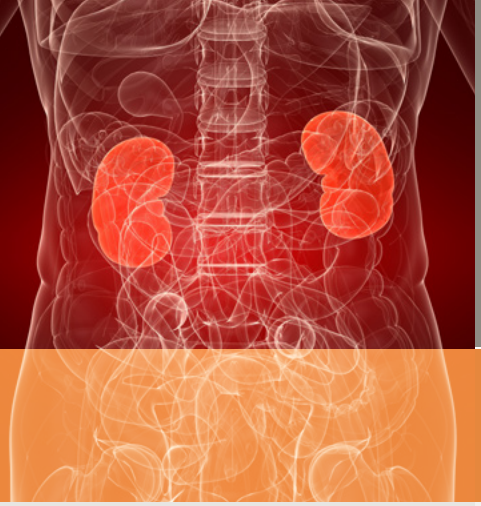

New Developments in the Diagnosis, Pathophysiology, and Treatment of **Chronic Kidney Disease (CKD)**

National Kidney Conference Highlights

Release Date: **April 2020**

ACCREDITATION STATEMENT

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CHAIR

Daniel W. Coyne, MD
Professor of Medicine, Nephrology/Internal Medicine
Washington University School of Medicine in St. Louis

TARGET AUDIENCE:

This activity has been designed to meet the educational needs of physicians involved in the care of patients with CKD.

GOAL:

To provide an overview of novel and exciting research presented at a national kidney conference, focused on rare CKDs in which chronic inflammation is believed to play a role.

LEARNING OBJECTIVES:

1. Describe recent data surrounding novel therapeutic targets in CKD
2. Examine the role of chronic inflammation in the development and progression of CKD, including rare CKD states
3. Identify emerging and novel risk factors for CKD progression
4. Evaluate the clinical utility of new sequencing technologies for the characterization of rare CKD states
5. Discuss the efficacy and safety data of new and emerging therapies for the treatment of CKD and related conditions

FACULTY DISCLOSURE

Daniel W. Coyne, MD: Dr. Coyne has been a speaker for Fresenius Medical Care, and a consultant for AstraZeneca, Fresenius Medical Care, GlaxoSmithKline plc, MediBeacon, and Reata Pharmaceuticals, Inc.

This activity is supported by an educational grant from Reata Pharmaceuticals, Inc.

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Chair

Daniel W. Coyne, MD
Professor of Medicine, Nephrology/Internal Medicine
Washington University School of Medicine in St. Louis

Dr. Daniel William Coyne is a board-certified nephrologist and a professor of medicine in the Division of Nephrology of Washington University School of Medicine. He is also the director of the Internal Medicine Multispecialty Outpatient Center of Washington University School of Medicine and a member of the Advisory Council for the BJC/WUMS Renal Network. His clinical practice focuses on providing comprehensive care to patients with CKD, hypertension, glomerular diseases, and inherited kidney diseases, among others. He has authored more than 100 peer-reviewed articles and more than 15 book chapters.

"Chronic kidney disease (CKD) affects about 37 million adults in the United States—nearly 15% of the adult population.[1] The morbidity and mortality in this population is immense. Patients with CKD have elevated risk for premature death, cardiovascular disease, stroke, and end-stage kidney disease (ESKD).[1,2] Patients with CKD have more than a 2-fold higher adjusted mortality rate than those without CKD.[2] There has been progress in slowing CKD progression to ESKD, but the prevalence and therefore burden of CKD on society is increasing in the United States.[3]

Slowing CKD progression and reducing the prevalence of ESKD will require translating recent basic science and animal model insights into better treatments in the clinic setting. Accumulating evidence suggests chronic inflammation is involved in the pathophysiology of CKD, and that anti-inflammatory therapeutic strategies may improve CKD outcomes. The goal of this Conference Highlights is to enhance understanding of the inflammatory mechanisms of CKD progression, and the novel treatments disrupting those pathways that may reduce CKD-related morbidity and mortality."

– Daniel W. Coyne, MD

Introduction to Inflammation in CKD

Inflammation has been linked with CKD since the late 1990s, when an association among chronic inflammation, kidney function, and cardiovascular disease was identified.[4,5] Since then, the pathophysiologic role of inflammation in CKD and ESKD has been of interest to researchers and clinicians, and inflammation has become an established risk factor for morbidity and mortality in CKD.[6] For example, several inflammatory mediators have been inversely correlated with estimated glomerular filtration rate (eGFR) and positively correlated with albuminuria in people with CKD.[7,8] Furthermore, elevated erythrocyte sedimentation rate in adolescence is predictive of ESKD in middle-aged men,[9] suggesting an early and ongoing role for inflammation in CKD pathophysiology.

