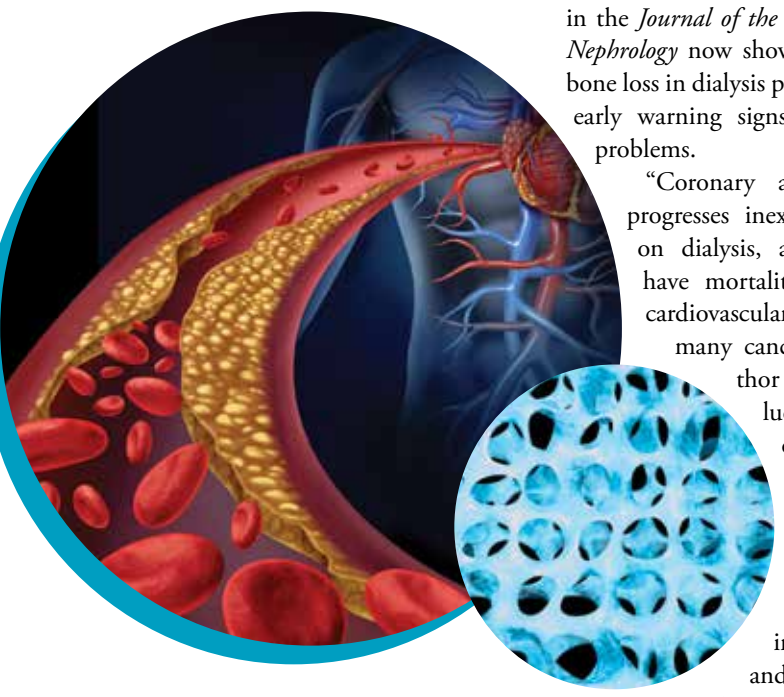
ASN LEADING THE FIGHT AGAINST KIDNEY DISEASE

KidneyNews

May 2015 | Vol. 7, Number 5

Hormone and Bone Tests May Predict Progression of Coronary Artery Calcification in Patients on Dialysis



Many patients with chronic kidney disease (CKD) and end stage renal disease exhibit coronary artery calcification as well as low bone mass. A new study published in the *Journal of the American Society of Nephrology* now shows that monitoring bone loss in dialysis patients may provide early warning signs of cardiovascular problems.

"Coronary artery calcification progresses inexorably in patients on dialysis, and these patients have mortality rates related to cardiovascular events worse than many cancers," said lead author Hartmut Malluche, MD, FACP, of the University of Kentucky. "The link between bone and vascular calcifications is a potentially very important avenue, and studies need to be done to find out whether prevention of bone loss will reduce progression of vascular calcifications."

Malluche and his team noted that no information is available on the use of noninvasive bone mass assessments—such as dual energy x-ray absorptiometry or quantitative computed tomography—for predicting progression of coronary artery calcification. There's also little information on how traditional and novel serum biochemical parameters relate to progression.

To fill these gaps, the researchers conducted tests to analyze abnormalities in blood, bone, and heart vessels in 213 patients on dialysis over a 1-year period. About 80% of the patients had measurable coronary artery calcification at baseline, and almost 50% had levels that confer a high risk for cardiovascular events.

Independent positive predictors of baseline coronary artery calcification included coronary artery disease, diabetes, dialysis vintage, fibroblast growth factor-23 concentration, and age.

Bone mineral density of the spine measured by quantitative computed tomography was an inverse predictor. Contrary to other studies, the investigators did not find a sex difference in baseline coronary artery calcification. Baseline coronary

Continued on page 5

Latest ASN Initiatives to Support Nephrology: Match, All-In Policy

Applications to Nephrology fellowships have declined significantly since 2010, yet the number of training opportunities has increased. Nephrology fellowship programs increased from 127 in 2000 to 147 in 2013, and the number of fellows in the first or second year of training jumped from 626 to 930 in that time period. However, the number of applicants participating declined from 576 in 2010 to an all-time low of 254 in the Match for the 2015 appointment year.

The Nephrology Match was designed to provide applicants and program directors opportunities to thoughtfully consider all options. Position offers to applicants outside the Match sometimes exert pressure on applicants to make early decisions, and degrade confidence in the integrity of the Match process.

