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Scientists Study New Ways to Slow Diabetic Kidney Disease Progression

By Bridget M. Kuehn

Experimental strategies that reduce cell death or reverse epigenetic changes in kidney cells are being studied to help protect the kidneys in patients with diabetes.

Treatment options for diabetic kidney disease have grown in recent years with the availability of 2 new classes of drugs, the sodium-glucose cotransporter 2 inhibitors (SGLT2) and the glucagon-like peptide 1 agonists (GLP1), noted a recent review in *Nature Reviews Nephrology*. These agents help lower a patient's blood sugar levels and are used alongside renin angiotensin system inhibitors (RAS) and other traditional diabetes management methods.

Mark Cooper, PhD, head of the department of diabetes at Monash University in Melbourne, Australia, noted that the hotly awaited final results of the CREDENCE trial of the SGLT2 inhibitor canagliflozin, which was stopped early in July 2018 because the kidney benefits for patients were positive, may seal the role of these drugs in clinical care. Cooper co-authored the review in *Nature Reviews Nephrology.*

Additionally, results from the AWARD-7 trial showed the GLP1 agonist dulaglutide helped control blood sugar and slow kidney decline in patients with diabetes.

Now, ongoing studies are exploring additional approaches that also help slow kidney damage caused by diabetes. One such approach aims to block an enzyme called apoptosis signal regulating kinase 1 (ASK1) and has entered clinical trials. Another, which is still being explored in animal studies, seeks to reverse epigenetic changes that may contribute to the loss of podocytes and kidney function. While these emerging strategies remain years from the clinic, they add to optimism that future therapies for kidney disease may better preserve kidney function.

"It is an exciting time for diabetic kidney disease; it looks like the SGLT inhibitors will turn out to be proven and then there's quite a few promising add-ons like the GLP1 agonist and then the ASK1 inhibitors," Cooper said. "If they turn out to deliver, you've actually got evidence that diabetic kidney disease [DKD] can really be treated, because, until now, they are really just trying to slow it down."

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2019 KidneyX Summit Highlights Promising Future Innovations in Kidney Care

By Ryan Murray

KidneyX, a public-private partnership between the US Department of Health and Human Services (HHS) and the American Society of Nephrology (ASN), aims to accelerate innovation in the prevention, diagnosis, and treatment of kidney diseases.

To introduce new voices and perspectives to the kidney space and seek to improve collaboration and communication across the nephrology community, KidneyX hosted its inaugural Summit on April 29–30, 2019, in Washington, DC. The 2019 KidneyX Summit brought together insights from a variety of fields outside of the traditional nephrology community and encouraged investment partnerships for innovative solutions to improve kidney care. The summit included panel discussions with patients and innovators, as well as presentations from industry leaders and government representatives from HHS, the Food and Drug Administration, the National Institutes of the Health, and the Centers for Medicare and Medicaid Services.

"The Department of Health and Human Services is placing an emphasis on accelerating innovation on be-

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> — *Jillian, RN*

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Diabetic Kidney Disease

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SGLT2 inhibitors

The CREDENCE trial results presented at the 2019 World Congress of Nephrology in Melbourne in April showed that canagliflozin reduced the risk of a composite of end-stage kidney disease, doubling of serum creatinine, or death from kidney or cardiovascular disease by 30% in patients with type 2 diabetes compared to placebo. The results were published simultaneously in the *New England Journal of Medicine*.

"Canagliflozin is the first medical breakthrough in nearly 20 years proven to slow the progression of chronic kidney disease in patients with diabetes at high risk of developing kidney failure," stated lead author Vlado Perkovic, MBBS, PhD, executive director of the George Institute for Global Health in Australia, in a press release from the drug's maker Johnson & Johnson. "These impressive results from the CREDENCE study have significant clinical implications for preventing kidney failure and improving health for millions of people living with chronic kidney disease and type 2 diabetes."

Despite the excitement about SGLT2 inhibitors, some safety issues have arisen in patients being treated with the SGLT2 inhibitors currently approved by the US Food and Drug Administration (FDA). The FDA issued a warning about the risk of severe genital infections in patients treated with SGLT2 inhibitors for diabetes. Between 2013 and 2018, the agency identified 12 cases of Fournier's gangrene in patients taking a SGLT2 inhibitor. Though these cases are rare, the agency recommends patients seek immediate medical care if they develop a tenderness, redness, or swelling of the genitals and a fever over 100.4 F°. They suggest physicians start treatment with broad spectrum antibiotics immediately if such an infection is suspected.

More recently in March, the FDA declined to approve another SGLT2 inhibitor, sotagliflozin, according to the drug's maker Sanofi. In January, an FDA advisory committee vote on whether to recommend the drug's approval ended in an 8 to 8 tie, in part owing to concerns about the risk of diabetic ketoacidosis in patients taking the drug.

ASK1 inhibitors

Managing hypertension using drugs like angiotensin converting enzyme (ACE) inhibitors helps protect the kidneys of patients with diabetes. But these drugs target just one part of the damage that occurs. Other important contributors to diabetes-related kidney damage are inflammation, cell death, and scarring or fibrosis.

To reduce these effects, scientists are studying a drug that stops apoptosis signal-regulating kinase 1 (ASK1), an enzyme that sets off a cascade of these harms. A team of researchers from Gilead Sciences showed that an experimental drug called GS-444217 that inhibits ASK1 reduces cell death and fibrosis in rodents with conditions similar to human DKD. The treatment also stopped the decline in glomerular filtration rates and decreased proteinuria. Combining this ASK1 inhibitor with an ACE inhibitor led to even better results.

"Combining ASK1 inhibition with RAAS inhibitors is an attractive combination for [DKD or chronic kidney disease] because these biological pathways are distinct and our current results demonstrate that ASK1 inhibition can provide additional benefits when administered concomitantly with ACE inhibitors," said the study's lead author, John Liles, PhD, director of biology at Gilead Sciences.

"It's a completely novel pathway," Cooper said. He noted such drugs would likely be used in combination with existing DKD therapies.

Results of a phase 2 clinical trial of the ASK1 inhibitor Selonsertib compared with placebo that enrolled 334 patients didn't meet its primary endpoint (Kidney Week 2018) (Abstract: TH-PO1148). Unexpectedly, the drug temporarily reduced creatinine clearance, but according to abstract authors post hoc analyses suggest the drug slows DKD progression in the longer term. The company is planning a phase 3 trial of the drug.

"There is an urgent unmet need for novel agents to slow progression of kidney disease and prevent kidney failure," said Liles. "Current treatments primarily target glomerular hemodynamics; however, there are no treatments that target apoptosis, inflammation, and fibrosis in the kidney."

Epigenetic protection

Patients with diabetes who are exposed to high blood sugar levels early in the course of their disease remain at increased risk for complications like diabetic kidney disease, even after treatment brings their blood sugar under better control, said endocrinologist Andrew Advani, MD, PhD, an associate professor and clinician scientist at St. Michael's Hospital in Toronto and the University of Toronto. This suggests that a "metabolic memory" persists, and some pioneering studies suggest that high blood sugar may cause lasting epigenetic changes that alter which genes are turned on and off.

"It's been proposed that epigenetic mechanisms may underlie the cellular basis of metabolic memory because epigenetic processes provide a means by which a transient environmental insult can have a long-lasting cellular effect," Advani explained.

That idea led Advani and his colleagues to question whether these epigenetic changes can be stopped or reversed to prevent diabetes complications in the kidney. They looked specifically at proteins called histones. DNA strands wind around histones to enable DNA to be packed inside the nucleus of a cell. The way in which these histones are modified by enzymes can help control which genes are turned on and off within a cell. Advani noted that histone-modifying drugs are already being used in cancer treatment.

In a 2018 study, Advani and colleagues showed that a histone modification called H3K27me3 turns off nearby developmental genes that aren't needed in adult kidneys. This helps protect key glomerular cells called podocytes from regressing into a less developed state. Advani and his colleagues have found that H3K27me3 is lost in mice with chronic kidney disease leaving them vulnerable to kidney damage. They also looked at samples from human patients with diabetic kidney disease and found they too lose this epigenetic mark and have a reactivation of developmental genes.

"Our work is important because it shows that histone modifications contribute to the natural history of chronic kidney diseases, and that it is possible to therapeutically manipulate histone modifications and alter the natural history of diabetes complications, particularly kidney disease," Advani said.

In animal experiments, they tested an experimental compound called GSK-J4 that protects these epigenetic marks. The experimental treatment slowed the development of kidney disease in mice with diabetic kidney disease and another form of kidney disease, focal segmental glomerulosclerosis. More research is needed to determine whether such a treatment would work in patients with kidney disease and which patients would benefit, Advani said.

Cooper thought it is possible the epigenetic therapies may prove useful in kidney disease, as they have in cancer. But he cautioned that the study of drugs that affect histone modifications is at a much earlier stage than the ASK1 inhibitors. Epigenetic mechanisms are at work throughout the body, so the drugs may have effects elsewhere, Advani noted. Cooper said off-target effects of epigenetic treatments are likely and that substantial safety testing will be necessary to understand potential effects on other parts of the body and whether they would be tolerable for a long duration of treatment.

"With cancer you're willing to take a higher risk profile, but I think for a condition like chronic kidney disease the concern is off-target effects," Cooper said. Cooper noted, however, that some off-target effects may actually be beneficial and help counter other diabetes complications. For example, these epigenetic mechanisms might also contribute to diabetic retinopathy or heart disease, and the drugs targeting them may also benefit these complications.

"We don't know at this stage whether a treatment that targets these kinds of processes is going to be feasible in chronic long-term diseases like diabetic kidney disease where side effect profiles need to be favorable," Advani said. "But studying the roles that epigenetics play in kidney disease could open up new therapeutic opportunities in the future."

2019 KidneyX Summit

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half of those living with kidney diseases," said Ed Simcox, JD, Chief Technology Officer, US Department of Health and Human Services. "My Office, the Office of the Chief Technology Officer, is uniquely suited to serve as the government partner in this public-private partnership due to its ability to convene the government's leading scientific and medical experts (NIH), regulators (FDA), and payors (CMS)."

In addition to HHS leadership, several congressional champions of KidneyX participated in the 2019 KidneyX Summit. Congresswoman Suzan DelBene (D-WA-01) and Congressman Larry Bucshon, MD (R-IN-08), both Congressional Kidney Caucus Co-Chairs, Congressman Brian Babin, DDS (R-TX-36), and Senator Todd Young (R-IN) provided remarks on KidneyX and its efforts to spur innovation and increase patient access to medical products and therapies.

The winners of KidneyX's inaugural prize competition, Redesign Dialysis Phase I, which asked innovators to create designs of possible solutions or solution components that can replicate normal kidney functions and improve patient quality of life, provided feature presentations on their winning submissions. The following finalists were awarded at the KidneyX Summit:

- *An Air Removal System For a Wearable Renal Therapy Device*, Qidni Labs, Inc.
- *The Ambulatory Kidney to Improve Vitality (AKTIV)*, University of Washington Center for Dialysis Innovation
- *Atomically Precise Membranes (APM) for High-Flux and Selective Removal of Blood Toxins*, Temple University
- *Building New Kidneys*, Miromatrix Medical Inc.
- *Development of a Dialysate- and Cell-Free Renal Replacement Technology*, Curion Research Corporation, David Geffen School of Medicine at UCLA, and University of Arkansas
- *Development of an Automated Multimodal Sensor to Improve Patient Outcomes in Hemodialysis*, Outset Medical, Inc.
- *Digitally-Delivered Behavior Change Program to Help Patients Delay Dialysis*, RenalTracker
- *Displacer-Enhanced Hemodialysis: Improving The Intradialytic Removal of Protein-Bound Uremic Toxins Using Binding Competitors*, Renal Research Institute LLC
- *Drug-Eluting Electrospun Hemodialysis Graft*, Beth Israel Deaconess Medical Center and BioSurfaces, LLC
- *Fluo Medical Fistula Monitoring Device*, Sanford Byers Center for Biodesign

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- *Intracorporeal Hemodialysis System*, Silicon Kidney, University of California—San Francisco, Vanderbilt University Medical Center
- *JEM—Sensor Enabled Hemodialysis*, Access for Life, Inc.
- *Nitric Oxide-Eluting, Disposable Hemodialysis Catheter Insert to Prevent Infection and Thrombosis*, University of Michigan Medical School
- *A Non-Invasive, Wearable Telehealth Device To Detect Thrombosis And Monitor Vascular Access Health of Arteriovenous Fistulas And Grafts In Hemodialysis Patients*, The University of Alabama at Birmingham
- *Utilizing Optical Interrogation Methods for Early Diagnosis of Peritonitis in Peritoneal Dialysis Patients*, Stanford University

The finalists, honorable mentions, and submissions that were granted permission to be posted online can be viewed on www.KidneyX.org.

"Kidney diseases remain in the shadows but are common, debilitating, and burdensome on patients, their families, and the economy," said John Sedor, MD, FASN, ASN KidneyX chair. "Unless and until we drive investment and innovation and open the pathways to commercialization for new technologies and therapies, we will live with the status quo. We can no longer wait. KidneyX is the spark to catalyze change."

Both the quality and quantity of submissions KidneyX received for Redesign Dialysis Phase I demonstrate there are great solutions to allow kidney health professionals to provide better therapies to their patients. KidneyX looks forward to seeing more innovative solutions to disrupt kidney care in future KidneyX prize competitions.

KidneyX also announced new prize competitions at the Summit. Redesign Dialysis Phase II, the second phase of KidneyX's inaugural prize competition, asks innovators to develop and demonstrate prototype solutions and was announced at the Summit. Recognizing that patients have innovative approaches to their own therapies, KidneyX also launched its Patient Innovators prize competition. The announcements for both new KidneyX prize competitions can be viewed in their entirety on www.KidneyX.org.