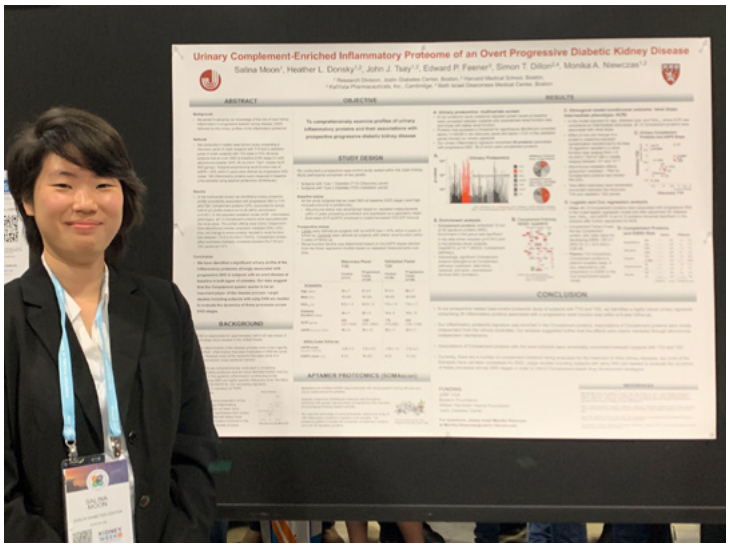
Although inflammation and CKD have been convincingly linked, several questions remain. For example, CKD encompasses a highly heterogeneous group of conditions. Within each of these CKD states, inflammation may operate in distinct ways, resulting in different inflammatory mediators, markers for progression, and therapeutic targets. At a recent national kidney meeting, several presentations added to the current state of knowledge surrounding CKD and inflammation through the utilization of new laboratory techniques, sequencing technologies, and pharmacotherapeutics. A summary of select abstracts is presented here, with a particular emphasis on rare disease states in which inflammation is believed to mediate pathophysiologic damage. These presentations spanned the spectrum from basic laboratory research to large-scale phase 3 clinical trials, which is representative of the wide breadth of research in this exciting field.

CKD Pathophysiology: Chronic Inflammation

Inflammatory markers and mediators in CKD

Inflammatory mediators and markers appear to vary both by disease state and by the type of inflammation (ie, systemic or local). In a poster presentation, Salina Moon and her colleagues from Joslin Diabetes Center evaluated protein signatures of local inflammation in 112 diabetic kidney disease (DKD) patients with progressive disease over 5 years.[10] In this case-control study, researchers found that DKD was associated with a urinary proteomic profile consisting of nearly 50% complement proteins. In this population, the second most abundant group of proteins consisted of chemokines.[10] Intriguingly, Moon pointed out that the urinary inflammatory proteome, which characterizes local kidney inflammation, was distinct from the systemic inflammatory proteome, which was previously shown to be enriched in tumor necrosis factor (TNF)-receptor superfamily members but not in complement proteins.[11] These results suggest a difference in local and systemic inflammatory signatures of DKD.

Furthermore, Moon and her colleagues showed that, among patients with DKD, inflammatory protein signatures were independently associated with renal function loss: a single unit change in the protein signature was associated with renal function loss of 1.5 to 7.3 mL/min/1.73 m^2 per year.[10] Based on these results, the researchers are hopeful that, in the future, inflammatory protein signatures may be able to predict CKD progression. Moon noted that their group plans to follow the cohort over 10 years to further assess the predictive and prognostic values for the urinary proteome.



Salina Moon, BSc, senior research assistant at the Joslin Diabetes Center, presents her group's work on inflammatory proteomes in DKD.[10]

> *If these data are confirmed, we may need to think about local inflammation and systemic inflammation as distinct entities with unique signatures in DKD. These distinct patterns, in turn, may guide more rational and effective treatment decisions.*
>
> – Daniel W. Coyne, MD

Jay Nath, MBBS, DM, and his colleagues from the University of Toronto also investigated urinary inflammatory markers. In this study of patients with type 1 diabetes (T1D), the urinary inflammatory protein signature was compared among patients with or without DKD.[12] Dr. Nath showed that most inflammatory markers were excreted at a lower level in those with DKD than in those without DKD or non-T1D controls. However, IL-6 was significantly higher in DKD than in non-DKD T1D.[12] Although it is unclear why DKD was not associated with higher inflammatory marker excretion, it should be noted that this study evaluated 42 urinary inflammatory markers,[12] compared with the 194 markers evaluated in the study by Moon and colleagues.[10]

An extracellular matrix molecule, TGF-β–induced (TGF-βI) has been shown to contribute to a number of physiological processes, including inflammation. In past studies, TGF-βI expression was upregulated in patients with DKD.[13] At the recent kidney conference, Wenjun Ju, PhD, of the University of Michigan Medical School, showed that TGF-βI expression levels were associated with CKD severity in both humans and mouse models. In humans with either DKD or systemic lupus erythematosus nephropathy, TGF-βI expression was inversely correlated with eGFR. Furthermore, TGF-βI was specifically enriched in immune cells and mesangial cells, which may suggest a role for TGF-β in inflammation and kidney injury via disruption of the podocyte actin skeleton.[14]

> *The precise mechanisms by which inflammatory mediators influence CKD remain unknown. Unraveling the role of inflammation in the pathophysiology of CKD will require additional investigations.*
>
> – Daniel W. Coyne, MD