As the sponsoring organization for the Match, the American Society of Nephrology (ASN) convened a Nephrology Match Task Force in January 2015 to review principles and practices of the Match and recommend improvements. The Task

Continued on page 5

Inside

INDICATION and Important Limitations

- SAMSCA is indicated for the treatment of clinically significant hypervolemic and euvolemic hyponatremia (serum sodium <125 mEq/L or less marked hyponatremia that is symptomatic and has resisted correction with fluid restriction), including patients with heart failure, and Syndrome of Inappropriate Antidiuretic Hormone (SIADH)
- Patients requiring intervention to raise serum sodium urgently to prevent or to treat serious neurological symptoms should not be treated with SAMSCA. It has not been established that raising serum sodium with SAMSCA provides a symptomatic benefit to patients

IMPORTANT SAFETY INFORMATION

SAMSCA should be initiated and re-initiated in patients only in a hospital where serum sodium can be monitored closely. Too rapid correction of hyponatremia (e.g., >12 mEq/L/24 hours) can cause osmotic demyelination resulting in dysarthria, mutism, dysphagia, lethargy, affective changes, spastic quadriparesis, seizures, coma and death. In susceptible patients, including those with severe malnutrition, alcoholism or advanced liver disease, slower rates of correction may be advisable

Contraindications: Urgent need to raise serum sodium acutely, inability of the patient to sense or appropriately respond to thirst, hypovolemic hyponatremia, concomitant use of strong CYP 3A inhibitors, anuric patients, and hypersensitivity (e.g. anaphylactic shock, rash generalized) to tolvaptan or its components

Warnings and Precautions:

- Subjects with SIADH or very low baseline serum sodium concentrations may be at greater risk for too-rapid correction of serum sodium. In patients receiving SAMSCA who develop too rapid a rise in serum sodium or develop neurologic sequelae, discontinue or interrupt treatment with SAMSCA and consider administration of hypotonic fluid. Fluid restriction should generally be avoided during the first 24 hours
- SAMSCA can cause serious and potentially fatal liver injury. Avoid use in patients with underlying liver disease, including cirrhosis, because the ability to recover may be impaired. Limit duration of therapy with SAMSCA to 30 days
- Dehydration and hypovolemia can occur, especially in potentially volume-depleted patients receiving diuretics or those who are fluid restricted. In patients who develop medically significant signs or symptoms of hypovolemia, discontinuation is recommended
- Co-administration with hypertonic saline is not recommended
- Avoid concomitant use with: CYP 3A inhibitors and CYP 3A inducers. The dose of SAMSCA may have to be reduced if co-administered with P-gp inhibitors
- Monitor serum potassium levels in patients with a serum potassium >5 mEq/L and in patients receiving drugs known to increase serum potassium levels

Adverse Reactions - The most common adverse reactions (SAMSCA incidence ≥5% more than placebo, respectively): thirst (16% vs 5%), dry mouth (13% vs 4%), asthenia (9% vs 4%), constipation (7% vs 2%), pollakiuria or polyuria (11% vs 3%) and hyperglycemia (6% vs 1%)

Gastrointestinal Bleeding in Patients with Cirrhosis – In patients with cirrhosis in the hyponatremia trials, GI bleeding was reported in 10% of tolvaptan-treated patients vs 2% for placebo

Please see Brief Summary of FULL PRESCRIBING INFORMATION, including Boxed WARNING, on following page.

Manufactured by Otsuka Pharmaceutical Co., Ltd., Tokyo, 101-8535 Japan.
Distributed and marketed by Otsuka America Pharmaceutical, Inc., Rockville, MD 20850.
SAMSCA is a registered trademark of Otsuka Pharmaceutical Co., Ltd., Tokyo, 101-8535 Japan.

For more information please visit SAMSCA.com

Otsuka
Otsuka America Pharmaceutical, Inc.

June 2014

07US14EBP2751

SAMSCA® (tolvaptan) tablets for oral use

Brief Summary of Prescribing Information. Please see Full Prescribing Information for complete product information.