In addition to launching its Patient Innovators prize competition, KidneyX aims to create a better collaborative relationship among patients and innovators. In each prize competition, innovators are asked that their submissions provide sufficient detail and information showing the nature and extent of anticipated benefit(s) to patients, including:

- Demonstrating efforts to incorporate patient feedback into the design
- Addressing one or more opportunities to improve a patient's quality of life

As many applicants will likely be entering the kidney space for the first time and will not have direct access to patients, KidneyX developed a list of contacts at reliable partner patient organizations who could help identify patients interested in providing direct feedback to KidneyX applicants. The following organizations serve as KidneyX partner patient organizations:

- American Association of Kidney Patients
- Home Dialyzors United
- IGA Nephropathy Foundation of America, Inc.
- National Kidney Foundation
- Oxalosis and Hyperoxaluria Foundation
- PKD Foundation

Kidney patient organizations interested in serving as a resource that can assist in patient engagement for KidneyX applicants are encouraged to email KidneyX@asn-online.org.

Are you a fellow and have a tip or idea you'd like to share with your fellow peers and the broader kidney community?

Send your idea to the Kidney News Fellows Corner column at kidneynews@asn-online.org

ANEMIA AND KIDNEY DISEASE

In this month's edition of ASN Kidney News*, we reintroduce the topic of the management of anemia in CKD and ESKD. Depending on your vintage as nephrologists, these articles may serve as either a review or an introduction to what we have learned and experienced in this field. From the early heady days following the introduction of rEPO offering a "solution" to the nightmare of managing anemia with blood transfusions or anabolic steroids to the reality that "too much of a good thing" has consequences, we follow the journey of the clinical trials and science that now take us into a new era.*

Phase 2 clinical trials with HIFs have suggested that they may present a more physiologic approach to anemia management, offering an effective oral agent that mobilizes iron and, at least to this point, has no serious short-term safety signals.

Drs. Coyne's and Szczech's review of the PIVOTAL trial helps clarify many outstanding questions about the safety and efficacy of iron in anemia management.

We have learned much, but there is more to learn; new questions, ideas, and opportunities will arise. We hope this series of articles engages and educates you on this topic and that you will help shape the future of anemia management.

—Robert Provenzano, MD, FACP, FASN, Edgar Lerma, MD, FASN, Editors

Anemia and Chronic Kidney Disease
WHERE WE'VE BEEN, WHERE WE'RE GOING

By Steven Fishbane

I recently gave a lecture in Chicago on anemia in chronic kidney disease. Afterward, an audience member told me he usually does not go to lectures on anemia any more, presumably because the subject can sometimes seem a bit "played out." In a sense I understand the sentiment, but I realized that this article might be an opportunity to rekindle interest in a subject that remains vitally important.

I believe that some gloss has been lost for several reasons: 1) Multiple dishearteningly negative studies have demonstrated the dangers of overtreating with erythropoietin analogues (EPO) (1). 2) Nurse-operated EPO and iron protocols have removed nephrologists from much active involvement with anemia management. 3) Most nephrologists practicing today are too young to have experienced the pre-EPO era, when severe anemia caused debilitating symptoms. 4) Awareness is lacking of exciting newer drugs being developed in an effort to improve anemia treatment.

This article title includes the words "where we've been" with anemia. It is still remarkable to me that as a medical student I cared for dialysis patients whose hemoglobin levels were often lower than 7 g/dL. Blood transfusions were common, and patients' quality of life was greatly diminished. How remarkable that in 1985 the seminal articles were published on the cloning of the erythropoietin gene (2) and by that December, Joseph Eschbach, MD, successfully treated the first patients with the recombinant substance (J. Eschbach, personal communication). Subsequent widespread treatment of anemia in dialysis patients was an advance that greatly improved patients' lives.

Early on, it became clear that EPO treatment was highly effective in raising hemoglobin concentrations and greatly reducing transfusion dependence. In the 1990s and 2000s, interest shifted to exploring the potential benefits of full hemoglobin correction to the normal range. Several randomized controlled trials were conducted, leading to a clear conclusion that targeting hemoglobin levels above 13 g/dL with EPO does not improve clinical outcomes and, in fact, results in an increase in cardiovascular and thromboembolic events (1). As a result, EPO treatment is far more conservative now than it had been until 2008 to 2012 (Figures 1 and 2).

It has remained unclear why raising hemoglobin to normal levels with EPO is harmful to patients. Several possible explanations exist. Most clear would be that increased hemoglobin with attendant increases in whole blood viscosity might be injurious in patients with atherosclerotic disease. However, a tantalizing fact is that observational studies and post hoc analyses of randomized controlled trials consistently find that the achievement (as opposed to targeting) of higher hemoglobin concentrations actually associates not with worse, but with better, outcomes. Rather, it is higher doses of EPO that strongly correlate in these analyses with adverse outcomes (3). This might suggest that the administration of nonphysiologic high doses of EPO could be harmful. Although these results are associations and do not prove causality, they do suggest that other methods of treating anemia that do not involve high-dose EPO injection could be of interest.

This has led to consideration of a new class of agents, alternatively called hypoxia-inducible factor stabilizers or prolyl-hydroxylase inhibitors. These drugs stimulate erythropoietin production and improve iron kinetics, leading to improvement in anemia. Importantly, they stimulate an increase in hemoglobin without a large rise in serum erythropoietin concentrations (4). A further article in this section will discuss this subject in more depth.

An important aspect of anemia management is iron supplementation. In 1995, it became clear that intravenous (IV) iron was an essential component of care for patients receiving dialysis and resulted in reduced EPO dose requirements (5). The important news in 2018 was the publication of the PIVOTAL trial by Macdougall et al (6). This landmark article compared a conservative approach to IV iron administration in hemodialysis patients with a more aggressive protocol (treatment with 400 mg monthly, unless serum ferritin was >700 µg/L or transferrin saturation was ≥40%. Not unexpectedly, the study found that EPO dose

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Anemia and Chronic Kidney Disease

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requirements were reduced with the more intensive iron protocol. What made the study notable was the surprise finding that intensive IV iron administration resulted in a reduction in the primary outcome: a composite of death, nonfatal myocardial infarction, stroke, and hospitalization for heart failure (6). This result, along with emerging data from studies of IV iron in heart failure (7), indicates a possible cardiovascular benefit to IV iron treatment.

In conclusion, it is important that we remember the importance of anemia treatment and the distressing anemic symptoms of patients without proper treatment. Over the next few years we will learn about new drugs to treat anemia, with hope for avoiding cardiovascular and thromboembolic risk.

I will end by making a plea to my colleagues in nephrology. In dialysis centers in the United States, much anemia treatment occurs without substantial input from physicians. Nurse-managed protocols drive EPO dose adjustments and IV iron courses. This generally works well, but if nephrologists don't carefully monitor the treatment, then a risk is created for missing chronic bleeding and other hematologic conditions that protocols simply cannot detect. Please stay involved in anemia management.

Steven Fishbane, MD, is professor of medicine, division of nephrology, department of medicine, Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, New York.

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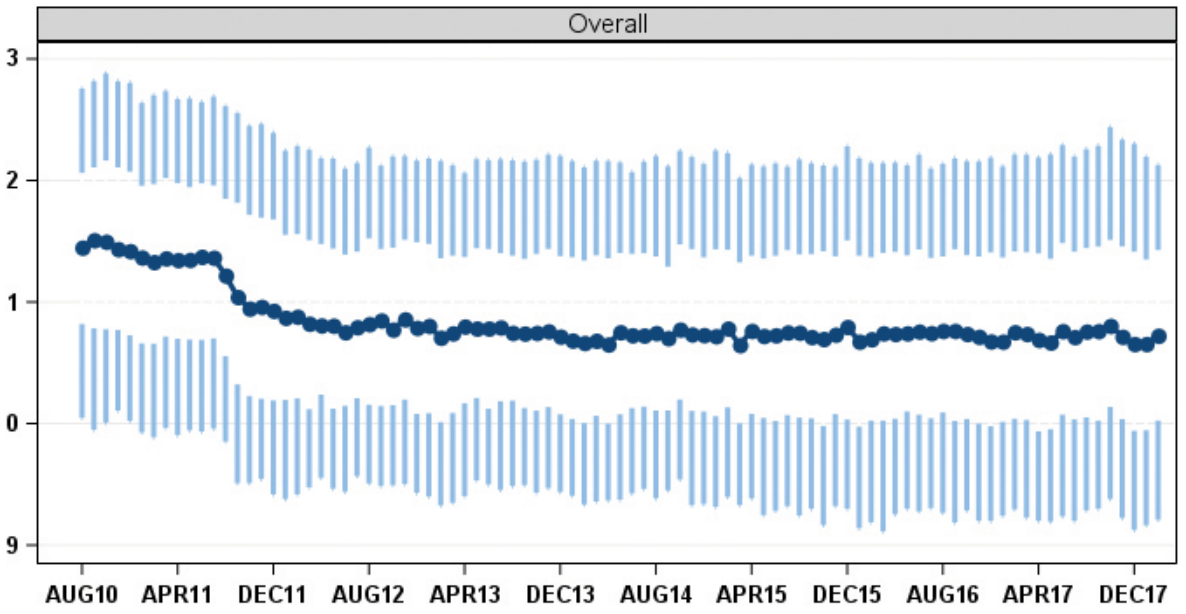
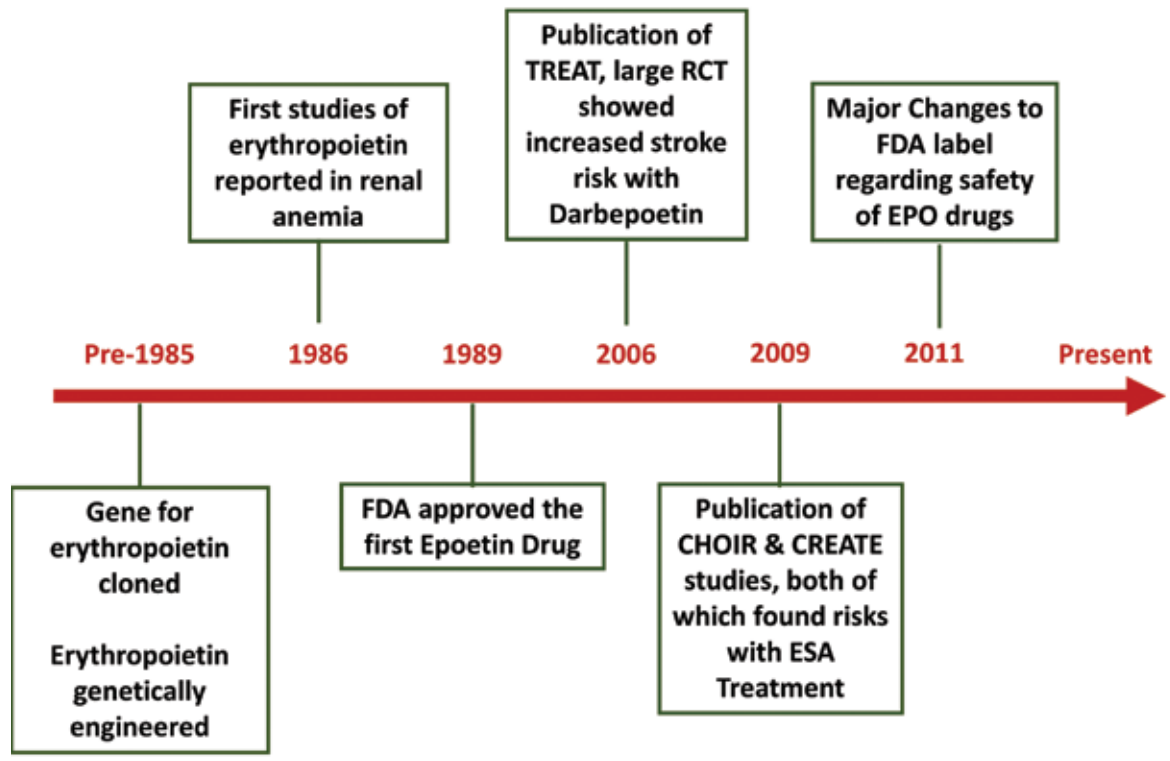
Figure 1. Hemoglobin trends among dialysis patients in the United States from 2010 to 2017, New York



The DOPPS Practice Monitor. Accessed January 23, 2019

Figure 2. Timeline of drug development of erythropoietin (EPO) analogues



RCT, randomized controlled trial; FDA, US Food and Drug Administration

Policy Update

Kidney Advocates Take to Capitol Hill in Support of KidneyX

American Society of Nephrology (ASN) and the American Association of Kidney Patients (AAKP) partnered for the Seventh Annual Kidney Advocacy Day. ASN and AAKP representatives met with nearly 100 congressional offices to discuss KidneyX and request $25 million in funding for the program to run a series of prize competitions.

Owing to their efforts, and calls from other ASN and AAKP advocates, a bipartisan group of nearly 60 members of Congress wrote to the House Appropriations Labor, Health and Human Services, and Education Subcommittee asking them to include $25 million in funding for KidneyX in Fiscal Year (FY) 2020. The letter was led by Congressional Kidney Caucus Co-Chairs Rep. Suzan DelBene (D-WA-01) and Rep. Larry Bucshon (R-IN-08), along with champions of patient-centered innovation, Rep. Terri Sewell (D-AL-07) and Rep. Brian Babin (R-TX-36).

Building on this momentum, Sen. Todd Young (R-IN) led a similar effort with the Senate Labor, Health and Human Services, and Education Appropriations Subcommittee supporting the $25 million request in FY 2020.

Although the effort to secure federal funding for KidneyX is certainly not over, ASN would like to thank several members of the kidney community for their extraordinary support of KidneyX through advocating on Capitol Hill, engaging activists, holding a congressional briefing, and other efforts:

- American Association of Kidney Patients
- American Kidney Fund
- Kidney Care Partners
- National Kidney Foundation
- Northwest Kidney Centers

ASN will continue to engage and partner with the kidney community in its advocacy work on KidneyX.

The Current Status of Anemia Management: KDIGO Guidelines

By Rebecca J. Schmidt

The introduction of erythropoietin-stimulating agents (ESAs) in the late 1980s revolutionized the treatment of anemia for patients with chronic kidney disease (CKD), with the ensuing parade of clinical trials serving as the scientific basis for current management principles. Unlike other fields, CKD-related anemia management has been challenged by a windstorm of regulatory events and payment policies affecting the particulars of managing this important complication of CKD. The principles of management today reflect this regulatory influence on scientific discovery and collective clinical experience.