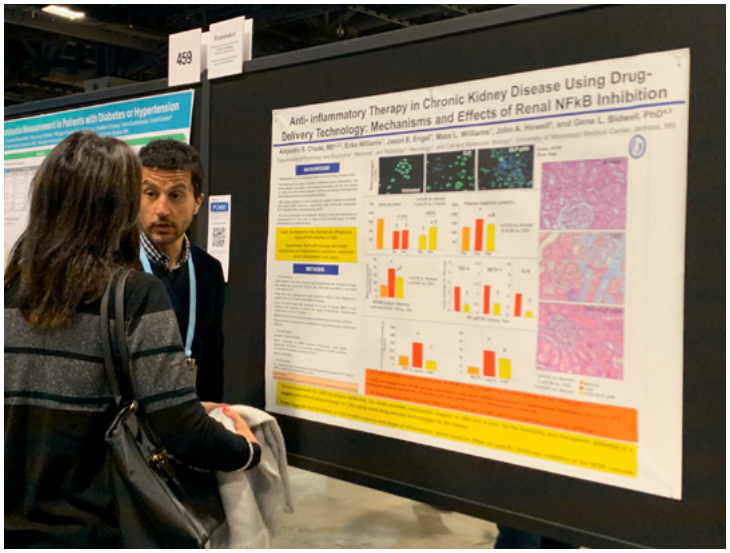
Preclinical studies of anti-inflammatory agents in CKD

Studying the effects of anti-inflammatory drugs in CKD models can further contribute to our knowledge of this disease state.

Alejandro Chade, MD, professor of physiology and radiology at the University of Mississippi Medical Center evaluated the effects of nuclear factor-kappaB (NF-κB) inhibition in an animal model of CKD.[15] The NF-κB family consists of inducible transcription factors that mediate inflammation and immune responses. Dysregulated NF-κB signaling is an important cause of inflammatory diseases and has been identified as a driver of renal inflammation.[16]

Using a domestic pig model of CKD, Dr. Chade and colleagues tested a peptide inhibitor of NF-κB fused to a cell-penetrating peptide carrier (ELP-p50i). After a single infusion of ELP-p50i, local markers of CKD (ie, plasma creatinine, GFR, and renal fibrosis) improved along with systemic inflammation markers (ie, circulating TNF alpha [TNF-α] and monocyte chemoattractant protein 1 [MCP-1]). According to Dr. Chade, the changes in both local and systemic inflammation suggest that the kidney is "both a source and target of inflammation" in CKD models.[15]

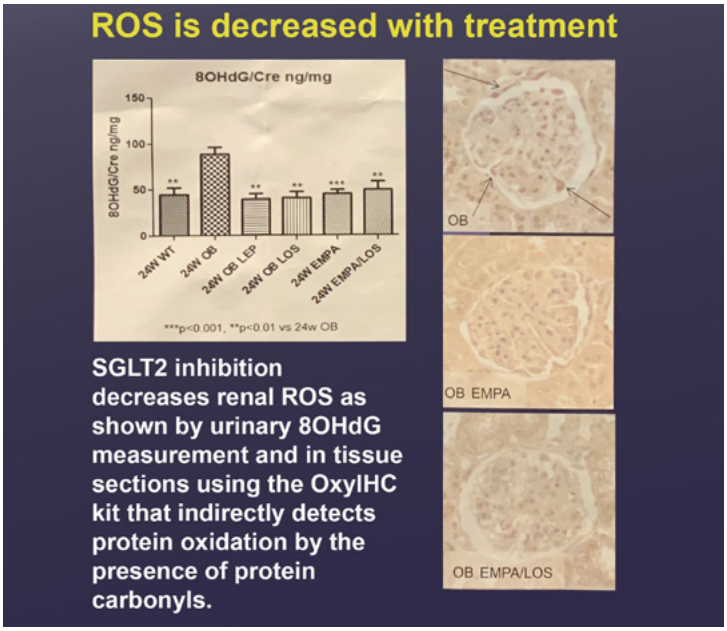
> *In CKD, the kidney is "both a source and target of inflammation."*[15]



Alejandro Chade, MD, professor of physiology and radiology at the University of Mississippi Medical Center, presents his group's work on the delivery of a novel NF-κB inhibitor in a porcine model of CKD.[15]

At the recent kidney conference, there was interest in the mechanism of action of sodium-glucose transport protein 2 (SGLT2) inhibitors, with several groups investigating the impact of SGLT2 inhibition on inflammation and oxidative stress. In a poster presentation, Kelly Hudkins, MS, of UW Medicine, University of Washington, investigated the molecular effects of empagliflozin in a mouse model of DKD. In this study, empagliflozin decreased reactive oxygen species (ROS) levels in the kidney based on the results of histopathologic detection of kidney oxidation and measurements of urinary ROS.[17] Similarly, Batoul Dia, MS, of the American University of Beirut, showed that dapagliflozin treatment decreased the levels of enzymes that facilitate ROS production and reduced the levels of superoxide anion in a mouse model of DKD. This study also showed that TGF-β expression in the kidneys was decreased with dapagliflozin treatment relative to control.[18]

