporters, what does that lead to increased renal tubular reabsorption which leads directly to cardiac injury and also directly to get married or Hypo filtration and Reno entry.
- 01:06:01Of note SG lt one and two are very, very closely linked with the energy system there structurally similar they're located in similar tissues.
- 01:06:11Remember sgt to is located in the proximal Congress, with the to bill essentially right next to energy three is in the kidney.
- 01:06:19So can we target this you know, a long time ago there was a chemical called corrupt arrived, which is thought to potentially be able to inhibit energy one in the cardiomyocytes.
- 01:06:28This was tested in surgical literature for patients undergoing bypass surgery to look for Perry procedural Am I and, in fact, there was a signal for benefit.
- 01:06:35Of this intravenous infusion of an nhl one inhibitor unfortunately we lost traction on this job because there was some signals from harm as well, or with trombone biotic strokes.
- 01:06:47So crypto right is kind of fallen away, but nevertheless the the idea of targeting and each one remains.
- 01:06:52In the kidney targeting energy three has also been of interest, and we know that mineral cortical receptor antagonist actually in vitro directly inhibit and he three.
- 01:07:02This activation of energy three can lead to plasma volume expansion and by vehicle America tubular feedback and reduction of sodium delivery increased regular hyper filtration.
- 01:07:14So, more recently, how does sgt to fit into this what we've learned is actually that multiple sgt two inhibitors ample data analysis and.

- 01:07:23can actually bind to the sodium binding site of energy one and in vitro and we did cardiomyocytes in vitro and expose them to the slt to inhibitors we have a reduction in intracellular calcium.
- 01:07:36So it's this is fascinating and potentially raises the the possibility that sgt two inhibitors via their direct actions and sodium hydrogen transport system may be protecting the kidney and protecting the heart.
- 01:07:51So I've brought up a few of the puter the mechanisms, there are many, many more and encourage any of you who are interested in reading more about this there's an excellent review.
- 01:07:59That was published a few years ago now, on a shield T inhibition and cardiovascular protection, some of the ones that I think are important that I did not mention.
- 01:08:07Our ketone body production and this idea that we are losing calories with sgt to as we.
- 01:08:13As glucose production as we with glucose area about 200 to 300 kilocalories last per day with that, and what that might do to our nutrients sensors in our body.
- 01:08:23I did not mention it all the increase in adequate and robots all masters that has also been observed, so lots of Peter the mechanisms and I think the next five to 10 years we're going to learn a lot about this class of medication.
- 01:08:34So, in summary sgt two inhibitors hopefully shown to you have proven efficacy for reducing both heart failure admissions and cardiovascular deaths in patients with diabetes and cardiovascular risk.
- 01:08:47Chronic kidney disease, independent of diabetes status heart failure with reduced ef independent of diabetes.
- 01:08:54And heart failure with preserved, yes, independent diabetes status importantly in those studies or that one study, there was no mortality benefit.
- 01:09:01And last I hope I've introduced you to this this kind of bedside to bench experience that we're having with this chemical.
- 01:09:08and show you that the exact mechanism is unclear, but it's probably independent of blood pressure and glycemic control and potentially is related to direct Reno Reno and cardiac toxicity.
- 01:09:18So with that Thank you all for the invitation to talk about this topic and I'm happy to take the last few minutes to answer any questions.

UVA Chiefs

01:09:31Thank you so much, Dr.

- 01:09:33folks feel free to send messages in the chat or I can also unmute you on zoom we have some residents here in the audience as well.
- 01:09:42 I'll start off with a question I was really struck by review, besides the rapid separation of the curves.
- 01:09:50In the emperor's trial and so many other trials and then with the MRI showing kind of those rapid remodeling effects within six months, how is that information.

- 01:10:00have affected, how you prioritize starting GM empty and these patients and is this kind of one that you want to you want to start sooner versus I think for us in the trucks in the Inpatient side, it can be hard to prioritize which medications we went on board with a patient.

Steven Philips

01:10:17Please yeah that's a that's a fantastic question and I don't have the answer I have a kind of my anecdotal experience.

- 01:10:24Having looked at this data closely and looked at the mechanism of actions, I actually am a believer I'm saying this from my anecdotal experience that.
- 01:10:32A shield T to inhibitions should be up front just given this rapid effect that we're seeing, particularly in heart failure hospitalization I think there's a lot of.
- 01:10:43kind of implementation, science, that is going to emerge over the next few years on, what is the best strategy for getting patients on optimal medical therapy.
- 01:10:53You know, we have three other arms or pillars of optimal medical therapy that are equally important and the timing is there's no right answer.
- 01:11:01I will say and I'm sure someone's going to ask they didn't in the chat yet about the cost of this medication it's certainly.
- 01:11:08A huge barrier and it's something that we struggle with on a day to day basis.
- 01:11:12I find that the Inpatient setting is a really opportune moment to address those issues we have.
- 01:11:17You know these internal interdisciplinary teams that are available and pharmacists can run prior odds in the hospital, we can answer the questions to their face.
- 01:11:26So I find that that's a really good moment to kind of initiate sgt two numbers, I will say, given the known a ferrant.
- 01:11:35Gold Medal or visa dilation that we see or vessel constriction that we see with a shelter two inhibitors.
- 01:11:41And the known different visa dilation that we see with Ras inhibitors I tend to avoid starting both of those like on the same day I kind of Washington, the slt to inhibitor and then introduced the Ras inhibitor later.