Current guidance

A comprehensive evidence-based guideline for managing CKD-related anemia, the Kidney Disease: Improving Global Outcomes (KDIGO) guideline, was developed by an international team of experts together with an evidence review team using the Grading of Recommendations, Assessments, Development, and Evaluation (GRADE) template for guideline recommendations by strength of recommendation (1, 2) and quality of supporting evidence (A–D) (1). Most of the recommendations are not graded but are presented as a consensus of expert opinion and serve as guidance for today's standard of practice. Most of the nongraded recommendations are noncontroversial and represent what might be characterized as common sense. The few recommendations graded as 1 (strong) or based on evidence of highest quality (A) relate to cautionary concerns such as targeting the hemoglobin (Hb) to a level below 13 g/dL and the administration of dextran-based intravenous iron. The quality of evidence throughout is not consistently strong, leaving significant room for clinical judgment (Figure 1).

A different form of guidance became dominant, with changes in reimbursement and regulatory policies beginning in 2011. The substantial reduction in ESA use and Hb levels occurring subsequently in the United States (2), along with concurrent increases in use of iron supplementation and blood transfusions between 2006 and 2015 (3, 4), has been seen as a response to reimbursement policy and regulatory directives.

Status quo versus quagmire state

Although much has changed for the nephrologist managing CKD-related anemia in the past 20 years, basic tenets remain. The evolution of protocols and the institutionalization of anemia management might seem to imply that less interpretation is needed; however, the wide scope of evidence strength acknowledged in the guideline suggests otherwise and underscores the primacy of clinical decision-making. A targeted clinical assessment with special attention to iron stores and the propensity of occult gastrointestinal bleeding in CKD patients remains the basis for evaluation of CKD-related anemia. Potentially correctable causes of anemia that might be operative in addition to erythropoietin deficiency constitute a priority of investigation. There continues to be no recognized role for erythropoietin levels.

Health-related quality of life benefits are not considered an indication for use by the U.S. Food and Drug Administration; therefore, the level of 11 g/dL is the upper limit of cutoff. Despite the acknowledgment by KDIGO that some patients may benefit from a higher Hb, widespread concern for reimbursement discourages efforts to supersede this level. The recommendation to decrease rather than hold ESAs in the event of a rising Hb remains, and protocols are designed to account for this.

Blood transfusions are appropriate for emergent anemia treatment; their avoidance is included as a criterion for warranting the use of ESAs. Finally, the rationale for the use of intravenous iron over oral preparations remains a matter of risk versus benefit. KDIGO generally recommends the intravenous over the oral route in adult CKD patients, although that recommendation is less than strong, requiring the individualization of a treatment plan balanced for benefit and risk.

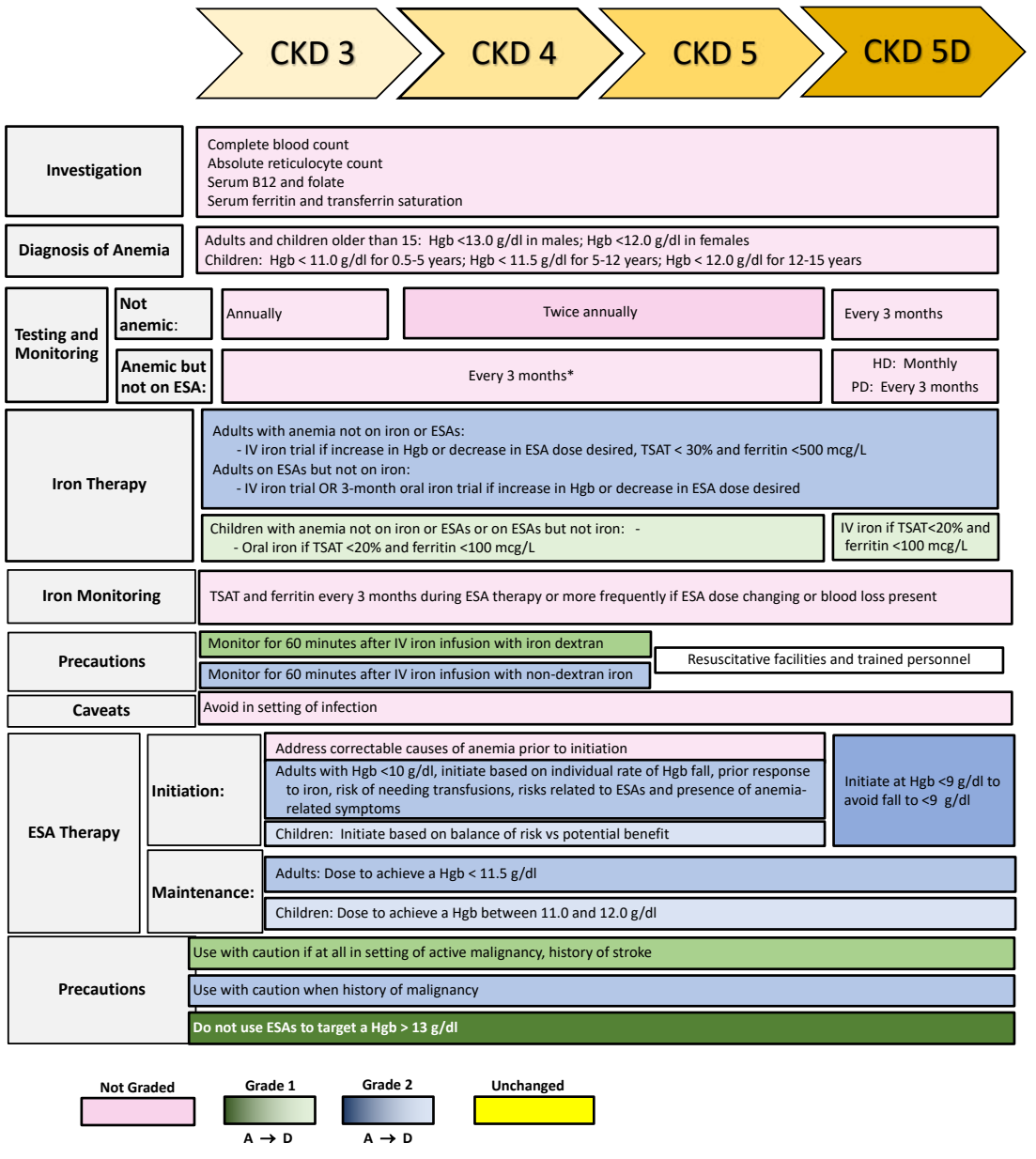
Strides forward versus entropic movement

Greater use of longer-acting ESAs has provided additional clinical experience: remarkably similar Hb levels have been achieved by a variety of short-acting and long-acting agents (5). In the spirit of entrepreneurship, biosimilar agents for stimulating erythropoiesis are on the horizon, promising more options for patients and physicians—this, of course, tempered by financial, practical, and institutional constraints. New oral agents for iron appear to be more effective than those traditionally purchased over the counter (6), and with their ability to act as binders, there is opportunity for reducing a patient's daily medication intake.

The iron story continues to garner attention and generate intrigue with recent reports that higher-dose intravenous iron is not associated with a higher risk of mortality, infection, cardiovascular events, or hospitalizations in adult patients receiving dialysis (7) but may be less effective than lower-dose iron (8). Most pivotal, a recent trial showed that high-dose intravenous iron administered proactively was superior to a low-dose regimen administered reactively and resulted in lower doses of ESA being administered (9) and also in reductions in cardiovascular events, deaths, and the need for transfusions.

The preferential use of ESAs as opposed to intravenous iron in the quest to achieve anemia targets was explored in two groups of patients treated according to the KDIGO anemia targets with an increased dose of intravenous iron or an increased dose of ESA (10). Mortality was not different for the two groups, and not surprisingly, the former was associated with more ferritin levels exceeding 800 and the latter with increased frequency of ESA resistance. Other reports that high ferritin levels are associated with increased mortality, with adjustment for markers of nutrition and inflammation attenuating this association more than adjustment for anemia measures and treatments (11),

Figure 1. Current status of anemia management



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Status of Anemia Management

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add to the lingering concerns and questions surrounding the iron aspects of anemia management.

Finally, greater scrutiny of costs of the ESRD program has prompted attention to the costly transition from CKD 4–5 to 5D, when incident patients without prior CKD care abruptly start dialysis. Patients treated with ESAs before and after hemodialysis initiation who maintained a Hb of 9.0 g/dL had a lower risk of all-cause mortality at 3, 6, and 12 months than did patients with a Hb of less than 9 g/dL before hemodialysis initiation (with or without ESAs) whose levels increased with ESAs after hemodialysis initiation (12). Findings of this nature, in addition to reports that healthcare resource utilization is higher in anemic patients than in nonanemic patients (3), pave the way for future research in this arena.

Primacy of clinical judgment and "first do no harm"

Clinical judgment is championed in the KDIGO guideline, underscoring the importance of physician involvement and oversight in clinical decision-making for any given patient. Evolving clinical experience coupled with fine-tuning of protocols has culminated in a management standard that integrates nurse-driven algorithm-directed treatment decisions with physician oversight. As scientific discovery continues to drive guideline development, and regulatory influences intertwine with clinical experience to affect protocols, there remains wisdom in clinical judgment and the simplicity of common sense. ■

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Anemia Management and Outcomes in Kidney Transplant Recipients

By Ahmed A. Awan, Wolfgang C. Winkelmayer, and Bhamidapati V. Murthy

Posttransplantation anemia (PTA) is an oft-neglected aspect of posttransplantation care that is associated with adverse outcomes for the kidney allograft and the recipient. The prevalence of anemia in kidney transplant recipients (KTRs) is very high, ranging from 25% to 40% depending on the definitions used, parameters measured, and average time since transplantation across study populations (1–3). The American Society of Transplantation (AST) and the World Health Organization have defined anemia as hemoglobin ≤13 g/dL in men or ≤12 g/dL in women. On the basis of these definitions, at the time of kidney transplantation, the majority of patients have anemia due to chronic kidney disease (CKD)–related erythropoietin (EPO) deficiency and resistance and also iron deficiency.

The customary treatment targets for the correction of anemia in CKD patients also do not aspire to normalize hemoglobin concentrations. After successful kidney transplantation, endogenous production of EPO may increase, and resistance to EPO may decline with improvement in the uremic milieu, leading to resolution of anemia 3 to 6 months after transplantation. However, the majority of KTRs have allograft function that corresponds to CKD stages 3 through 5, and they have persistent anemia for as long as 6 to 12 months after transplantation (late PTA).

Consequences of PTA

Cardiovascular disease remains the leading cause of death among KTRs (4), and some studies have purported a relation between PTA and cardiovascular death (5). A relationship between PTA and mortality has been described in some studies (6, 7), whereas others have found no such association (8). Molnar et al. (7) followed up 938 KTRs for 4 years and showed that all-cause mortality was 69% (95% confidence interval: 12% to 156%) higher in patients with anemia (per AST definition) at baseline. Conversely, a prospective study of 438 KTRs followed up for >7 years reported that a hemoglobin concentration <10 g/dL was not associated with increased mortality or graft loss (9). However, an association of PTA with increased risk of graft failure has been shown quite consistently (6–8). The adverse effects of anemia on quality of life are well known, and findings have been replicated in patients with PTA (10).

Causes of PTA

Besides the risk factors for anemia shared with CKD patients who have not undergone transplantation, PTA has a unique set of additional causes. Although every effort should be made to determine the precise cause of a patient's PTA, it usually is a multifactorial process. Transplant function is the most important correlate of anemia, and anemia worsens as graft function declines (3, 11). Transplant recipients who experience rejection episodes or have more than one transplant have a higher incidence of anemia (12). In the immediate posttransplantation period, surgical blood loss and induction immunosuppression contribute to anemia, and delayed graft function can amplify the problem.

Late PTA can be due to several causes (Figure 1). Antimetabolites (azathioprine and mycophenolic mofetil) and mTOR inhibitors (sirolimus and everolimus) can cause anemia by bone marrow suppression, and anemia is more severe when these two drug classes are combined. Interestingly, anemia of mTOR inhibitors presents with microcytosis. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, which are used in the treatment of posttransplantation erythrocytosis, also lead to PTA. Calcineurin inhibitors (tacrolimus and cyclosporine) can cause thrombotic microangiopathy. Donor-derived antibodies against recipients' red blood cells can cause immune-mediated hemolysis (passenger lymphocyte syndrome), which is a rare cause of PTA.

Management and hemoglobin targets

When we consider the adverse associations of anemia with quality of life, graft survival, and possibly mortality, it would stand to reason that correction of anemia and normalization of hemoglobin could potentially mitigate these consequences. Intuitively, the initial step in management would be to identify any reversible causes, including iron deficiency, and treat them appropriately. However, some of the potentially causative factors of PTA are difficult to avoid, including the medications used for immunosuppression and infection prophylaxis. One target amenable to therapeutic intervention is absolute or relative deficiency of endogenous erythropoietin, which can partly be treated by the administration of erythropoiesis stimulating agents (ESAs). Recent studies in animal models have shown that ESAs may prevent allograft nephropathy by mechanisms other than anemia correction, including preservation of intragraft expression of angiogenic factors, upregulation of antiapoptotic factors, and immunomodulating effects (13–15).

Owing to a lack of randomized controlled trials of the effects of anemia correction in KTRs, the transplantation community has been relying mostly on data from patients with CKD and anemia. The enthusiasm about the use of ESA for anemia correction was curbed by findings from the Normal Hematocrit Study in patients receiving dialysis and the CHOIR, CREATE, and TREAT studies in non–dialysis-dependent CKD (16–19). These trials showed either no benefit or even cardiovascular harm with the use of ESAs to achieve higher hemoglobin concentrations. Consequently, the current guidelines for the management of PTA recommend following the targets suggested for anemia in CKD patients without a transplant while acknowledging the dearth of data in KTRs (20, 21).

An observational study by Heinze et al. (22) retrospectively analyzed 1794 transplant recipients in the Austrian Dialysis and Transplant Registry and showed an increase in mortality if hemoglobin was corrected to more than 12.5 g/dL by the use of ESAs, thus reinforcing the trial data in CKD patients. Interestingly, patients with higher hemoglobin levels without the use of EPO had better survival rates in this study. However, this paradigm was challenged by two recent prospective studies showing a benefit of ESA use in KTRs. Choukroun et al. (23), in a randomized controlled trial, showed that targeting a hemoglobin level of 13.0 to 15.0 g/dL by using epoietin-β led to improved graft survival and quality of life without increasing the risk of adverse cardiovascular events.