> *"The mechanisms of SGLT2 inhibitors' beneficial renal effects are still under investigation. These 2 studies linking SGLT2 inhibition with inflammation support a multifactorial, systemic mechanism of action for these drugs. Future studies should investigate whether SGLT2 inhibition itself is anti-inflammatory or whether the anti-inflammatory effect is secondary to other outcomes, such as weight loss and decreased adiposity."*
>
> – Daniel W. Coyne, MD



In a poster by Kelly Hudkins, MS, research scientist at UW Medicine, and her colleagues at the University of Washington, data suggest that SGLT2 inhibition decreases renal ROS.[17]

Nuclear factor erythroid 2-related factor 2 (Nrf2) has been shown to protect tissues from inflammation and injury by mediating antioxidant responses to oxidative stress. Kelch-like ECH-associated protein 1 (Keap1), an Nrf2 repressor, has been shown to be upregulated in CKD, suggesting a role for Nrf2 upregulation as a therapeutic target.[19] The Nrf2 activator bardoxolone methyl, an investigational drug in phase 3 clinical trials, has been shown to improve eGFR in patients with CKD[20] and is currently in phase 3 clinical trials for use in Alport syndrome, autosomal polycystic kidney disease (APKD), and DKD.[21-23]

To investigate the mechanism of eGFR changes following Keap1/Nrf2 activation, Kengo Kidokoro, MD, PhD, and his colleagues in the Department of Nephrology and Hypertension at Kawasaki Medical School performed in vivo imaging using 2-photon microscopy in mice. In this study, Keap1/Nrf2 was activated genetically (through Keap1 knockdown) or pharmacologically (through treatment with bardoxolone methyl analog RTA-404).[24] Although both genetic and pharmacologic Keap1/Nrf2 activation increased glomerular volume, there were no significant effects on the afferent/efferent arteriole diameter ratio or on glomerular permeability, suggesting that Nrf2 activation does not mediate its effects on eGFR through hyperfiltration. ROS production and subsequent nitric oxide availability were decreased by Nrf2 activation, confirming the role of the Keap1/Nrf2 pathway in the oxidative stress response.

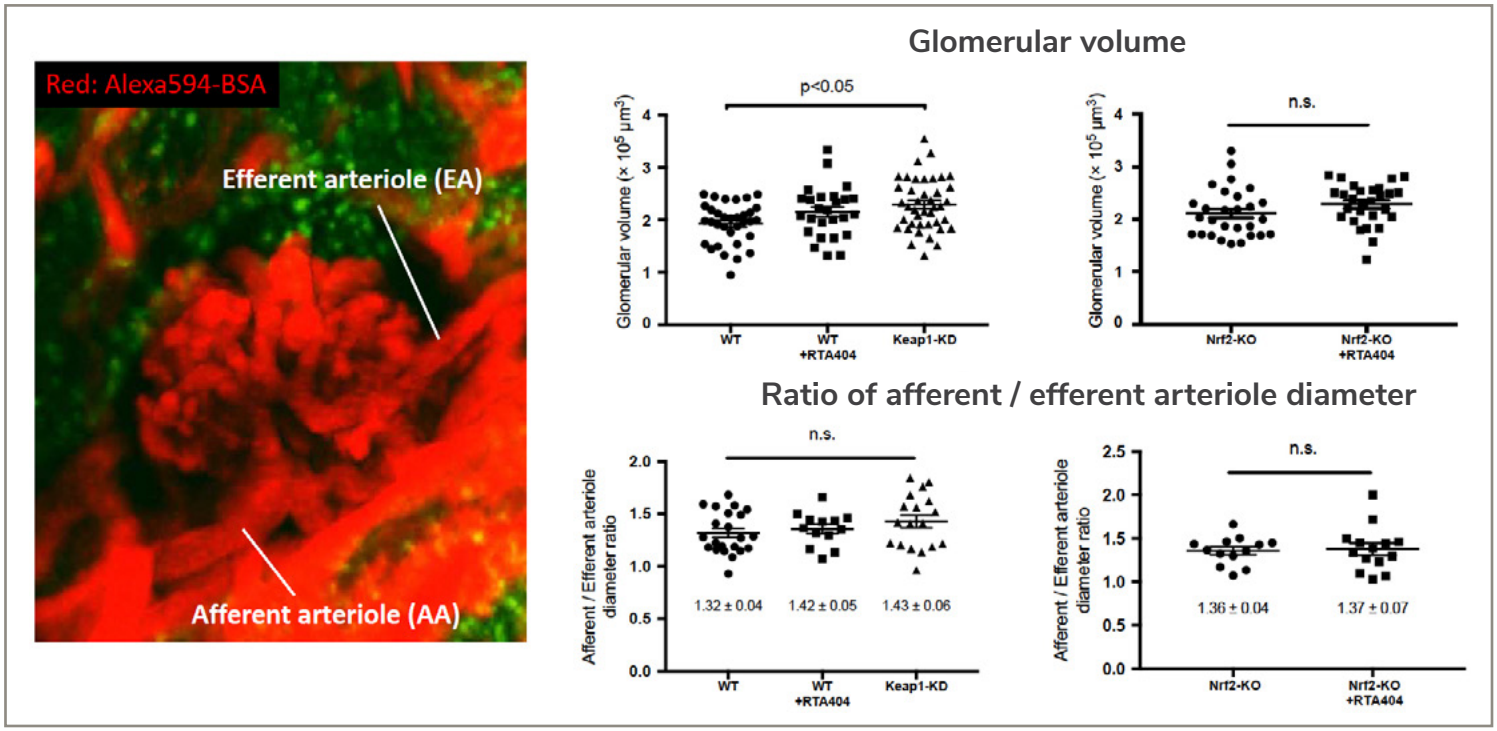
> *"These results suggest that Nrf2 activation may have a true anti-inflammatory effect that leads to improved kidney function, with no evidence for hyperfiltration."*
>
> – Daniel W. Coyne, MD