WARNING: INITIATE AND RE-INITIATE IN A HOSPITAL AND MONITOR SERUM SODIUM

SAMSCA should be initiated and re-initiated in patients only in a hospital where serum sodium can be monitored closely. Too rapid correction of hyponatremia (e.g., >12 mEq/L/24 hours) can cause osmotic demyelination resulting in dysarthria, mutism, dysphagia, lethargy, affective changes, spastic quadriparesis, seizures, coma and death. In susceptible patients, including those with severe malnutrition, alcoholism or advanced liver disease, slower rates of correction may be advisable.

INDICATIONS AND USAGE: SAMSCA is indicated for the treatment of clinically significant hypervolemic and euvolemic hyponatremia (serum sodium <125 mEq/L or less marked hyponatremia that is symptomatic and has resisted correction with fluid restriction), including patients with heart failure and Syndrome of Inappropriate Antidiuretic Hormone (SIADH).

Important Limitations: Patients requiring intervention to raise serum sodium urgently to prevent or to treat serious neurological symptoms should not be treated with SAMSCA. It has not been established that raising serum sodium with SAMSCA provides a symptomatic benefit to patients.

CONTRAINDICATIONS: SAMSCA is contraindicated in the following conditions:

Urgent need to raise serum sodium acutely: SAMSCA has not been studied in a setting of urgent need to raise serum sodium acutely.

Inability of the patient to sense or appropriately respond to thirst: Patients who are unable to auto-regulate fluid balance are at substantially increased risk of incurring an overly rapid correction of serum sodium, hypernatremia and hypovolemia.

Hypovolemic hyponatremia: Risks associated with worsening hypovolemia, including complications such as hypotension and renal failure, outweigh possible benefits.

Concomitant use of strong CYP 3A inhibitors: Ketoconazole 200 mg administered with tolvaptan increased tolvaptan exposure by 5-fold. Larger doses would be expected to produce larger increases in tolvaptan exposure. There is not adequate experience to define the dose adjustment that would be needed to allow safe use of tolvaptan with strong CYP 3A inhibitors such as clarithromycin, ketoconazole, itraconazole, ritonavir, indinavir, nelfinavir, saquinavir, nefazodone, and telithromycin.

Anuric patients: In patients unable to make urine, no clinical benefit can be expected.

Hypersensitivity: SAMSCA is contraindicated in patients with hypersensitivity (e.g. anaphylactic shock, rash generalized) to tolvaptan or any component of the product *[see Adverse Reactions (6.2)]*.

WARNINGS AND PRECAUTIONS:

Too Rapid Correction of Serum Sodium Can Cause Serious Neurologic Sequelae (see BOXED WARNING): Osmotic demyelination syndrome is a risk associated with too rapid correction of hyponatremia (e.g., >12 mEq/L/24 hours). Osmotic demyelination results in dysarthria, mutism, dysphagia, lethargy, affective changes, spastic quadriparesis, seizures, coma or death. In susceptible patients including those with severe malnutrition, alcoholism or advanced liver disease, slower rates of correction may be advisable. In controlled clinical trials in which tolvaptan was administered in titrated doses starting at 15 mg once daily, 7% of tolvaptan-treated subjects with a serum sodium <130 mEq/L had an increase in serum sodium greater than 8 mEq/L at approximately 8 hours and 2% had an increase greater than 12 mEq/L at 24 hours. Approximately 1% of placebo-treated subjects with a serum sodium <130 mEq/L had a rise greater than 8 mEq/L at 8 hours and no patient had a rise greater than 12 mEq/L/24 hours. Osmotic demyelination syndrome has been reported in association with SAMSCA therapy *[see Adverse Reactions (6.2)]*. Patients treated with SAMSCA should be monitored to assess serum sodium concentrations and neurologic status, especially during initiation and after titration. Subjects with SIADH or very low baseline serum sodium concentrations may be at greater risk for too-rapid correction of serum sodium. In patients receiving SAMSCA who develop too rapid a rise in serum sodium, discontinue or interrupt treatment with SAMSCA and consider administration of hypotonic fluid. Fluid restriction during the first 24 hours of therapy with SAMSCA may increase the likelihood of overly-rapid correction of serum sodium, and should generally be avoided.