In a recent randomized controlled trial from Japan, a hemoglobin target of 12.5 to 13.5 g/dL (with use of ESA) was associated with a reduction of decline in kidney function over a follow-up time of >3 years in the chronic phase of allograft nephropathy, without any serious adverse events (24). Of note, the target hemoglobin in the high-hemoglobin group was achieved after 18 months in this 3-year study. These studies are compared in Table 1. The contradictory results among various studies of ESAs in CKD and KTRs can theoretically be explained by the differences in baseline cardiovascular risk status, the doses of ESAs used, and the rate of correction of anemia, along with the immunologic and nonimmunologic mechanisms of anemia in KTRs that are different from those in patients with CKD without KTR.

In summary, the burden of PTA in KTR remains high and causes significant morbidity and mortality in these patients. Any PTA should be proactively addressed as part of holistic management of KTRs. Identifying a specific cause remains vital so that any reversible factors can be eliminated. The target hemoglobin and use of ESAs remain controversial, but recent evidence challenges the

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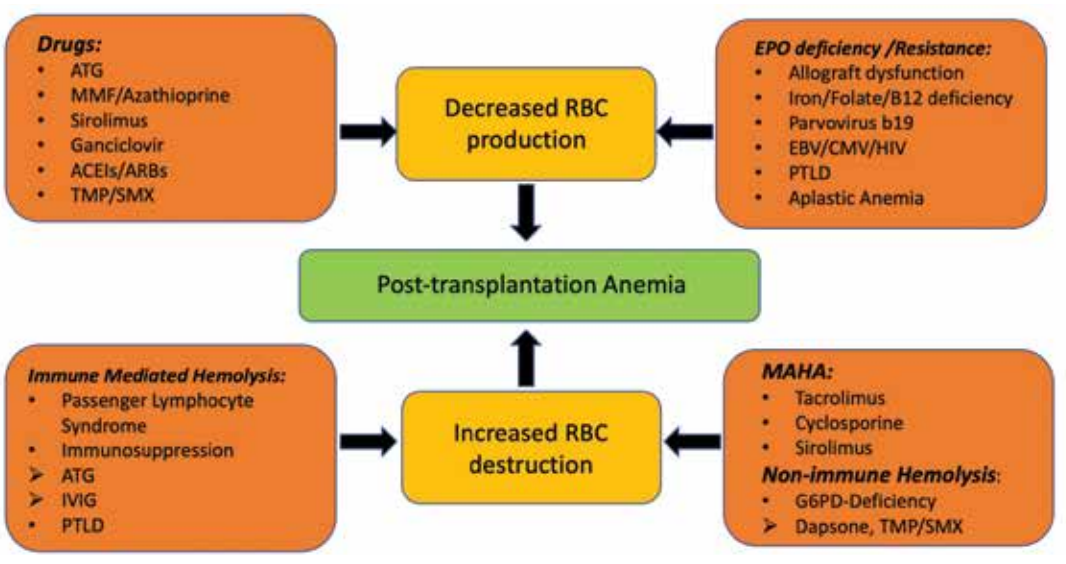
Figure 1. Common causes of posttransplanation anemia



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paradigm of extrapolating the evidence in CKD patients to KTRs and suggests that trying to normalize hemoglobin by using ESAs may be beneficial by appropriate patient selection and by decelerating the rate of correction of anemia. Newly introduced therapeutic agents targeting hypoxia-inducible factor pathways have the potential for a positive impact but also for undesired off-target effects. Therefore, it is mandatory that these new agents be specifically and thoroughly studied in KTRs.

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Table 1. Comparison of 3 recent studies analyzing ESAs in posttransplantation anemia

Study description	Heinze, et al., 2009 (22)	Choukroun, et al., 2012 (23)	Tsujita, et al., 2018 (24)
Study design	Retrospective cohort study (Austrian Dialysis and Transplant Registry)	Open-label, multicenter, randomized controlled trial	Open-label, multicenter, randomized controlled trial
Setting	Transplantation centers in Austria	17 centers in France	2 hospitals in Japan
Participants	1794 patients who received transplants between 1992 and 2004	120 patients who received transplants at least 12 months before enrollment	127 patients who received transplants at least 12 months before enrollment period of January 2012 to March 2014
Number of kidney transplants	Primary kidney allograft	Primary or secondary kidney allograft	Primary allograft (except one patient)
Patients with cardiovascular disease at baseline	Included	Included	Excluded
Intervention group	Erythropoietin	Epoetin-β to normalize hemoglobin (13.0–15.0 g/dL)	Darbepoetin-α or epoetin-β pegol to target hemoglobin 12.5–13.5 g/dL
Control	No erythropoietin	Epoetin-β to partially correct hemoglobin (10.5–11.5 g/dL)	Target hemoglobin 10.5–11.5 g/dL
Type and dose of erythropoeitin	Not specified	Epoetin-β	Darbepoetin-α or epoetin-β pegol
Hemoglobin target	12.5 g/dL (cutoff)	13–15 g/dL vs 10.5–11.5 g/dL	12.5–13.5 g/dL vs 10.5–11.5 g/dL
Follow-up	Median 5.6 years (interquartile range 3.0–8.7 years)	2 years	3 years
Mortality in intervention group	Increased at hemoglobin >14 g/dL	1 patient died (compared with 3 patients in control group)	None in either group
Number of cardiovascular events in intervention group	Increased	Low but similar to control group	None in either group
Rate of mean decline in eGFR in intervention group	Not evaluated	−1 mL/min/1.73 m^2 vs −5.1 mL/min/1.73 m^2 in low-hemoglobin group	−2.4 mL/min/1.73 m^2 vs. −5.9 mL/min/1.73 m^2 in low-hemoglobin group

Trials and Tribulations: NHT, CHOIR, TREAT, PIVOTAL

The balance between iron and ESA dose

By Lynda Szczech, MD, practicing nephrologist, Durham, NC

To boldly restate the obvious, trials in anemia have provided surprising, controversial, and dramatic, practice-changing results for the last 20 years. The latest key trial to add to our knowledge on how to treat the anemia of kidney disease is the PIVOTAL trial (1).

The PIVOTAL trial compared higher-dose, proactive IV iron (400 mg monthly) to lower-dose, reactive iron (0 to 400 mg if ferritin <200 µg/L or TSAT <20%) on the risk of the composite endpoint of death, myocardial infarction, stroke, and congestive heart failure. The higher dose proactive arm was found to have a (first) non-inferior association with cardiovascular outcomes of death, myocardial infarction (MI), stroke, and heart failure, and second, a superior effect on that composite. The Hazard Ratio (HR) for the high-dose as compared to the low-dose group was 0.85 (95% CI 0.33 to 1.00; p=0.04). When individual events were compared, it should be noted that the HRs all favored the high-dose group, but the point estimate for both congestive heart failure and MI were numerically lower than the point estimates for the other events in the composite.

To provide maximal benefit in the application of these findings to clinical practice, the potential mechanism for this benefit deserves careful scrutiny. First, the effect of each arm on hemoglobin should be considered. In the high-dose, proactive arm of the PIVOTAL trial, hemoglobin began to rise immediately after randomization. After only 3 months, hemoglobin was 0.6 g/dL higher than baseline. The curves of cumulative ESA dose by treatment arm in the supplemental material began to split immediately after randomization also, with the group in the high-dose, proactive arm receiving cumulatively less ESA. Patients in the lower dose reactive arm also saw a similar rise in hemoglobin. This change, however, occurred at a seemingly slower pace not maximizing until about 24 months of treatment.

Multiple studies suggest that a higher hemoglobin target results in a greater risk of cardiovascular events (2, 3, 4). The Normalization of Hematocrit Trial demonstrated that randomizing to a normal target hematocrit of 42% caused a greater risk of MI and death than a hematocrit of 30%. The authors suggest in the discussion that this could be due to the increased IV iron that was required to attempt to achieve the 42% hematocrit because it was clear that higher achieved hemoglobin was associated with better outcomes. This hypothesis was subsequently supported by observational studies that fueled a controversy over the relative safety of IV iron (5). The CHOIR trial was published 8 years later, demonstrating that targeting a hemoglobin of 13.1 g/dL as compared to 11.3 g/dL in CKD patients resulted in a greater risk of death, MI, stroke, and heart failure. The TREAT trial subsequently demonstrated that in a population of patients with diabetes mellitus, targeting a hemoglobin of 13 g/dL as compared to placebo resulted in no significant change in overall cardiovascular risk (good or bad); however, the trial did note an increased risk of stroke when it was examined as a separate endpoint.

Following the relative consistency of outcomes among these trials, secondary analyses of both CHOIR and TREAT were undertaken to attempt to discern the mechanism of the risk identified. These analyses supported the hypothesis that there is a relationship between ESA dose and cardiovascular risk with patients receiving the highest doses at the greatest risk (6, 7, 8).

So it is not unreasonable to hypothesize that the potential benefit seen in the PIVOTAL trial could be at least in part due to the decreased ESA doses that occurred sooner and to a greater extent in the higher proactive iron arm. In these observational trials, higher achieved hemoglobin was associated with better outcomes and the risk of targeting higher hemoglobin seemed to be mediated through higher doses among those patients who failed to respond to ESAs and whose hemoglobin didn't achieve target.

It is important, however, to consider the implications of the immediate increase in hemoglobin in PIVOTAL. In the high dose proactive arm, hemoglobin rose and ESA dose was reduced immediately after beginning treatment with similar changes occurring later in the lower dose reactive arm. In that functional iron deficiency has been defined as a state in which there is insufficient iron incorporation into erythroid precursors in the face of apparently adequate body iron stores (9), *does the immediate increase in hemoglobin suggest that erythropoiesis was previously limited by iron availability in both arms?*

If so, could it be that what was really being tested was quicker iron repletion (or the ability of supplemental iron to overcome functional iron deficiency) as compared to slower iron repletion?

This should be interpreted in the context of studies that assess the effect of iron supplementation on cardiovascular outcomes. Most notably, a trial by Anker et al. randomized patients with congestive heart failure and iron deficiency to receive 200 mg of IV iron (ferric carboxymaltose) versus placebo (10). Patients treated had a greater likelihood of improving their heart failure functional class and had greater improvements in functional outcomes such as the 6-minute walk test. These results suggested that the cardiovascular performance of congestive heart failure patients (even those without a dedicated history of chronic kidney disease) benefited from the presence of adequate and available iron. Interpreting PIVOTAL in the setting of the randomized trial by Anker et al. suggests a potential role for iron repletion/availability of adequate iron in cardiac function. This is an important consideration in the potential mechanism in PIVOTAL.

In that patients who are inflamed are likely to have a functional iron deficiency due to increased levels of hepcidin with the subsequent sequestration of iron in the reticuloendothelial system, the totality of this literature also seems to point to this as a key feature of anemia management that has not been fully investigated. The pieces of the puzzle are different trials of different sizes, treatments, and populations, but they all seem to fit together. They point to the treatment of anemia being far more complex than only increasing hemoglobin. The importance of having iron truly available to the bone marrow, not just adequate levels of TSAT and ferritin, and iron's relationship to the

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cardiovascular system should be our next focus if we really want to maximize patient outcomes.

Disclosure: Lynda Szczech, MD, is an employee of FibroGen, Inc., a company developing treatments for anemia.

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Clinical Place of Iron in the 21st Century

By Daniel W. Coyne

In 2018, expert opinion that our present strategies for the use of intravenous (IV) iron were harming chronic kidney disease (CKD) patients took a severe thrashing. Despite clear evidence that iron is essential for treating the anemia of CKD, generous IV iron use has been discouraged by guidelines and by many experts. Despite this advice, physicians in the United States have given more IV iron to dialysis patients than those in other regions of the world. The results from the Proactive IV Iron Therapy in Haemodialysis Patients (PIVOTAL) trial, paired with the results from IV iron trials that include nondialysis CKD (CKD-ND) patients, demonstrate IV iron is not only safe but superior to conservative iron strategies (1).

Warnings about IV iron

Since at least 2006, guidelines have recommended very conservative IV iron use because of safety concerns. Experts pointed to a lack of long-term safety studies of IV iron and to some observational, in vitro, and preclinical studies suggesting that IV iron could increase cardiovascular injury and infections.

Other experts note that dialysis patients have high liver iron content (LIC) after IV iron, and high LIC values in hemochromatosis patients indicate severe iron overload. These experts recommend even stricter limits on IV iron use (2).

The 2006 KDOQI guidelines recommended that IV iron was clearly needed only when ferritin was below 200 ng/mL and should not be routinely used in patients with ferritin >500 ng/mL (3). Despite this, average ferritin levels in the dialysis population in the United States slowly increased from ~600 ng/mL in 2006 to ~850 ng/mL by 2011, and remain fairly stable (4).

The superiority of proactive IV iron use

The PIVOTAL trial randomized 2141 newer dialysis patients to a proactive IV iron strategy or a reactive iron strategy and followed them for as long as 42 months. The proactive group received an average of 3.8 g IV iron in the first year, then ~200 mg/month thereafter. The reactive group received the cautious experts' guideline advice: IV iron only when ferritin was less than 200 ng/mL or transferrin saturation (TSAT) less than 20% (1).

Proactive use of IV iron significantly reduced cardiovascular events and deaths (Figure 1), transfusions, and doses of erythropoiesis-stimulating agents (ESA), and it did not increase infections in patients using hemodialysis (1). Given that IV iron is relatively inexpensive, proactive iron use pays for itself by reducing or eliminating costly ESA therapy.

Trials of IV iron versus placebo in patients with heart failure have also demonstrated significant benefits (5, 6). About 40% of patients in the heart failure trials have CKD. Regardless of CKD status, IV iron improves heart failure functional status, appears to decrease heart failure–related hospitalizations and possibly mortality, and does not increase infections (6).

Claims that dialysis patients in the United States have severe iron overload based on high LIC have also been proved wrong. Whereas IV iron is stored in the liver, total body iron is far lower than in hemochromatosis (7). Additionally, the proactive iron arm in the PIVOTAL trial would be considered severely iron overloaded; yet, the outcomes were superior.

Overall, iron guidelines and anti-iron experts' egos took a big hit in 2018.