Diagnosing and Characterizing Rare CKD States

Clinical presentation of Alport syndrome

Alport syndrome (AS) is a heterogeneous group of genetic disorders caused by mutations in the collagen IV a345 protein, encoded by the *COL4A* genes.[25,26] Because inheritance is commonly X-linked, AS has been primarily classified in adult women, boys, and men. However, improved understanding of AS classification and better genetic sequencing technology has led to an appreciation for the burden of AS in girls and young women.

Selasie Goka, MD, of the Children's Hospital of Philadelphia, reported the characteristics of AS in female children with a diagnosis of AS, familial hematuria, or hereditary nephritis who were seen at Children's Hospital of Philadelphia between 1987 and 2018. In this single center retrospective review of 217



In a poster by Kengo Kidokoro, MD, PhD, and colleagues from the Department of Nephrology and Hypertension at Kawasaki Medical School, data indicate that genetic and pharmacologic activation of the Nrf2 pathway increase glomerular volume but have no effect on the ratio of the afferent to efferent arteriole diameter.[24]

pediatric girls, 164 were excluded, leaving 37 with confirmed AS diagnosis (mean age 5.4 years). Among the 14 patients who received genetic testing, 80% had heterozygous mutations in *COL4A5*. Although AS has historically been considered presymptomatic in young girls, 11% of patients in this study had an eGFR of less than 90 mL/min/1.73 m^2, while 89% had microscopic hematuria. Furthermore, of the 23 patients who underwent an audiogram, 30% had abnormal hearing. Over a mean follow-up of 6.3 years, the proportion of patients with hematuria, proteinuria, and hypertension increased.[25]

> *"This study highlights the unappreciated burden of Alport syndrome on women, who were previously considered merely carriers for the disorder. By the end of study follow up, patients were an average of only 12 years of age, and yet the majority of these girls had proteinuria and microscopic hematuria, and 30% had impaired hearing."*
>
> – Daniel W. Coyne, MD

	Presentation (n=37)	End of Follow Up (n=37)
Family History	29 (78.4%)	29 (78.4%)
Hematuria (microscopic)	33 (89.2%)	35 (94.6%)
Hematuria (gross)	13 (35.1%)	15 (40.5%)
Proteinuria	12 (32.4%)	21 (56.8%)
Mean GFR (mL/min/1.73 m^2)	116 ± 23	119 ± 36
Patients with GFR <90 mL/min/1.73 m^2	3/27* (11.1%)	3/26* (11.5%)
Hypertension (SBP or DBP ≥95th %)	2 (5.4%)	3 (8.1%)
Abnormal audiogram	7/23 tested (30.4%)	

*Serum creatinine available for this number of subjects.

In a poster presentation, Selasie Goka, MD, of the Children's Hospital of Philadelphia, reported her institution's experience with female children with Alport syndrome, both at presentation and after a mean follow-up of 6.3 years.[25]

Genetic characterization of rare CKD states

CKD progression varies greatly among people with diabetes and has not yet been fully explained by known risk factors. It is therefore assumed that genetics contribute to the rate of eGFR decline, but no genes have conclusively been linked with CKD progression. In this genome-wide association study (GWAS) presented by Cassianne Robinson-Cohen, PhD, of the Vanderbilt University Medical Center, 41,348 people with CKD and no diabetes at baseline were enrolled from the Million Veteran Program and stratified by race. Among black patients with CKD, the presence of 2 high-risk *APOL1* variants increased the risk of eGFR decline by 3% per year compared with people with no high-risk variants. A single nucleotide polymorphism (SNP) in *UMOD* was associated with a 1% per year faster decline in eGFR. According to Dr. Robinson-Cohen, these data support the genetic basis for kidney disease progression but underscore the difficulty of detection of these genetic drivers.[27]

> *"Clearly, factors that contribute to CKD progression are complex and multifactorial. More work is needed to resolve the genetic drivers of CKD progression beyond established APOL1 risk factors."*
>
> – Daniel W. Coyne, MD

High-Risk Variants	N	eGFR Slope %/year	
		Mean (SD)	Median (IQR)
0	2321	-3.80 (13.2)	-0.83 (-4.29, 1.62)
1	2733	-4.54 (17.1)	-1.01 (-4.54, 1.40)
2	927	-8.88 (25.1)	-1.76 (-7.49, 0.96)

$P=4.01\times10^{-9}$

In a GWAS study of people with progressive CKD, the presence of 2 high-risk APOL1 variants increases the risk of eGFR slope decline from 3.8% per year to -8.88% per year among black patients with CKD.[27]