Liver Injury: SAMSCA can cause serious and potentially fatal liver injury. In a placebo-controlled and open label extension study of chronically administered tolvaptan in patients with autosomal dominant polycystic kidney disease, cases of serious liver injury attributed to tolvaptan were observed. An increased incidence of ALT greater than three times the upper limit of normal was associated with tolvaptan (42/958 or 4.4%) compared to placebo (5/484 or 1.0%). Cases of serious liver injury were generally observed starting 3 months after initiation of tolvaptan although elevations of ALT occurred prior to 3 months. Patients with symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine or jaundice should discontinue treatment with SAMSCA. Limit duration of therapy with SAMSCA to 30 days. Avoid use in patients with underlying liver disease, including cirrhosis, because the ability to recover from liver injury may be impaired. *[see Adverse Reactions (6.1)]*.

Dehydration and Hypovolemia: SAMSCA therapy induces copious aquaresis, which is normally partially offset by fluid intake. Dehydration and hypovolemia can occur, especially in potentially volume-depleted patients receiving diuretics or those who are fluid restricted. In multiple-dose, placebo-controlled trials in which 607 hyponatremic patients were treated with tolvaptan, the incidence of dehydration was 3.3% for tolvaptan and 1.5% for placebo-treated patients. In patients receiving SAMSCA who develop medically significant signs or symptoms of hypovolemia, interrupt or discontinue SAMSCA therapy and provide supportive care with careful management of vital signs, fluid balance and electrolytes. Fluid restriction during therapy with SAMSCA may increase the risk of dehydration and hypovolemia. Patients receiving SAMSCA should continue ingestion of fluid in response to thirst.

Co-administration with Hypertonic Saline: Concomitant use with hypertonic saline is not recommended.

Drug Interactions:

Other Drugs Affecting Exposure to Tolvaptan:

CYP 3A Inhibitors: Tolvaptan is a substrate of CYP 3A. CYP 3A inhibitors can lead to a marked increase in tolvaptan concentrations *[see Dosage and Administration (2.3), Drug Interactions (7.1)]*.

Do not use SAMSCA with strong inhibitors of CYP 3A *[see Contraindications (4.4)]* and avoid concomitant use with moderate CYP 3A inhibitors.

CYP 3A Inducers: Avoid co-administration of CYP 3A inducers (e.g., rifampin, rifabutin, rifapentin, barbiturates, phenytoin, carbamazepine, St. John's Wort) with SAMSCA, as this can lead to a reduction in the plasma concentration of tolvaptan and decreased effectiveness of SAMSCA treatment. If co-administered with CYP 3A inducers, the dose of SAMSCA may need to be increased *[see Dosage and Administration (2.3), Drug Interactions (7.1)]*.

P-gp Inhibitors: The dose of SAMSCA may have to be reduced when SAMSCA is co-administered with P-gp inhibitors, e.g., cyclosporine *[see Dosage and Administration (2.3), Drug Interactions (7.1)]*.

Hyperkalemia or Drugs that Increase Serum Potassium: Treatment with tolvaptan is associated with an acute reduction of the extracellular fluid volume which could result in increased serum potassium. Serum potassium levels should be monitored after initiation of tolvaptan treatment in patients with a serum potassium >5 mEq/L as well as those who are receiving drugs known to increase serum potassium levels.

ADVERSE REACTIONS:

Clinical Trials Experience: Because clinical trials are conducted under widely varying conditions, adverse reactions rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The adverse event information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates. In multiple-dose, placebo-controlled trials, 607 hyponatremic patients (serum sodium <135 mEq/L) were treated with SAMSCA. The mean age of these patients was 62 years; 70% of patients were male and 82% were Caucasian. One hundred eighty nine (189) tolvaptan-treated patients had a serum sodium <130 mEq/L, and 52 patients had a serum sodium <125 mEq/L. Hyponatremia was attributed to cirrhosis in 17% of patients, heart failure in 68% and SIADH/other in 16%. Of these patients, 223 were treated with the recommended dose titration (15 mg titrated to 60 mg as needed to raise serum sodium). Overall, over 4,000 patients have been treated with oral doses of tolvaptan in open-label or placebo-controlled clinical trials. Approximately 650 of these patients had hyponatremia; approximately 219 of these hyponatremic patients were treated with tolvaptan for 6 months or more. The most common adverse reactions (incidence ≥5% more than placebo) seen in two 30-day, double-blind, placebo-controlled hyponatremia trials in which tolvaptan was administered in titrated doses (15 mg to 60 mg once daily) were thirst, dry mouth, asthenia, constipation, pollakiuria or polyuria and hyperglycemia. In these trials, 10% (23/223) of tolvaptan-treated patients discontinued treatment because of an adverse event, compared to 12% (26/220) of placebo-treated patients; no adverse reaction resulting in discontinuation of trial medication occurred at an incidence of >1% in tolvaptan-treated patients.