Iron strategies for the 21st century

Iron deficiency affects millions of CKD and dialysis patients, and treatment improves health and saves lives. Hemochromatosis is also serious and should be avoided by stopping iron when TSAT is above 50%. A broad safe therapeutic window exists between those two disorders, and achieving it improves clinical outcomes, possibly by reducing ESA use, which increases the risks for death, serious adverse cardiovascular reactions, and stroke.

Functional or absolute iron deficiency may be present despite ferritin values of 1200 ng/mL and TSAT of 30%, and occasionally higher (8, 9). A trial of IV iron is superior to ferritin and TSAT testing for determination of iron deficiency.

Oral iron and IV iron are effective in nondialysis CKD patients, despite seemingly normal ferritin (in the range of 50 to 300 ng/mL) and TSAT (>15% up to 30%) values. A trial of oral iron in CKD-related anemia is appropriate, and IV iron is the next best treatment. Both can raise the hemoglobin sufficiently to preclude the use of ESAs. IV iron is the first choice if anemia is severe or a more rapid rise in hemoglobin is desired.

In the dialysis population, ferritin has limited value; a high ferritin level resulting from inflammation may preclude the proper use of IV iron. TSAT is also a poor marker in this population, but a value above 50% in a patient who has not received IV iron in the previous 2 weeks is strongly suggestive of replete or high iron stores, and iron therapy should be stopped. The PIVOTAL trial shows that most incident patients should receive ~1000 mg over the first 2 months to replete iron stores, then ~200 mg/month to maintain stores. Adequate iron repletion should result in TSAT above 25% (ideally >30%), and monthly maintenance IV iron should lead to stable ferritin values in the range of 500 to 1200 ng/mL. The payoff for this is fewer transfusions, lower ESA doses (including no ESA), and better clinical outcomes.

Other iron therapy options

In all CKD populations, ferric citrate (Auryxia), given with meals, has been shown to increase iron stores, raise hemoglobin levels, and/or reduce ESA doses. This agent has the potential advantage of binding dietary phosphorus. It is an attractive alternative to standard oral iron and IV iron in all populations. It should be stopped when TSAT exceeds 50%.

Ferric pyrophosphate citrate (FPC, Triferic) is added to the bicarbonate concentrate prepared each day for hemodialysis. The FPC provides a steady infusion of the iron complex throughout the hemodialysis treatment. The very high affinity of pyrophosphate is surpassed only by the affinity of transferrin for iron, so FPC transfers iron directly to transferrin. Most hemodialysis patients might need some IV iron, but their requirements may be cut in half.

Last, hypoxia-inducible factor-β prolyl hydroxylase inhibitors (HIF-PHI) may improve oral iron absorption sufficiently that oral iron supplements could preclude the need for IV iron. Roxadustat is the first of this class of products to complete phase 3 studies, and we should be hearing some results at the World Congress of Nephrology in spring 2019. Of course, proactive IV iron use might reduce the dose or preclude the need for an HIF-PHI. ■

Daniel W. Coyne, MD, is professor of medicine, division of nephrology at Washington University, St. Louis, MO.

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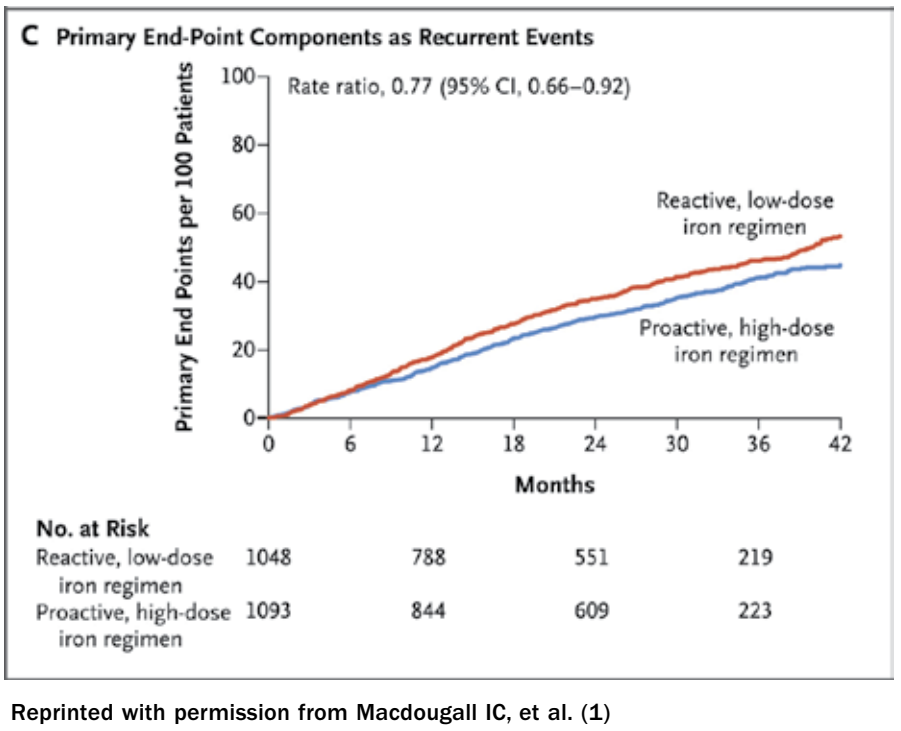
Figure 1. Rates of death by any cause and a composite of myocardial infarction, stroke, and hospitalization for heart failure as recurrent events



Reprinted with permission from Macdougall IC, et al. (1)

HIF Stabilizers: Will They Have a Place?

By Jay Wish

Hypoxia-inducible factor prolyl-hydroxylase inhibitors (commonly known as HIF stabilizers or PHIs) belong to a new class of orally administered drugs to treat anemia in patients with CKD.

Hypoxia-inducible factor (HIF) is present in nearly all tissues and constitutes the body's natural mechanism to adapt to hypoxic conditions. HIF is a heterodimer consisting of an alpha and beta subunit. The alpha subunit is rapidly degraded by a proline hydroxylase (PH) enzyme in the presence of oxygen, thereby preventing the heterodimerization with the beta subunit and its transcriptional effects on over 4000 genes, depending on the tissue.

Activation of these genes leads to increased red blood cell (RBC) production through increased synthesis of erythropoietin and the erythropoietin receptor, as well as increased synthesis of a variety of iron handling proteins including transferrin, transferrin receptor, duodenal cytochrome B, divalent metal transporter-1, and ceruloplasmin. The net effect is a more "complete" stimulation of erythropoiesis than can be achieved by erythropoiesis stimulating agents (ESAs) alone, which do not affect iron metabolism. However, HIF stabilizers also stimulate a variety of genes not affecting erythropoiesis including those that affect angiogenesis, glucose metabolism, extracellular matrix production, and cellular proliferation.

The HIF stabilizers under development have attempted to achieve specificity for erythropoiesis by targeting specific PH enzymes and with pharmacokinetics that allow for periods between doses during which there is no PH inhibition so that the effect of these agents on non-targeted genes can be minimized. There are three HIF stabilizers currently under development in the US: roxadustat, vadadustat and daprodustat.

Roxadustat has a half-life of 12–13 hours and has been shown to be effective in raising hemoglobin (Hb) levels when administered three times weekly; vadadustat and daprodustat have half-lives of around 4 hours and are administered daily. Multiple phase 2 studies have been published with all three agents demonstrating comparable efficacy in maintaining Hb levels within target range when dialysis patients are switched from ESAs and in raising Hb levels to target range in ESA-naïve dialysis and non–dialysis-dependent (NDD)-CKD patients. Because of their beneficial effects on iron metabolism, which lead to an increase in oral iron absorption, increased release of stored iron from macrophages, and increased transport of iron to the erythroid marrow, HIF stabilizers have been shown to be equally effective with oral or intravenous iron in the short term (although it is unlikely this can be sustained over the long term in hemodialysis [HD] patients given their ongoing iron losses).

The use of HIF stabilizers has been shown to decrease hepcidin levels, although this is thought to be mediated by increased erythroferrone released by RBC precursors in the setting of accelerated erythropoiesis, not a direct effect of the HIF stabilizers. Nonetheless, HIF stabilizer therapy has demonstrated comparable responsiveness in raising Hb levels among patients with normal or high C-reactive protein (CRP) levels, the latter being a surrogate for the inflammatory conditions that typically lead to "ESA resistance." Chinese phase 3 studies of roxadustat (presented at Kidney Week 2018) demonstrated efficacy superiority to placebo in NDD-CKD patients and non-inferiority to ESA in ESKD patients. However, these studies were not adequately powered for major adverse cardiovascular event (MACE) outcomes (<1000 patients, 6 months duration). Roxadustat has been approved for use in China by Chinese regulatory authorities.

The phase 3 studies of roxadustat in the US and Europe have been completed. Top-line efficacy data have been released by the sponsor (not yet published) and revealed: superiority to placebo in NDD-CKD patients (n=922, mean f/u 1.7 years); superiority to ESA in the US and non-inferiority to ESA in Europe in ESA-naïve incident ESKD patients (n=1043, mean f/u 1.8 years); and superiority to ESA in prevalent ESKD patients converted from ESA (n=741, mean f/u 1.9 years). It is thought that the superiority to ESA stems from the HIF stabilizers' improved efficacy in the subset of inflamed ESA-resistant patients. The top-line safety data from the roxadustat phase 3 US and European studies have not yet been released, and may not be until late 2019. Phase 3 studies of vadadustat and daprodustat are still underway, and will likely be completed in 2020 and 2021, respectively.

Prior to the release of long-term (3-year) safety data, it is difficult to predict what the role of HIF stabilizers will be in the treatment of anemia in patients with CKD. Even with 3-year MACE data, there may still be reservations regarding the widespread adoption of these agents because it may take more than 3 years to determine their non-MACE effects such as angiogenesis (tumor growth, diabetic retinopathy), altered glucose metabolism, rate of renal function decline in NDD-CKD patients, and pulmonary hypertension. There are several possible 3-year safety scenarios, each of which will likely have a different effect on the short-term adoption of these new agents. If the HIF stabilizers demonstrate superior safety (MACE outcomes being of greatest interest) to ESAs in dialysis patients, it is likely the uptake of the HIF stabilizers will be robust, although there may be some providers who wish to take more of a "wait and see" attitude regarding longer-term safety issues. If the HIF stabilizers demonstrate non-inferior safety to ESAs in dialysis patients, it is likely the HIF stabilizers will be preferred to ESAs in inflamed "ESA resistant" patients to decrease transfusion risk and costs.

Given the failing record of interventional trials of all sorts in dialysis patients to demonstrate superior outcomes in one arm, it is felt by many to be unlikely that HIF stabilizers will demonstrate safety superiority in this population. In some phase 3 trials in NDD-CKD patients, HIF stabilizers are being compared to placebo. If the safety of a HIF stabilizer is non-inferior to placebo in such trials does that mean that the HIF stabilizer is safer than ESA even if the head-to-head trials with ESA did not demonstrate the safety superiority of the former? If the safety of a HIF stabilizer is non-inferior to placebo does that mean the FDA would not require a black box warning as it does for ESAs? Even if that were the case, would there be enough reservations regarding the long-term non-MACE safety issues of HIF stabilizers that their adoption might be sluggish? The appeal of an oral anemia therapy in non-HD patients is undeniable, even without longer-term safety data. A reasonable approach in the non-HD population would be to discuss the risks and benefits of ESAs vs. HIF stabilizers so the patient can make an informed decision balancing convenience with possible unknown risk. The same risk vs. benefit discussion applies to the HD population where the motivation to abandon the parenterally administered ESA class of drugs with 30 years clinical experience is less compelling except if the patient is ESA-resistant.

The answer to the question posed in the title of this article, "Will HIF stabilizers have a place?" is "It depends." It depends on their safety in phase 3 clinical trials. It depends on how much clinicians are satisfied by the MACE outcomes of these agents in phase 3 clinical trials or remain concerned regarding possible angiogenesis, tumor growth, abnormal glucose metabolism, accelerated decline of kidney function, and pulmonary hypertension that are not addressed in phase 3 trials to their satisfaction. It depends on costs, payment policies, formularies, prior authorizations, and dialysis organization protocols. Unless there is a safety signal in phase 3 trials, it is likely HIF stabilizers will initially be favored in patients unable to reach target Hb levels on high doses of ESAs ("ESA resistant") and in non-HD patients who favor an oral drug over an injection. Further uptake is likely once concerns regarding safety over longer than the 3 years in the phase 3 trials are satisfied. ■

Jay Wish, MD, is medical director of the outpatient dialysis unit at Indiana University Hospital and professor of clinical medicine at Indiana University School of Medicine in Indianapolis, IN.

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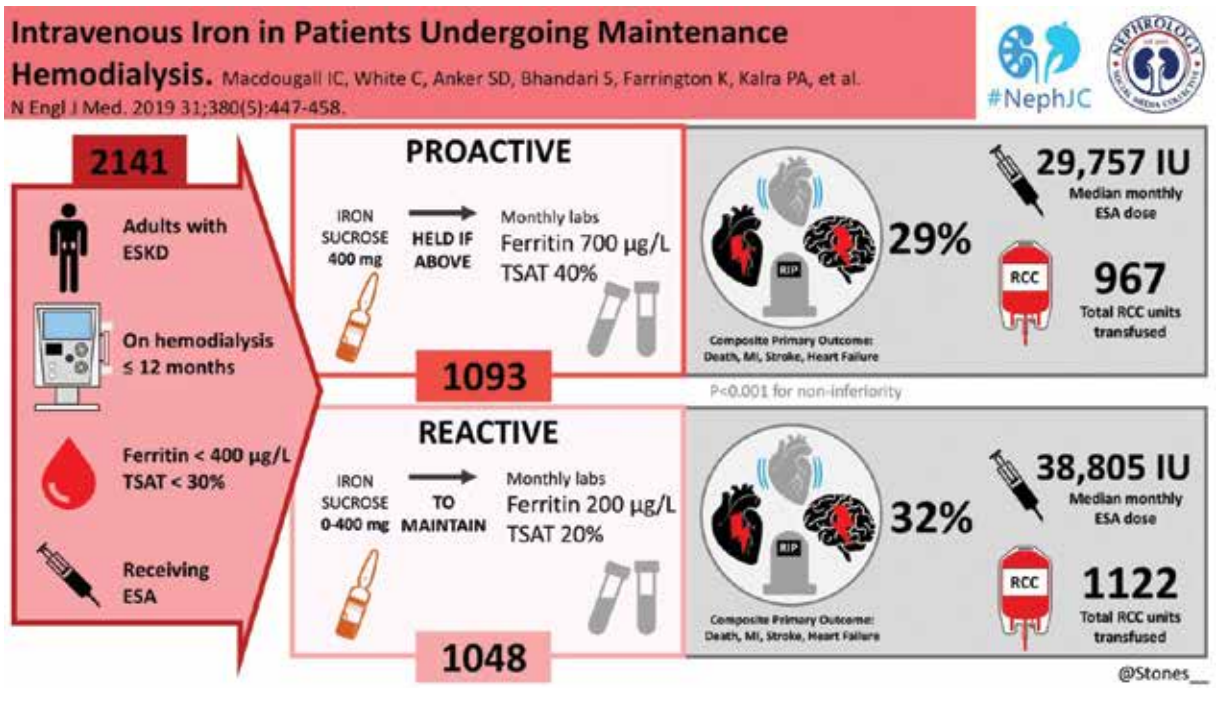
Figure 1.