UVA Chiefs

01:11:55Thank you, and we have a question for Dr Kramer I'm going to ask us.

Christopher Kramer

01:12:04yeah thanks, can you hear me Steve.

- 01:12:06yeah yeah great talk.
- 01:12:08excellently comprehensive so I'm more of a comment than a question so getting at the.

- 01:12:13Some of the mechanisms, just to make sure you and others are aware so matt I don't know if matt Wilson on the zoom but he and Fred Epstein and be me just got an hour one funded to look at EPA Cardio fat in in in mouse models and mouse models of.
- 01:12:31diet induced.
- 01:12:34metabolic syndrome, essentially, as well as humans to look and Fred Epstein has developed a way to look at fatty acid composition of the EPA Cardio adipose tissue and to tease out.
- 01:12:47How slt tues will affect that in my son humans as well as myocardial perfusion So hopefully there'll be some mechanistic data coming from uva and next couple years.

UVA Chiefs

01:13:02Dr bullock and also asked to be I needed to go again.

Rasheed A Balogun

01:13:08Thank you very much, Dr Phillips, this has been an excellent presentation, thank you very much.

- 01:13:14I like your.
- 01:13:15bedside bench.
- 01:13:18description of this I haven't very.
- 01:13:23practical question that.
- 01:13:26I these medicines consider cardiology medicines, I did nephrology or primary care so we've had significant trouble.
- 01:13:40In my I mean nephrologist in my seeking the clinic kind to start people on slt to inhibitors.
- 01:13:50While we frequently get is all use another diabetic medication, this is too expensive.
- 01:13:56and going back and forth with the I think you started addressing it if you move into gold suggesting that starting as an Inpatient might be a good idea.
- 01:14:07For the vast majority of patients, I see I'm seeing them as an outpatient and I'm not sure yet if I myself in nephrologist should be touching them or suggesting to the primary physician to be the one to stop them, I wondered what your opinion is about that.

Steven Philips

01:14:28yeah that's a that's a great question.

- 01:14:32I don't have the answer I would I can I can speak from my area of expertise and.
- 01:14:39The short answer is, I view these as heart failure drugs.
- 01:14:44That that's what they seem to do I think they have the benefit of reducing.
- 01:14:50Blood glucose and I think you and I are worlds collide, a lot more often in that this this renal and cardiac protection overlap quite a bit.
- 01:14:58So I don't know the answer to that I tend not to punt it back to PCP because.

- 01:15:03That can be just a challenging for them to get prescribed and pilots and things like that, but you're right, this is a challenge, this is, this is very much john so if anyone has a good solution to it I'm all yours.

UVA Chiefs

01:15:16If I come into that chat from Dr Rao kind of following up on that and kind of nephrologist send cardiologists taking an active role and prescribing and we have a question, is there a role and starting these meds and heart transplant recipients to promote good remodeling.

Steven Philips

01:15:32yeah that's a great question I i'm not familiar with the with transplant data honesty lt tues I should know the answer to that, but certainly, particularly when it comes to the renal protection in our in our cardiac transplant population which is kind of the inevitable.

- 01:15:50outcome in patients who are on call Center and inhibitors drugs to that effect, the idea that we could maybe.
- 01:15:57delay that or avoid that with a shortage of nurses fascinating.

UVA Chiefs

01:16:05To have time for one more question Dr grant at the beginning of the questions asked if you had any comment or information on primary cardiomyopathy like Emily.

Steven Philips

01:16:16yeah that's a good question you know amyloidosis is a special interest of mine, and I think it's.

- 01:16:23My guess is it's probably different it was different types of amyloidosis there's the.
- 01:16:27The light chain form and the translate written form, and then they behave differently once more inflammatory than the other.
- 01:16:33So the effect of direct cardiomyocytes targeting and those populations is probably different.
- 01:16:38I will say that it's likely that are have trials are probably diluted by patients with amyloid and because we think that our standard therapies don't work as well in Emily patients the FF trials, the results are more than likely diluted by.
- 01:16:55A negative effect in the amyloid subpopulation but.
- 01:16:59yeah that's a great question.

UVA Chiefs

01:17:05Very last question from student doctor will way, are there any putative mechanisms for our slt to inhibitors tribe cardiac modeling.

Steven Philips

01:17:14yeah I hope I showed you some of them, but yeah you're, this is thE core question and will, I encourage you to.

- 01:17:20get into a basic science lab if you're really interested in this because I think this is there's this is right for investigation, I personally think that the.
- 01:17:28This this idea of calcium handling and the cell is very important, we actually know that from our.
- 01:17:33Studies and there's a new field of heart failure therapeutics called kelsey troops that are potentially trying to take advantage of that.
- 01:17:41But nevertheless, I, personally, I think that I on handling specifically sodium and calcium handling in the cardiomyocytes is where sgt two inhibitors are working, I don't I don't know that, obviously, but I'm pretty convinced by the evidence I've seen.

UVA Chiefs

01:17:57Wonderful Thank you so much, Dr Phillips, for your time and for a really great talk, I really enjoyed it.

Steven Philips

01:18:03Thank you.