Table 1 lists the adverse reactions reported in tolvaptan-treated patients with hyponatremia (serum sodium <135 mEq/L) and at a rate at least 2% greater than placebo-treated patients in two 30-day, double-blind, placebo-controlled trials. In these studies, 223 patients were exposed to tolvaptan (starting dose 15 mg, titrated to 30 and 60 mg as needed to raise serum sodium). Adverse events resulting in death in these trials were 6% in tolvaptan-treated-patients and 6% in placebo-treated patients.

Table 1. Adverse Reactions (>2% more than placebo) in Tolvaptan-Treated Patients in Double-Blind, Placebo-Controlled Hyponatremia Trials

System Organ Class MedDRA Preferred Term	Tolvaptan 15 mg/day-60 mg/day (N = 223) n (%)	Placebo (N = 220) n (%)
Gastrointestinal Disorders		
Dry mouth	28 (13)	9 (4)
Constipation	16 (7)	4 (2)
General Disorders and Administration Site Conditions		
Thirst[a]	35 (16)	11 (5)
Asthenia	19 (9)	9 (4)
Pyrexia	9 (4)	2 (1)
Metabolism and Nutrition Disorders		
Hyperglycemia[b]	14 (6)	2 (1)
Anorexia[c]	8 (4)	2 (1)
Renal and Urinary Disorders		
Pollakiuria or polyuria[d]	25 (11)	7 (3)

The following terms are subsumed under the referenced ADR in Table 1:

[a]polydipsia; [b]diabetes mellitus; [c]decreased appetite; [d]urine output increased, micturition, urgency, nocturia

In a subgroup of patients with hyponatremia (N = 475, serum sodium <135 mEq/L) enrolled in a double-blind, placebo-controlled trial (mean duration of treatment was 9 months) of patients with worsening heart failure, the following adverse reactions occurred in tolvaptan-treated patients at a rate at least 2% greater than placebo: mortality (42% tolvaptan, 38% placebo), nausea (21% tolvaptan, 16% placebo), thirst (12% tolvaptan, 2% placebo), dry mouth (7% tolvaptan, 2% placebo) and polyuria or pollakiuria (4% tolvaptan, 1% placebo).

Gastrointestinal bleeding in patients with cirrhosis: In patients with cirrhosis treated with tolvaptan in the hyponatremia trials, gastrointestinal bleeding was reported in 6 out of 63 (10%) tolvaptan-treated patients and 1 out of 57 (2%) placebo treated patients. The following adverse reactions occurred in <2% of hyponatremic patients treated with SAMSCA and at a rate greater than placebo in double-blind placebo-controlled trials (N = 607 tolvaptan; N = 518 placebo) or in <2% of patients in an uncontrolled trial of patients with hyponatremia (N = 111) and are not mentioned elsewhere in the label: *Blood and Lymphatic System Disorders: Disseminated intravascular coagulation; Cardiac Disorders: Intracardiac thrombus, ventricular fibrillation; Investigations: Prothrombin time prolonged; Gastrointestinal Disorders: Ischemic colitis; Metabolism and Nutrition Disorders: Diabetic ketoacidosis; Musculoskeletal and Connective Tissue Disorders: Rhabdomyolysis; Nervous System: Cerebrovascular accident; Renal and Urinary Disorders: Urethral hemorrhage; Reproductive System and Breast Disorders (female): Vaginal hemorrhage; Respiratory, Thoracic, and Mediastinal Disorders: Pulmonary embolism, respiratory failure; Vascular disorder: Deep vein thrombosis.*