Management of Anemia: Final Thoughts

By Robert Provenzano, MD

The editors hope that this issue of *ASN Kidney News* focusing on anemia and its management will allow readers to review lessons learned from our use of rEPO and to take pause as we thoughtfully embark on anemia treatment strategies utilizing newer agents that may soon be available.

CKD affects over 10% of the US population, with anemia being present as this disorder progresses, ultimately terminating in ESKD, preemptive kidney transplantation, or conservative management. Even with these clinical endpoints, anemia often remains a critical comorbidity. With increased focus on value-based payment and most important, patient-centered care, the management of this population cannot and should no longer be delivered in a fragmented manner.

Hypertension control, management of metabolic bone disease, nutritional support, fluid optimization, and other co-morbidity control will be delivered in an integrated fashion more so than ever. The management of anemia in this environment must be completely reevaluated. Front and center are the recurrent questions: How do my patients feel when their anemia is managed? Is hemoglobin of 9–11 g adequate to suppress symptoms? Are there advantages to higher hemoglobin levels with newer agents? HIFs are not erythropoietin; how will the FDA view the labeling for them? Will there be restrictions? What are their short- and long-term safety profiles?

As physician-scientists we all must get comfortable reliving many of the same issues we now understand of earlier agents but answer them in an accelerated manner, not over a 30-year period.

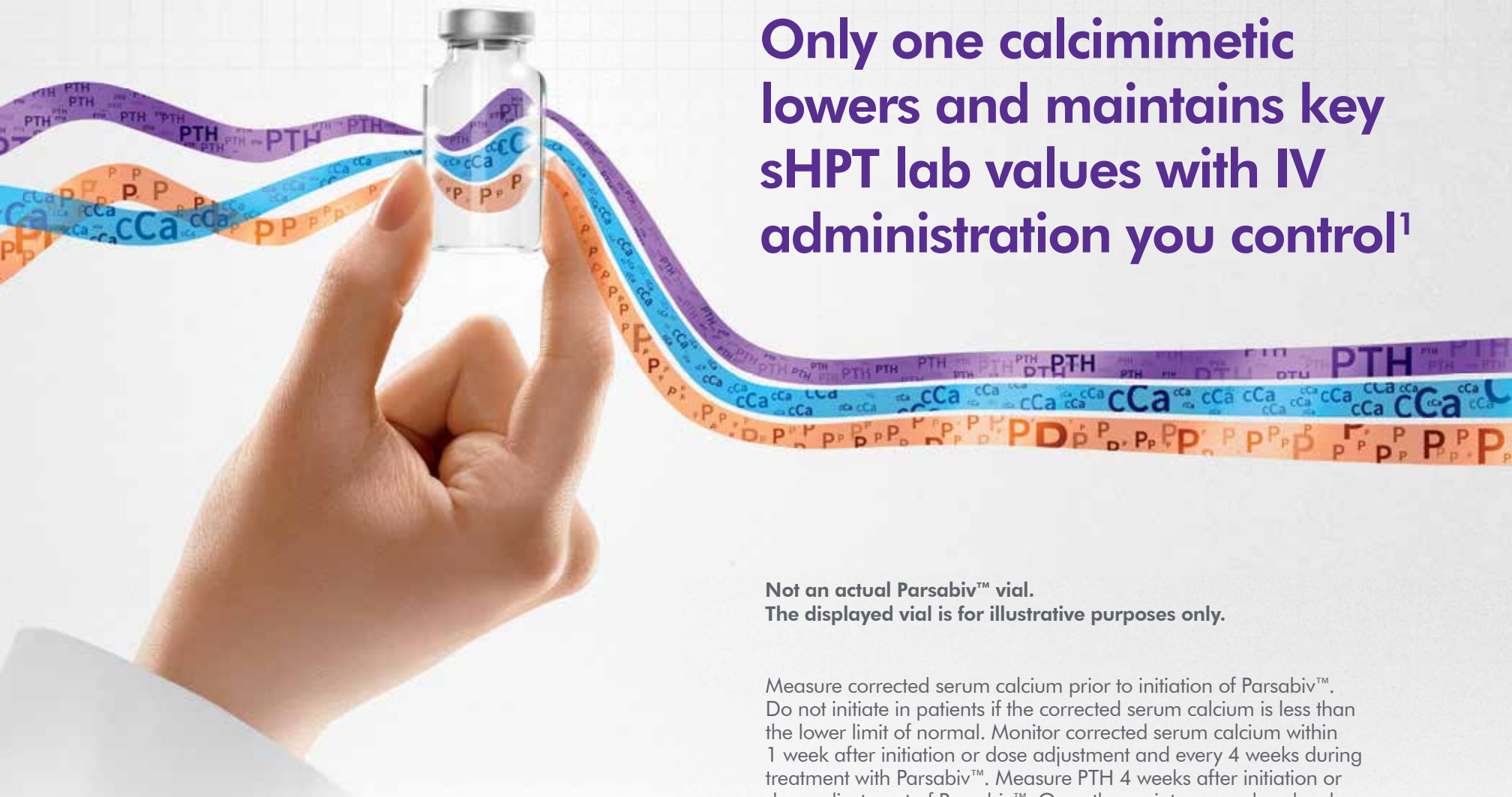
Finally, understanding our payment systems and how they drive pharmaceutical utilization cannot be underestimated. I spoke with Dr. Jay Wish, one of the authors in this special section, and he passionately believes no discussion of pharmacotherapy can occur without consideration of cost and payment. The pricing of HIF stabilizers has yet to be determined, so a value proposition cannot be quantified.

Because HIF stabilizers will be approved by the FDA during or after 2020, their use in ESKD patients will qualify for the "transitional drug add-on payment adjustment (TDAPA)" to the ESKD prospective payment system. Each HIF stabilizer will be paid for by the Centers for Medicare and Medicaid Services (CMS) outside the dialysis payment "bundle" for two years following its approval by the FDA. In other words, for those two years the HIF stabilizer with be paid for through Medicare Part D or Medicaid and will not cost the dialysis provider anything. The bundled payment for patients using a HIF stabilizer through TDAPA will be reduced by the average cost of ESA per treatment, which is about $30. Thus, if a patient's ESA dose costs more than an average of $30/treatment, the dialysis facility will save money if a HIF stabilizer is used rather than an ESA. This provides a perverse economic, non-clinical, non-patient–centered incentive to use HIF stabilizers, which, it is hoped, will be resisted. After its 2-year TDAPA period, each HIF stabilizer will not go into the dialysis payment bundle, but will rather be charged to CMS by the dialysis provider as an "outlier payment" that is not fully reimbursed. At that point, there may again be a perverse economic incentive to return to ESAs, which remain in the bundle, or there may be competition, which brings the price of all anemia treatments down.

Phase 3 trial results for HIFs will be available soon and will answer some, but not all, the questions posited here. In anticipation of the many additional questions bound to be generated from these trials, the National Kidney Foundation empaneled some of the world experts March 22–23, 2019, in Philadelphia, PA, to review all available data and ask, where do we go next? Their white paper will be available soon in the *American Journal of Kidney Diseases*.

In closing, we hope this series of articles by industry experts and your colleagues, has helped educate and shape your understanding of the next generation of agents available for anemia management.

Robert Provenzano, MD, FASN, is Vice President, Medical Affairs, Office of Chief Medical Officer, and CMO, Nephrology Practice Solutions, at DaVita in Denver, Colorado.



Only one calcimimetic lowers and maintains key sHPT lab values with IV administration you control[1]

Not an actual Parsabiv™ vial.
The displayed vial is for illustrative purposes only.

Indication

Parsabiv™ (etelcalcetide) is indicated for the treatment of secondary hyperparathyroidism (HPT) in adult patients with chronic kidney disease (CKD) on hemodialysis.

Limitations of Use:

Parsabiv™ has not been studied in adult patients with parathyroid carcinoma, primary hyperparathyroidism, or with CKD who are not on hemodialysis and is not recommended for use in these populations.

Important Safety Information

Contraindication: Parsabiv™ is contraindicated in patients with known hypersensitivity to etelcalcetide or any of its excipients. Hypersensitivity reactions, including pruritic rash, urticaria, and face edema, have occurred.

Hypocalcemia: Parsabiv™ lowers serum calcium and can lead to hypocalcemia, sometimes severe. Significant lowering of serum calcium can cause QT interval prolongation and ventricular arrhythmia. Patients with conditions that predispose to QT interval prolongation and ventricular arrhythmia may be at increased risk for QT interval prolongation and ventricular arrhythmias if they develop hypocalcemia due to Parsabiv™. Closely monitor corrected serum calcium and QT interval in patients at risk on Parsabiv™.

Significant reductions in corrected serum calcium may lower the threshold for seizures. Patients with a history of seizure disorder may be at increased risk for seizures if they develop hypocalcemia due to Parsabiv™. Monitor corrected serum calcium in patients with seizure disorders on Parsabiv™.

Concurrent administration of Parsabiv™ with another oral calcimimetic could result in severe, life-threatening hypocalcemia. Patients switching from cinacalcet to Parsabiv™ should discontinue cinacalcet for at least 7 days prior to initiating Parsabiv™. Closely monitor corrected serum calcium in patients receiving Parsabiv™ and concomitant therapies known to lower serum calcium.

Measure corrected serum calcium prior to initiation of Parsabiv™. Do not initiate in patients if the corrected serum calcium is less than the lower limit of normal. Monitor corrected serum calcium within 1 week after initiation or dose adjustment and every 4 weeks during treatment with Parsabiv™. Measure PTH 4 weeks after initiation or dose adjustment of Parsabiv™. Once the maintenance dose has been established, measure PTH per clinical practice.

Worsening Heart Failure: In Parsabiv™ clinical studies, cases of hypotension, congestive heart failure, and decreased myocardial performance have been reported. Closely monitor patients treated with Parsabiv™ for worsening signs and symptoms of heart failure.

Upper Gastrointestinal Bleeding: In clinical studies, 2 patients treated with Parsabiv™ in 1253 patient years of exposure had upper gastrointestinal (GI) bleeding at the time of death. The exact cause of GI bleeding in these patients is unknown and there were too few cases to determine whether these cases were related to Parsabiv™.

Patients with risk factors for upper GI bleeding, such as known gastritis, esophagitis, ulcers or severe vomiting, may be at increased risk for GI bleeding with Parsabiv™. Monitor patients for worsening of common Parsabiv™ GI adverse reactions and for signs and symptoms of GI bleeding and ulcerations during Parsabiv™ therapy.

Adynamic Bone: Adynamic bone may develop if PTH levels are chronically suppressed.

Adverse Reactions: In clinical trials of patients with secondary HPT comparing Parsabiv™ to placebo, the most common adverse reactions were blood calcium decreased (64% vs. 10%), muscle spasms (12% vs. 7%), diarrhea (11% vs. 9%), nausea (11% vs. 6%), vomiting (9% vs. 5%), headache (8% vs. 6%), hypocalcemia (7% vs. 0.2%), and paresthesia (6% vs. 1%).

Please see Brief Summary of full Prescribing Information on adjacent page.

IV = intravenous; sHPT = secondary hyperparathyroidism; PTH = parathyroid hormone; P = phosphate; cCa = corrected calcium.

Reference: 1. Parsabiv™ (etelcalcetide) prescribing information, Amgen.

Parsabiv™ (etelcalcetide) Injection for intravenous use

2.5mg/0.5mL | 5mg/1mL | 10mg/2mL

Visit **ParsabivHCP.com** for more information.

BRIEF SUMMARY OF PRESCRIBING INFORMATION

Parsabiv™
(etelcalcetide) Injection for intravenous use
2.5mg/0.5mL | 5mg/1mL | 10mg/2mL

Please see package insert for full Prescribing Information.

INDICATIONS AND USAGE

PARSABIV is indicated for the treatment of secondary hyperparathyroidism (HPT) in adult patients with chronic kidney disease (CKD) on hemodialysis.

Limitations of Use:

PARSABIV has not been studied in adult patients with parathyroid carcinoma, primary hyperparathyroidism, or with chronic kidney disease who are not on hemodialysis and is not recommended for use in these populations.

CONTRAINDICATIONS

Hypersensitivity

PARSABIV is contraindicated in patients with known hypersensitivity to etelcalcetide or any of its excipients. Hypersensitivity reactions, including pruritic rash, urticaria, and face edema, have occurred with PARSABIV *[see Adverse Reactions (6.1) in PARSABIV full prescribing information]*.

WARNINGS AND PRECAUTIONS

Hypocalcemia

PARSABIV lowers serum calcium *[see Adverse Reactions (6.1) in PARSABIV full prescribing information]* and can lead to hypocalcemia, sometimes severe. Significant lowering of serum calcium can cause paresthesias, myalgias, muscle spasms, seizures, QT interval prolongation, and ventricular arrhythmia.