With the advent of new technology, rare kidney diseases are becoming increasingly well understood at the molecular level. Using advanced single-cell epigenomic and transcriptomic sequencing technologies, (ATAC-seq and snRNA-seq),

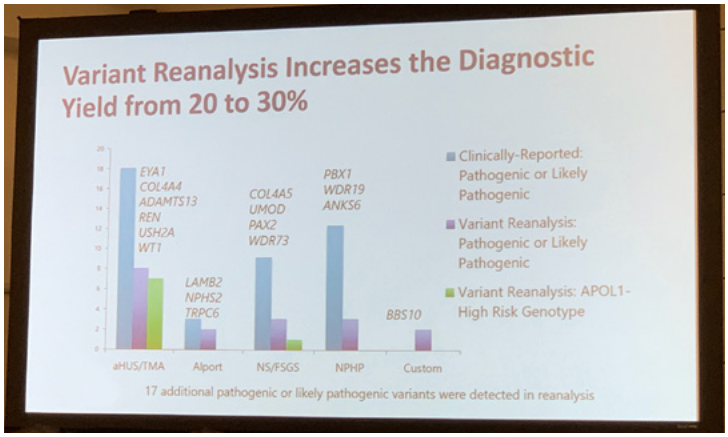
Yoshiharu Muto, MD, PhD, and colleagues at Washington University in St. Louis evaluated 2 kidney samples: one from a healthy donor and one from a 42-year-old transplant patient with new-onset proteinuria and focal segmental glomerulosclerosis (FSGS). The kidney samples were homogenized, and cells from the samples were classified into clusters, which distinguished among kidney cell types (eg, podocytes, endothelial cells, etc).[28]

Genetic and epigenetic differences between samples and across cell types were evaluated. In the FSGS podocytes, atypical protein kinase C λ/ι (aPKCλ/ι) was upregulated relative to the healthy podocytes.[28] Dr. Muto noted that previous studies have shown that podocyte aPKCλ/ι levels were associated with glomerular maintenance and development and may cause nephrotic syndrome.[29] Furthermore, vascular endothelial growth factor A (VEGF-A) expression was upregulated in FSGS podocytes, and E26 transformation-specific transcription factor members, which are downstream from VEGF signaling, were upregulated in FSGS endothelial cells.[28] Dr. Muto noted that VEGF-A expression has previously been linked with the development of FSGS in mice.[30] In his concluding remarks, Dr. Muto noted that integrated multiomics analysis using combined single-cell ATAC-seq and snRNA-seq is "perfect for deconvolution of complicated kidney diseases like FSGS."[28]

In an oral presentation by Yoshiharu Muto, MD, PhD, VEGF-A expression was shown to be increased among FSGS podocytes relative to control podocytes.

Advanced sequencing technology is also making its way into the clinic, as evidenced by the oral presentation by Parker Wilson, MD, PhD, of Washington University in St. Louis, who discussed his laboratory's use of clinical exome sequencing. Usual clinical practice relies on clinically established gene sets, but clinical exome sequencing allows for "reflexive testing," which is retrospective analysis of an expanded gene set to identify additional pathogenic and likely pathogenic variants. Among 324 patients with AS, hemolytic uremic syndrome, FSGS, or cystic renal disease and nephronophthisis who underwent clinical exome sequencing using a typical panel and a retrospectively applied extended panel, 42 pathogenic and likely pathogenic variants were identified in 97 patients. An additional 101 patients had a variant of uncertain significance. Use of an extended gene panel increased the overall yield of the sequencing to 30%. Parker noted that this "reflexive testing may be especially useful in diseases like Alport syndrome and FSGS with overlapping phenotypes."[31]

> *"Genetic sequencing is evolving at a rapid rate, and clinicians should take note of the various techniques that are being used. It won't be long before clinical exome sequencing and other emerging techniques become a part of routine clinical practice, especially to identify rare genetic CKD states, which may benefit both the patient and their relatives."*
>
> – Daniel W. Coyne, MD



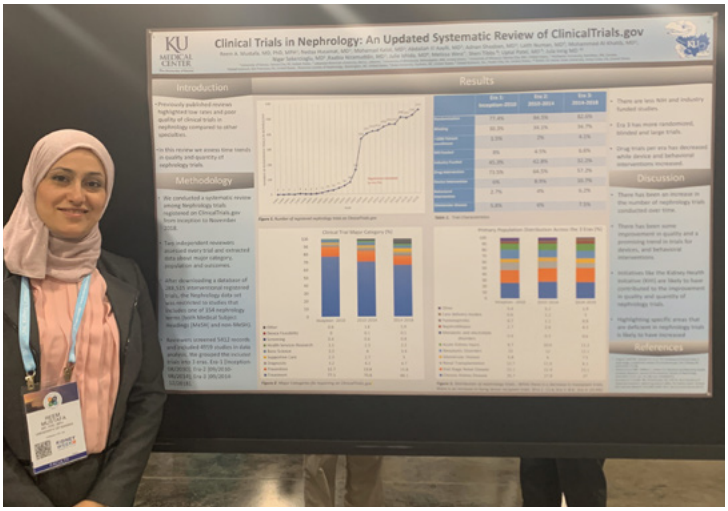
In an oral presentation on clinical exome sequencing for rare renal disorders, Parker Wilson, MD, PhD, of Washington University in St. Louis, explained that application of an extended sequencing panel for select samples resulted in an increased detection of pathogenic or likely pathogenic variants.