Postmarketing Experience: The following adverse reactions have been identified during post-approval use of SAMSCA. Because these reactions are reported voluntarily from a population of an unknown size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Neurologic: Osmotic demyelination syndrome; *Investigations:* Hypernatremia. Removal of excess free body water increases serum osmolality and serum sodium concentrations. All patients treated with tolvaptan, especially those whose serum sodium levels become normal, should continue to be monitored to ensure serum sodium remains within normal limits. If hypernatremia is observed, management may include dose decreases or interruption of tolvaptan treatment, combined with modification of free-water intake or infusion. During clinical trials of hyponatremic patients, hypernatremia was reported as an adverse event in 0.7% of patients receiving tolvaptan vs. 0.6% of patients receiving placebo; analysis of laboratory values demonstrated an incidence of hypernatremia of 1.7% in patients receiving tolvaptan vs. 0.8% in patients receiving placebo. *Immune System Disorders:* Hypersensitivity reactions including anaphylactic shock and rash generalized *[see Contraindications (4.6)]*.

DRUG INTERACTIONS:

Effects of Drugs on Tolvaptan:

Ketoconazole and Other Strong CYP 3A Inhibitors: SAMSCA is metabolized primarily by CYP 3A. Ketoconazole is a strong inhibitor of CYP 3A and also an inhibitor of P-gp. Co-administration of SAMSCA and ketoconazole 200 mg daily results in a 5-fold increase in exposure to tolvaptan. Co-administration of SAMSCA with 400 mg ketoconazole daily or with other strong CYP 3A inhibitors (e.g., clarithromycin, itraconazole, telithromycin, saquinavir, nelfinavir, ritonavir and nefazodone) at the highest labeled dose would be expected to cause an even greater increase in tolvaptan exposure. Thus, SAMSCA and strong CYP 3A inhibitors should not be co-administered *[see Dosage and Administration (2.3) and Contraindications (4.4)]*.

Moderate CYP 3A Inhibitors: The impact of moderate CYP 3A inhibitors (e.g., erythromycin, fluconazole, aprepitant, diltiazem and verapamil) on the exposure to co-administered tolvaptan has not been assessed. A substantial increase in the exposure to tolvaptan would be expected when SAMSCA is co-administered with moderate CYP 3A inhibitors. Co-administration of SAMSCA with moderate CYP3A inhibitors should therefore generally be avoided *[see Dosage and Administration (2.3) and Warnings and Precautions (5.5)]*. **Grapefruit Juice:** Co-administration of grapefruit juice and SAMSCA results in a 1.8-fold increase in exposure to tolvaptan *[see Dose and Administration (2.3) and Warnings and Precautions (5.5)]*. **P-gp Inhibitors:** Reduction in the dose of SAMSCA may be required in patients concomitantly treated with P-gp inhibitors, such as e.g., cyclosporine, based on clinical response *[see Dose and Administration (2.3) and Warnings and Precautions (5.5)]*. **Rifampin and Other CYP 3A Inducers:** Rifampin is an inducer of CYP 3A and P-gp. Co-administration of rifampin and SAMSCA reduces exposure to tolvaptan by 85%. Therefore, the expected clinical effects of SAMSCA in the presence of rifampin and other inducers (e.g., rifabutin, rifapentin, barbiturates, phenytoin, carbamazepine and St. John's Wort) may not be observed at the usual dose levels of SAMSCA. The dose of SAMSCA may have to be increased *[Dosage and Administration (2.3) and Warnings and Precautions (5.5)]*. **Lovastatin, Digoxin, Furosemide, and Hydrochlorothiazide:** Co-administration of lovastatin, digoxin, furosemide, and hydrochlorothiazide with SAMSCA has no clinically relevant impact on the exposure to tolvaptan.

Effects of Tolvaptan on Other Drugs: Digoxin: Digoxin is a P-gp substrate. Co-administration of SAMSCA with digoxin increased digoxin AUC by 20% and Cmax by 30%. **Warfarin, Amiodarone, Furosemide, and Hydrochlorothiazide:** Co-administration of tolvaptan does not appear to alter the pharmacokinetics of warfarin, furosemide, hydrochlorothiazide, or amiodarone (or its active metabolite, desethylamiodarone) to a clinically significant degree. **Lovastatin:** SAMSCA is a weak inhibitor of CYP 3A. Co-administration of lovastatin and SAMSCA increases the exposure to lovastatin and its active metabolite lovastatin-β hydroxyacid by factors of 1.4 and 1.3, respectively. This is not a clinically relevant change.