QT Interval Prolongation and Ventricular Arrhythmia

In the combined placebo-controlled studies, more patients treated with PARSABIV experienced a maximum increase from baseline of greater than 60 msec in the QTcF interval (0% placebo versus 1.2% PARSABIV). In these studies, the incidence of a maximum post-baseline predialysis QTcF > 500 msec in the placebo and PARSABIV groups was 1.9% and 4.8%, respectively *[see Adverse Reactions (6.1) in PARSABIV full prescribing information]*. Patients with congenital long QT syndrome, history of QT interval prolongation, family history of long QT syndrome or sudden cardiac death, and other conditions that predispose to QT interval prolongation and ventricular arrhythmia may be at increased risk for QT interval prolongation and ventricular arrhythmias if they develop hypocalcemia due to PARSABIV. Closely monitor corrected serum calcium and QT interval in patients at risk receiving PARSABIV.

Seizures

Significant reductions in corrected serum calcium may lower the threshold for seizures. Patients with a history of seizure disorder may be at increased risk for seizures if they develop hypocalcemia due to PARSABIV. Monitor corrected serum calcium in patients with seizure disorders receiving PARSABIV.

Concurrent administration of PARSABIV with another oral calcium-sensing receptor agonist could result in severe, life-threatening hypocalcemia. Patients switching from cinacalcet to PARSABIV should discontinue cinacalcet for at least 7 days prior to initiating PARSABIV *[see Dosage and Administration (2.4) in PARSABIV full prescribing information]*. Closely monitor corrected serum calcium in patients receiving PARSABIV and concomitant therapies known to lower serum calcium.

Measure corrected serum calcium prior to initiation of PARSABIV. Do not initiate in patients if the corrected serum calcium is less than the lower limit of normal. Monitor corrected serum calcium within 1 week after initiation or dose adjustment and every 4 weeks during treatment with PARSABIV *[see Dosage and Administration (2.2) in PARSABIV full prescribing information]*. Educate patients on the symptoms of hypocalcemia, and advise them to contact a healthcare provider if they occur.

If corrected serum calcium falls below the lower limit of normal or symptoms of hypocalcemia develop, start or increase calcium supplementation (including calcium, calcium-containing phosphate binders, and/or vitamin D sterols or increases in dialysate calcium concentration). PARSABIV dose reduction or discontinuation of PARSABIV may be necessary *[see Dosage and Administration (2.2) in PARSABIV full prescribing information]*.

Worsening Heart Failure

In clinical studies with PARSABIV, cases of hypotension, congestive heart failure, and decreased myocardial performance have been reported. In clinical studies, heart failure requiring hospitalization occurred in 2% of PARSABIV-treated patients and 1% of placebo-treated patients. Reductions in corrected serum calcium may be associated with congestive heart failure, however, a causal relationship to PARSABIV could not be completely excluded. Closely monitor patients treated with PARSABIV for worsening signs and symptoms of heart failure.

Upper Gastrointestinal Bleeding

In clinical studies, two patients treated with PARSABIV in 1253 patient-years of exposure had upper gastrointestinal (GI) bleeding noted at the time of death while no patient in the control groups in 384 patient-years of exposure had upper GI bleeding noted at the time of death. The exact cause of GI bleeding in these patients is unknown, and there were too few cases to determine whether these cases were related to PARSABIV.

Patients with risk factors for upper GI bleeding (such as known gastritis, esophagitis, ulcers, or severe vomiting) may be at increased risk for GI bleeding while receiving PARSABIV treatment. Monitor patients for worsening of common GI adverse reactions of nausea and vomiting associated with PARSABIV *[see Adverse Reactions (6.1) in PARSABIV full prescribing information]* and for signs and symptoms of GI bleeding and ulcerations during PARSABIV therapy. Promptly evaluate and treat any suspected GI bleeding.

Adynamic Bone

Adynamic bone may develop if PTH levels are chronically suppressed. If PTH levels decrease below the recommended target range, the dose of vitamin D sterols and/or PARSABIV should be reduced or therapy discontinued. After discontinuation, resume therapy at a lower dose to maintain PTH levels in the target range *[see Dosage and Administration (2.1) in PARSABIV full prescribing information]*.

ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the labeling:

- Hypocalcemia *[see Warnings and Precautions (5.1) in PARSABIV full prescribing information]*
- Worsening Heart Failure *[see Warnings and Precautions (5.2) in PARSABIV full prescribing information]*
- Upper Gastrointestinal Bleeding *[see Warnings and Precautions (5.3) in PARSABIV full prescribing information]*
- Adynamic Bone *[see Warnings and Precautions (5.4) in PARSABIV full prescribing information]*

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The data in Table 2 are derived from two placebo-controlled clinical studies in patients with chronic kidney disease and secondary hyperparathyroidism on hemodialysis. The data reflect exposure of 503 patients to PARSABIV with a mean duration of exposure to PARSABIV of 23.6 weeks. The mean age of patients was approximately 58 years, and 60% of the patients were male. Of the total patients, 67% were Caucasian, 28% were Black or African American, 2.6% were Asian, 1.2% were Native Hawaiian or Other Pacific Islander, and 1.6% were categorized as Other.

Table 2 shows common adverse reactions associated with the use of PARSABIV in the pool of placebo-controlled studies. These adverse reactions occurred more commonly on PARSABIV than on placebo and were reported in at least 5% of patients treated with PARSABIV.

Table 2: Adverse Reactions Reported in ≥ 5% of PARSABIV-Treated Patients

Adverse Reaction*	Placebo (N = 513)	PARSABIV (N = 503)
Blood calcium decreased[a]	10%	64%
Muscle spasms	7%	12%
Diarrhea	9%	11%
Nausea	6%	11%
Vomiting	5%	9%
Headache	6%	8%
Hypocalcemia[b]	0.2%	7%
Paresthesia[c]	1%	6%

*Included adverse reactions reported with at least 1% greater incidence in the PARSABIV group compared to the placebo group

[a] Asymptomatic reductions in calcium below 7.5 mg/dL or clinically significant asymptomatic reductions in corrected serum calcium between 7.5 and < 8.3 mg/dL (that required medical management)

[b] Symptomatic reductions in corrected serum calcium < 8.3 mg/dL

[c] Paresthesia includes preferred terms of paresthesia and hypoesthesia

Other adverse reactions associated with the use of PARSABIV but reported in < 5% of patients in the PARSABIV group in the two placebo-controlled clinical studies were:

- Hyperkalemia: 3% and 4% for placebo and PARSABIV, respectively.
- Hospitalization for Heart Failure: 1% and 2% for placebo and PARSABIV, respectively.
- Myalgia: 0.2% and 2% for placebo and PARSABIV, respectively.
- Hypophosphatemia: 0.2% and 1% for placebo and PARSABIV, respectively.

Description of Selected Adverse Reactions

Hypocalcemia

In the combined placebo-controlled studies, a higher proportion of patients on PARSABIV developed at least one corrected serum calcium value below 7.0 mg/dL (7.6% PARSABIV, 3.1% placebo), below 7.5 mg/dL (27% PARSABIV, 5.5% placebo), and below 8.3 mg/dL (79% PARSABIV, 19% placebo). In the combined placebo-controlled studies, 1% of patients in the PARSABIV group and 0% of patients in the placebo group discontinued treatment due to an adverse reaction attributed to a low corrected serum calcium.

Hypophosphatemia

In the combined placebo-controlled studies, 18% of patients treated with PARSABIV and 8.2% of patients treated with placebo had at least one measured phosphorus level below the lower normal limit (i.e., 2.2 mg/dL).

QTc Interval Prolongation Secondary to Hypocalcemia

In the combined placebo-controlled studies, more patients treated with PARSABIV experienced a maximum increase from baseline of greater than 60 msec in the QTcF interval (0% placebo versus 1.2% PARSABIV). The patient incidence of maximum post-baseline predialysis QTcF > 500 msec in the placebo and PARSABIV groups was 1.9% and 4.8%, respectively.

Hypersensitivity

In the combined placebo-controlled studies, the subject incidence of adverse reactions potentially related to hypersensitivity was 4.4% in the PARSABIV group and 3.7% in the placebo group. Hypersensitivity reactions in the PARSABIV group were pruritic rash, urticaria, and face edema.

Immunogenicity

As with all peptide therapeutics, there is potential for immunogenicity. The detection of anti-drug binding antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to etelcalcetide with the incidence of antibodies to other products may be misleading.

In clinical studies, 7.1% (71 out of 995) of patients with secondary hyperparathyroidism treated with PARSABIV for up to 6 months tested positive for binding anti-etelcalcetide antibodies. Fifty-seven out of 71 had pre-existing anti-etelcalcetide antibodies.

No evidence of altered pharmacokinetic profile, clinical response, or safety profile was associated with pre-existing or developing anti-etelcalcetide antibodies. If formation of anti-etelcalcetide binding antibodies with a clinically significant effect is suspected, contact Amgen at 1-800-77-AMGEN (1-800-772-6436) to discuss antibody testing.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

There are no available data on the use of PARSABIV in pregnant women. In animal reproduction studies, effects were seen at doses associated with maternal toxicity that included hypocalcemia. In a pre- and post-natal study in rats administered etelcalcetide during organogenesis through delivery and weaning, there was a slight increase in perinatal pup mortality, delay in parturition, and transient effects on pup growth at exposures 1.8 times the human exposure for the clinical dose of 15 mg three times per week. There was no effect on sexual maturation, neurobehavioral, or reproductive function in the rat offspring. In embryo-fetal studies, when rats and rabbits were administered etelcalcetide during organogenesis, reduced fetal growth was observed at exposures 2.7 and 7 times exposures for the clinical dose, respectively.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

There were no effects on embryo-fetal development in Sprague-Dawley rats when etelcalcetide was dosed at 0.75, 1.5, and 3 mg/kg/day by the intravenous route during organogenesis (pre-mating to gestation day 17) at exposures up to 1.8 times human exposures at the clinical dose of 15 mg three times per week based on AUC. No effects on embryo-fetal development were observed in New Zealand White rabbits at doses of etelcalcetide of 0.375, 0.75, and 1.5 mg/kg by the intravenous route (gestation day 7 to 19), representing up to 4.3 times human exposures based on AUC. In separate studies at higher doses of 4.5 mg/kg in rats (gestation days 6 to 17) and 2.25 mg/kg in rabbits (gestation days 7 to 20), representing 2.7 and 7 fold clinical exposures, respectively, there was reduced fetal growth associated with maternal toxicities of hypocalcemia, tremoring, and reductions in body weight and food consumption.

In a pre- and post-natal development study in Sprague-Dawley rats administered etelcalcetide at 0.75, 1.5, and 3 mg/kg/day by the intravenous route (gestation day 7 to lactation day 20), there was a slight increase in perinatal pup mortality, delay in parturition, and transient reductions in post-natal growth at 3 mg/kg/day (representing 1.8-fold human exposures at the clinical dose of 15 mg three times per week based on AUC), associated with maternal toxicities of hypocalcemia, tremoring, and reductions in body weight and food consumption. There were no effects on sexual maturation, neurobehavioral, or reproductive function at up to 3 mg/kg/day, representing exposures up to 1.8-fold human exposure based on AUC.

Lactation

Risk Summary

There are no data regarding the presence of PARSABIV in human milk or effects on the breastfed infant or on milk production. Studies in rats showed [^{14}C]-etelcalcetide was present in the milk at concentrations similar to plasma. Because of the potential for PARSABIV to cause adverse effects in breastfed infants including hypocalcemia, advise women that use of PARSABIV is not recommended while breastfeeding.

Data

Presence in milk was assessed following a single intravenous dose of [^{14}C]-etelcalcetide in lactating rats at maternal exposures similar to the exposure at the human clinical dose of 15 mg three times per week. [^{14}C]-etelcalcetide-derived radioactivity was present in milk at levels similar to plasma.

Pediatric Use

The safety and efficacy of PARSABIV have not been established in pediatric patients.

Geriatric Use

Of the 503 patients in placebo-controlled studies who received PARSABIV, 177 patients (35.2%) were ≥ 65 years old and 72 patients (14%) were ≥ 75 years old.

No clinically significant differences in safety or efficacy were observed between patients ≥ 65 years and younger patients (≥ 18 and < 65 years old). No differences in plasma concentrations of etelcalcetide were observed between patients ≥ 65 years and younger patients (≥ 18 and < 65 years old).

OVERDOSAGE

There is no clinical experience with PARSABIV overdosage. Overdosage of PARSABIV may lead to hypocalcemia with or without clinical symptoms and may require treatment. Although PARSABIV is cleared by dialysis, hemodialysis has not been studied as a treatment for PARSABIV overdosage. In the event of overdosage, corrected serum calcium should be checked and patients should be monitored for symptoms of hypocalcemia, and appropriate measures should be taken *[see Warnings and Precautions (5.1) in PARSABIV full prescribing information]*.

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ABSTRACTS

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Serum T50 Test Reflects CAC Progression Risk in CKD

A new serum test of calcification propensity provides useful information on the severity and progression of coronary artery calcification (CAC) in patients with chronic kidney disease, reports the *American Journal of Kidney Diseases*.

The prospective study included patients with stage 2 to 4 CKD, mean age 57.5 years, enrolled in the Chronic Renal Insufficiency Cohort (CRIC) study. Serum calcification propensity was measured as the transformation time from primary to secondary calciprotein particles (T50), with lower T50 values reflecting a higher calcification propensity. The analysis included baseline samples from 1274 patients and follow-up samples (average 3 years) from 780 patients.

On baseline CT scans, 65% of patients had CAC. Median T50 value was 321 minutes. Lower T50 values (higher calcification propensity) were associated with a wide range of factors: non-Hispanic black race/ethnicity, history of cardiovascular disease and diabetes, higher blood pressure, and lower kidney function.

In multivariable-adjusted models, T50 was unrelated to the presence of CAC. However, among patients with prevalent CAC, lower T50 was linked to increased CAC severity: a 21% increase in severity per 1-standard deviation decrease in T50.

During follow-up, 20% of patients developed incident CAC while 19% had progression (annual increase of 100 Agatston units or more) of baseline CAC. On adjusted analysis, T50 was unrelated to the development of new CAC, but was significantly associated with CAC progression. For each 1-standard deviation in T50, the risk of CAC progression increased by 28%.

Coronary artery calcification is common in patients with CKD and is associated with increased cardiovascular risks. By evaluating the transformation from primary to secondary calciprotein particles, the T50 test might provide a useful marker of CAC and the associated risks.