Key Clinical Trials in CKD

In the past, systematic reviews have reported that the field of nephrology had few clinical trials, and those that were registered were of low quality[32]; however, as evidenced by a systematic review presented by Reem Mustafa, MBBS, PhD, MPH, of the University of Kansas, both the quantity and quality of nephrology trials are increasing. In this recent

systematic review, quality was measured by the proportion of trials that used randomization, blinding, and large sample size (>1000 patients). Another intriguing observation reported by Dr. Mustafa is that nephrology clinical trials are increasingly including rare diseases. From 2014 through 2018, rare diseases made up about half of all nephrology clinical trials.[33]

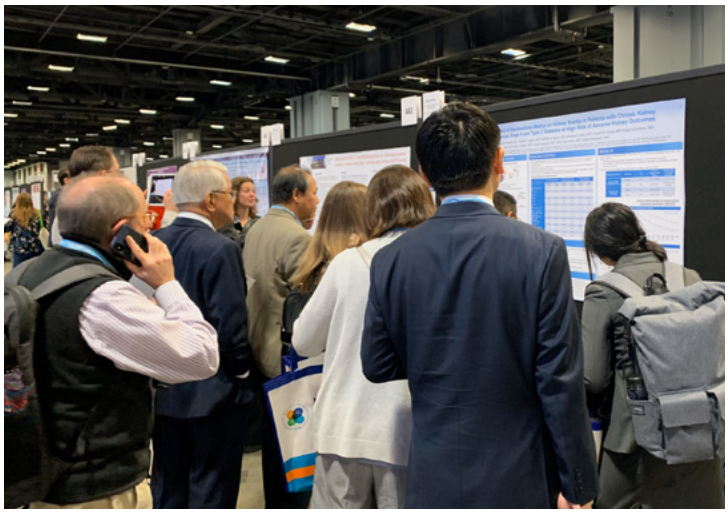
> *"Clinical trials in nephrology have long been difficult to perform. Achieving sufficient patient numbers, evaluating kidney-specific outcomes, and optimizing adherence have all presented challenges in the past. However, I am not surprised that we have seen an improvement in quality and quantity over the past several years—we have solved many of these early issues, and several promising therapeutic targets have emerged. I imagine that this will only improve with time."*
>
> – Daniel W. Coyne, MD



Reem Mustafa, MBBS, PhD, MPH, an associate professor in the Division of Nephrology and Hypertension at the University of Kansas, presents her group's systematic review of nephrology trials in ClinicalTrials.gov.[32]

Bardoxolone methyl

Although the phase 3 BEACON trial of bardoxolone methyl was terminated for safety events, post hoc analyses of patients from BEACON have elucidated potential benefits of bardoxolone methyl in carefully selected patients, according to results presented in a poster by Christoph Wanner, MD, from University Hospital, Würzburg, Germany. Among patients with baseline eGFR less than 22 mL/min/1.73 m^2 (n=503 for bardoxolone; n=514 for placebo), those who received bardoxolone methyl were 61% less likely to reach the composite kidney outcome (ie, sustained decline from baseline in eGFR of 30% or greater, sustained eGFR of less than 15 mL/min/1.73 m^2, or ESKD). Furthermore, for patients with baseline urine albumin-to-creatinine ratio (UACR) of more than 300 mg/g (n=540 for bardoxolone; n=578 for placebo), patients who received bardoxolone were 42% less likely to reach the composite kidney outcome.[34]



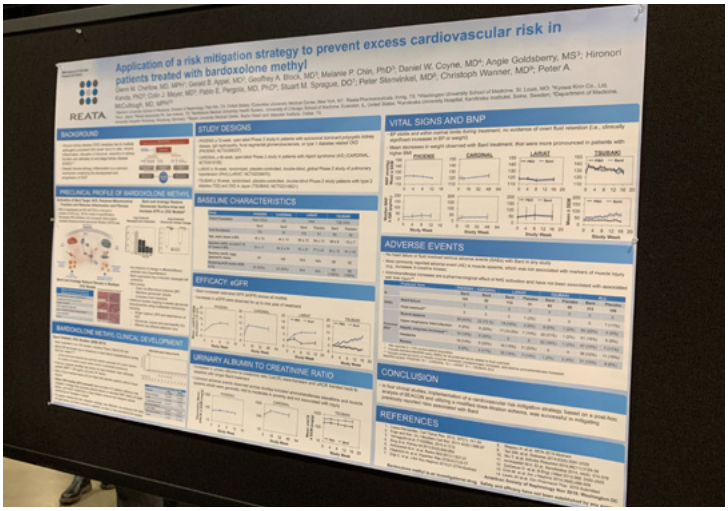
Post hoc analyses of the BEACON study, led by Christoph Wanner, MD, from University Hospital, Germany, were presented in a poster and showed that bardoxolone methyl decreased the risk of ESKD and reversed the decline in eGFR in a selected group of patients.