This study finds that a lower serum T50, indicating increased calcification propensity, is associated with greater CAC severity and an increased risk of CAC progression in patients with CKD. The T50 test does not appear to reflect prevalent CAC. Noting that further studies are needed to establish causality, the investigators conclude, "These findings provide valuable insights into the development of calcification and atherosclerosis in patients with CKD and highlight potential pathways for risk stratification and therapeutic intervention" [Bundy JD, et al. Serum calcification propensity and coronary artery calcification among patients with CKD: The CRIC (Chronic Renal Insufficiency Cohort) Study. *Am J Kidney Dis* 2019; https://doi.org/10.1053/j.ajkd.2019.01.024].

Moderate Sodium plus High Potassium Yields Lowest Mortality

The risks of cardiovascular events and mortality are lowest with the combination of moderate sodium intake and higher potassium intake, concludes an international prospective cohort study in the *British Medical Journal*.

The "Prospective Urban Rural Epidemiology" (PURE) study enrolled more than 103,000 adults, aged 35 to 70, from 628 urban and rural communities in low-, middle-, and high-income countries. Twenty-four-hour urinary sodium and potassium excretion were estimated (as surrogates for intake) from morning fasting urine samples.

During a median follow-up of 8 years, 6.1% of patients died or experienced a cardiovascular event. Risks of these outcomes were assessed for participants with low, moderate, and high sodium excretion (less than 3 mg/d, 3 to 5 mg/d, and over 5 mg/d, respectively) and those with high versus low potassium excretion (greater versus equal or less than the median of 2.1 g/d).

Very few individuals—0.002% of the study population—met the World Health Organization target of sodium excretion combined with potassium excretion greater than 3.5 g/d. Risk of the combined outcomes was lowest for individuals

with moderate sodium excretion (3 to 5 g/d) plus higher potassium excretion, who comprised 21.9% of the study population. Compared to this group, hazard ratios were 1.23 for the combination of low sodium/low potassium excretion and 1.21 for high sodium and low potassium excretion. These groups accounted for 7.4% and 13.8% of the study cohort, respectively.

Among participants with higher potassium excretion, hazard ratios were 1.19 for those with low sodium excretion (3.3% of the cohort) and 1.18 for those with high sodium excretion (29.6% of the cohort). The increased cardiovascular risk associated with high sodium excretion was attenuated by potassium excretion above the median.

Current dietary recommendations for adults include a very low sodium intake and high potassium intake. Reported associations with mortality vary for sodium, while most studies report a linear reduction in mortality with higher potassium intake.

A very small percentage of the population meets current recommendations for low sodium intake and high potassium intake, this international study suggests. The risk of cardiovascular events and mortality appears lowest with a combination of moderate sodium intake and high potassium intake, found in about 22% of the PURE study cohort. The researchers conclude: "The J-shaped association of sodium intake with mortality and cardiovascular events does not lend support to the current WHO recommendation to consume low sodium diets (<2.0 g/day), and it also argues against use of the sodium:potassium ratio" [O'Donnell M, et al. Joint association of urinary sodium and potassium excretion with cardiovascular events and mortality: prospective cohort study. *BMJ* 2019; 364:1772].

Higher eGFR Linked to Higher Mortality in Pediatric Dialysis Patients

Exposure to high doses of nonsteroidal anti-inflammatory drugs (NSAIDs) shows a modest but significant association with kidney disease in a military population, reports a study in the open-access journal *JAMA Network Open*.

The retrospective analysis included data on more than 764,000 US Army soldiers on active duty from 2011 through 2014. Eighty-six percent of participants were men; median age was 27 years. Dispensing and dose of prescription NSAIDs were evaluated for association with incident diagnoses of acute kidney injury (AKI) and chronic kidney disease (CKD).

The participants received a total of 1.6 million distinct NSAID prescriptions during the observation period: mean 2.1 prescriptions per person. Nearly two-thirds of personnel had no NSAID prescriptions in the previous 6 months. About 18% were dispensed 1 to 7 mean total daily defined doses (DDDs) per month, while 16% received more than 7 DDDs. There were a total of 2356 AKI outcomes, affecting 0.3% of participants; and 1634 CKD outcomes, affecting 0.2% of participants.

Participants with 7 or more DDDs per month had significant increases in both kidney disease outcomes: adjusted hazard ratio 1.2 for both AKI and CKD. At this level of exposure, there were 17.6 additional cases of AKI and 30.0 additional cases of CKD per 100,000 exposed individuals. Obese individuals were at significantly increased risk of both outcomes: adjusted hazard ratio 1.5 for AKI and 1.6 for CKD. The hazards were more than doubled for individuals with a history of hypertension and rhabdomyolysis. For diabetes, the hazard ratio was 1.8 for both outcomes.

Most studies of NSAID associations with kidney disease have focused on older adults or patients with chronic diseases. There has been little concern about the renal effects of these widely used medications in young, healthy adults. Some studies have suggested a possible increase in kidney disease risk among NSAID users engaging in endurance exercise.

This large study of Army personnel finds "modest but statistically significant" associations between high doses of NSAIDs and the risk of acute and chronic kidney disease outcomes. "Dosage reduction represents an approach that may decrease associated kidney disease outcome rates," the researchers write. They also note the contribution of modifiable factors such as body mass index and hypertension [Nelson DA, et al. Association of nonsteroidal anti-inflammatory drug prescriptions with kidney disease among active young and middle-aged adults. *JAMA Netw Open* 2019; 2 (2):e187896. doi:10.1001/jamanetworkopen.2018.7896].

Industry Spotlight

Pain-Free Glucose Monitoring

Abbott Laboratories (Chicago, IL) currently leads the market in pain-free glucose monitoring, Crain's Chicago Business reports. Abbott offers the FreeStyle Libre, which measures glucose via a sensor without fingersticks. According to Crain's, Abbott's device has more than 1.3 million users worldwide and posted 37% sales growth to $1.9 billion in 2018.

Dexcom (San Diego, CA) and Medtronic (Minneapolis, MN) also offer pain-free monitors. The latest Dexcom device, the G6 CGM, warns users of an urgently low or high level of glucose minutes before it hits. Data can also be shared with others through smart devices, for example, with parents who would like to be able to know about dangerously low glucose levels in their children.

According to the Business Wire, the new report "Blood Glucose Monitoring Devices Market—Global Outlook and Forecast 2019–2024" forecasts market revenues of more than $25 billion by 2024. Conventional devices like self-blood glucose testing (with fingersticks) still represented two-thirds of the total market in 2018.

New Pharma/Device Deals

The US Food and Drug Administration (FDA) has approved a new stent for use in the treatment of kidney failure patients who are on hemodialysis.

Bard, now a part of healthcare tech giant Becton Dickinson (Franklin Lakes, NJ) was the originator of the Covera vascular covered stent. The stent, which is used to re-open narrowed access circuits in an arteriovenous fistula, has a "helical design for radial strength and flexibility" and an "atraumatic" tip for insertion comfort, according to CRBard.com. According to Becton Dickinson, it is the first and only covered stent to be approved in the US market for treating stenoses in non-stented fistulae.

Bard joined Becton Dickinson in December 2017, in a $24 billion acquisition.

Baxter (Deerfield, IL) and bioMérieux (Marcy L'Etoile, France) have signed a deal to partner in the development of biomarkers to identify and help inform treatment of acute kidney injury (AKI). In April 2019, bioMérieux acquired Astute Medical (San Diego, CA), which developed the NEPHROCHECK test, an FDA-approved test for early risk assessment of AKI based on two biomarker levels.

"As a leader in pioneering diagnostic solutions, we're looking forward to collaborating with Baxter. . . . To accomplish this, the team at the recently acquired Astute Medical is committed to the development of additional high medical value biomarkers for improved patient care," said Mark Miller, bioMérieux executive VP and chief medical officer.

Akebia, based in Cambridge, MA, has expanded its pharmaceutical deal with Vifor Pharma to extend beyond one dialysis firm, Fresenius North America. The two companies drew up a new license agreement that would allow Vifor to sell vadadustat to certain third-party dialysis organizations for use in the United States. Vadadustat is an investigational oral hypoxia-inducible factor prolyl hydroxylase inhibitor in phase 3 development and is intended for anemia treatment in patients with chronic kidney disease (CKD). The drug is not yet approved by any regulatory authority.

The deal, according to the companies, could expand the potential opportunity for vadadustat under the agreement to include "up to 60% of US dialysis patients." The expanded license agreement is subject to vadadustat's approval by the FDA and also its inclusion in the Centers for Medicare & Medicaid Services ESRD Prospective Payment System.

Rural Dialysis Focus

Rural dialysis does not pay as well as dialysis in urban facilities, according to a recent report from the Medicare Payment Advisory Commission (MedPAC).

The March 2019 report noted that facilities with high volumes of dialysis earned higher margins because cost per treatment falls with efficiencies, and that urban facilities had higher financial margins (-0.4%) than do rural facilities (–5.5%).

Treatment volume accounted for most of the differential in margins between urban and rural facilities. In 2017, urban facilities averaged about 12,000 treatments, while rural facilities each performed about 7800 treatments. A "low-volume facility" is defined as one that provides fewer than 4000 treatments total in each of three years before the payment year and with certain unchanged ownership criteria. A volume of 4000 treatments is the cutoff at which facilities receive more funds—a low-volume Medicare program adjustment of 23.9%. MedPAC staff member Nancy Ray noted a "so-called 'cliff effect' might be encouraging some facilities to limit services," so they can keep their increased funding, according to Modern Healthcare.

Distance is a focus of the report, which highlighted that about 47% of facilities that receive the low-volume program adjustment of 23.9% under the prospective payment system are still within five miles of the next closest facility, while MedPAC wants the low-volume and rural payment adjustments to "focus on protecting only facilities that are critical to beneficiary access."

In a statement, Chief Medical Officer Jeffrey Hymes, MD, of Fresenius Kidney Care, said that his company is pursuing more use of home dialysis and telehealth services to help "reduce these disparities and improve outcomes" for those who need treatment for kidney failure in rural areas. He also noted that the average distance to dialysis facilities in rural areas is at a minimum 2.5 times farther than average travel distances to urban facilities.

DaVita has been working to improve outcomes in rural dialysis centers. The company touted its outcomes for rural and low-income facilities under the Medicare ESRD Quality Incentive Program, which reduces payments if facilities do not meet or exceed certain performance standards. In 2018, DaVita said it achieved a 21% reduction in rural and low income centers that missed the top clinical tier since the program's inception in 2012. The company stated that rural and low-income areas present the greatest challenges to delivering top-tier clinical results.

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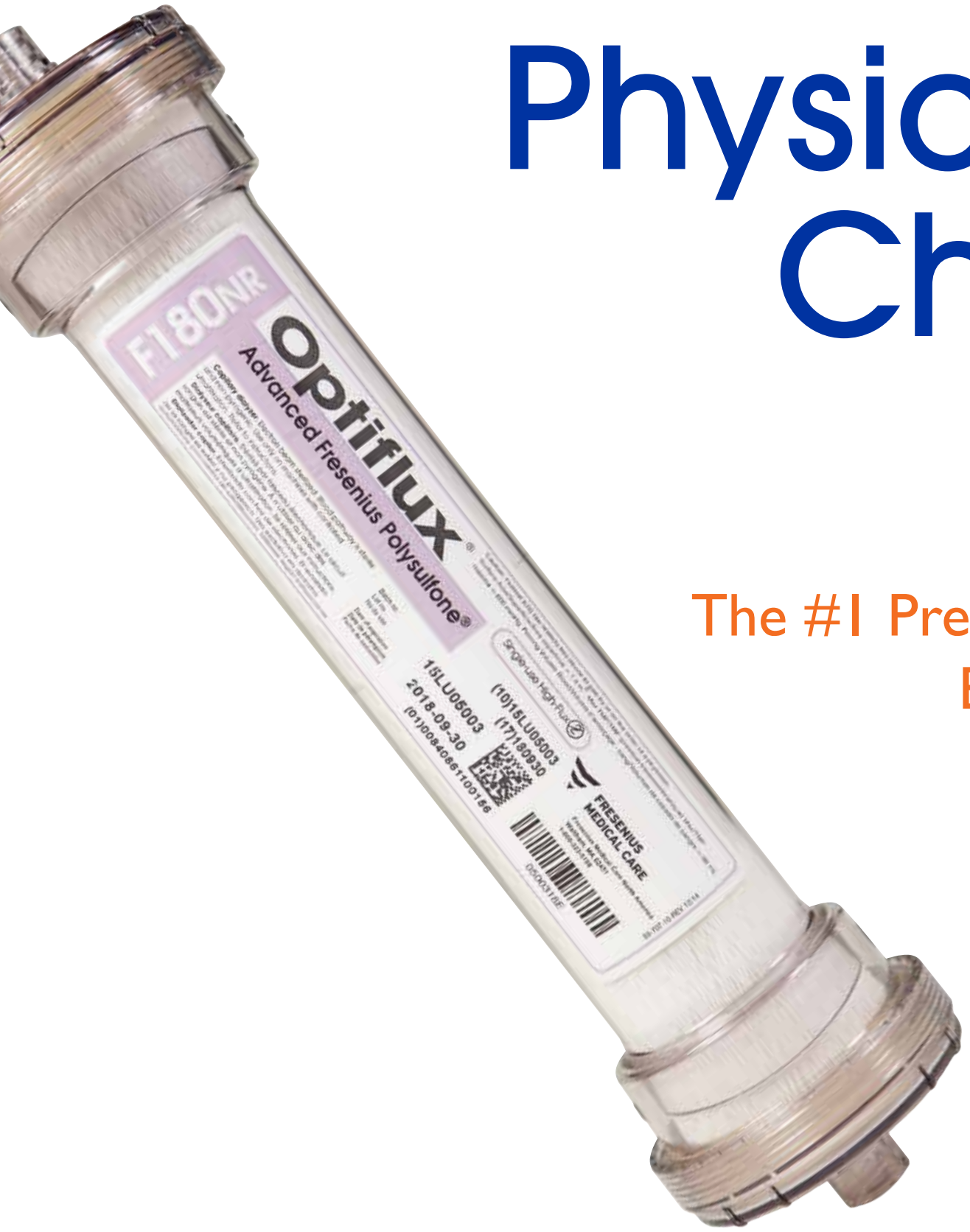

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