BEACON was terminated because of an increased risk in heart failure that occurred within the first 4 weeks of the study. In a poster presented at the conference, cardiovascular risk mitigation strategies were described by Glenn Chertow, MD, MPH, of Stanford University School of Medicine. According to the researchers, post hoc analyses of BEACON identified 2 baseline risk factors for heart failure in patients receiving bardoxolone methyl: history of heart failure and baseline concentration of B-type natriuretic peptide (BNP) over 200 pg/mL. In addition, dose titration schemes employed in post-BEACON studies allowed for flexible dosing, and careful monitoring of weight during the first few weeks facilitated early identification of heart failure risk.[35]

To assess the effectiveness of these risk mitigation strategies, data from four phase 2 trials of bardoxolone methyl were evaluated, including data from CARDINAL (48-week open-label study in Alport syndrome), PHOENIX (12-week open-label study in autosomal dominant polycystic kidney disease (ADPKD), immunoglobulin A (IgA) nephropathy, FSGS,

or T1D CKD), TSUBAKI (16-week randomized controlled trial in T2D CKD), and LARIAT (16-week randomized controlled trial in pulmonary hypertension). There were no clinically significant signs of fluid retention observed with bardoxolone methyl treatment.[35]

> *"With over 1500 patients treated with bardoxolone methyl since the BEACON termination, there have been no heart failure events related to the drug. These data suggest that the cardiovascular risk mitigation strategies for these populations are effective. I am eagerly awaiting the results of the phase 3 trials."*
>
> – Daniel W. Coyne, MD



In a poster presentation, data showed that strategies to mitigate cardiovascular risk resulted in a relatively good safety profile, with no increase in risk for heart failure or overt fluid overload among patients without elevated BNP and with no history of heart failure.

Roxadustat

Roxadustat is a hypoxia-inducible factor prolyl hydroxylase inhibitor (HIF-PHI) that is being investigated for anemia associated with CKD. Robert Provenzano, MD, from the Wayne State University presented pooled cardiovascular safety results from 3 roxadustat clinical trials in a late-breaking session at the kidney conference. In these clinical trials, roxadustat was compared with epoetin alfa (for dialysis-dependent [DD] and incident dialysis [ID] patients) or placebo (for nondialysis-dependent [NDD] patients). Pooled cardiovascular safety analyses showed no increase in the risk of major adverse cardiovascular events (MACE) or all-cause mortality in the NDD group (n=4270) or DD group (n=3880). Among ID patients (those on dialysis for 4 months or less), roxadustat reduced the risk of MACE and MACE+, which included MACE as well as hospitalization from unstable angina or congestive heart failure.[36]

In the pooled NDD population, the primary end point of hemoglobin change from baseline to the average over weeks 28 to 52 was 1.85 g/dL in the roxadustat group compared with 0.13 g/dL in the placebo group ($P<0.0001$). In the pooled DD population, roxadustat was associated with an increase of 1.22 g/dL compared with 0.99 g/dL in the epoetin alfa group ($P<0.0001$). Furthermore, the additional efficacy end points of lowering the use of rescue therapies and reducing transfusion were achieved for the NDD and DD groups.[36]

During a late-breaking session presented to a standing-room-only crowd, Robert Provenzano, MD, section chief of nephrology at St. John Hospital and Medical Center, presented the cardiovascular benefits of roxadustat use relative to epoetin alfa in patients with incident dialysis.

In a separate presentation, Steven Fishbane, MD, of Northwell Health, reported on the outcomes of the phase 3 ROCKIES trial of roxadustat compared with epoetin alfa in DD patients with CKD. In this trial, roxadustat improved hemoglobin levels from baseline by 0.77 g/dL from weeks 28 to 52; epoetin alfa increased hemoglobin by 0.68 g/dL. Furthermore, in a subgroup of patients with elevated hsCRP levels of more than 5 mg/L, the mean increase in the roxadustat group was 0.80 g/dL, compared with 0.59 g/dL in the epoetin alfa group. According to Dr. Fishbane, this subgroup of patients with chronic inflammation "are more difficult to treat than the overall CKD patient population."[37]

> *"Since use of epoetin and other erythropoiesis-stimulating agents (ESA) have been shown to increase strokes, cardiovascular events, and death, use of ESAs in patients with CKD-NDD has fallen significantly. We have waited nearly 10 years to see the realization of these roxadustat trials. If approved, I expect that roxadustat will be a major advance for patients with anemia related to CKD."*
>
> – Daniel W. Coyne, MD

Conclusions

At the recent national kidney conference, a number of groups presented their work on the pathophysiology, diagnosis, and treatment of CKD, with a focus on inflammatory and anti-inflammatory pathways in rare conditions. These preclinical and clinical studies paint a picture of a complex disease state that has benefited from new and emerging laboratory techniques and pharmacotherapeutic tactics. As the underlying mechanisms of CKD become increasingly clear, new and emerging therapeutic targets hold increasing promise, signaling an encouraging future for this once-neglected disease state.

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