Pharmacodynamic Interactions: Tolvaptan produces a greater 24 hour urine volume/excretion rate than does furosemide or hydrochlorothiazide. Concomitant administration of tolvaptan with furosemide or hydrochlorothiazide results in a 24 hour urine volume/excretion rate that is similar to the rate after tolvaptan administration alone. Although specific interaction studies were not performed, in clinical studies tolvaptan was used concomitantly with beta-blockers, angiotensin receptor blockers, angiotensin converting enzyme inhibitors and potassium sparing diuretics. Adverse reactions of hyperkalemia were approximately 1-2% higher when tolvaptan was administered with angiotensin receptor blockers, angiotensin converting enzyme inhibitors and potassium sparing diuretics compared to administration of these medications with placebo. Serum potassium levels should be monitored during concomitant drug therapy. As a V_2 receptor antagonist, tolvaptan may interfere with the V_2 agonist activity of desmopressin (dDAVP). In a male subject with mild Von Willebrand (vW) disease, intravenous infusion of dDAVP 2 hours after administration of oral tolvaptan did not produce the expected increases in vW Factor Antigen or Factor VIII activity. It is not recommended to administer SAMSCA with V_2 agonist.

USE IN SPECIFIC POPULATIONS: There is no need to adjust dose based on age, gender, race, or cardiac function *[see Clinical Pharmacology (12.3)]*.

Pregnancy: Pregnancy Category C. There are no adequate and well controlled studies of SAMSCA use in pregnant women. In animal studies, cleft palate, brachymelia, microphthalmia, skeletal malformations, decreased fetal weight, delayed fetal ossification, and embryo-fetal death occurred. SAMSCA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. In embryo-fetal development studies, pregnant rats and rabbits received oral tolvaptan during organogenesis. Rats received 2 to 162 times the maximum recommended human dose (MRHD) of tolvaptan (on a body surface area basis). Reduced fetal weights and delayed fetal ossification occurred at 162 times the MRHD. Signs of maternal toxicity (reduction in body weight gain and food consumption) occurred at 16 and 162 times the MRHD. When pregnant rabbits received oral tolvaptan at 32 to 324 times the MRHD (on a body surface area basis), there were reductions in maternal body weight gain and food consumption at all doses, and increased abortions at the mid and high doses (about 97 and 324 times the MRHD). At 324 times the MRHD, there were increased rates of embryo-fetal death, fetal microphthalmia, open eyelids, cleft palate, brachymelia and skeletal malformations *[see Nonclinical Toxicology (13.3)]*.

Labor and Delivery: The effect of SAMSCA on labor and delivery in humans is unknown.

Nursing Mothers: It is not known whether SAMSCA is excreted into human milk. Tolvaptan is excreted into the milk of lactating rats. Because many drugs are excreted into human milk and because of the potential for serious adverse reactions in nursing infants from SAMSCA, a decision should be made to discontinue nursing or SAMSCA, taking into consideration the importance of SAMSCA to the mother.

Pediatric Use: Safety and effectiveness of SAMSCA in pediatric patients have not been established.

Geriatric Use: Of the total number of hyponatremic subjects treated with SAMSCA in clinical studies, 42% were 65 and over, while 19% were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. Increasing age has no effect on tolvaptan plasma concentrations.

Use in Patients with Hepatic Impairment: Moderate and severe hepatic impairment do not affect exposure to tolvaptan to a clinically relevant extent. No dose adjustment of tolvaptan is necessary. Avoid use of tolvaptan in patients with underlying liver disease.

Use in Patients with Renal Impairment: No dose adjustment is necessary based on renal function. There are no clinical trial data in patients with CrCl <10 mL/min, and, because drug effects on serum sodium levels are likely lost at very low levels of renal function, use in patients with a CrCl <10 mL/min is not recommended. No benefit can be expected in patients who are anuric *[see Contraindications 4.5) and Clinical Pharmacology (12.3)]*.

Use in Patients with Congestive Heart Failure: The exposure to tolvaptan in patients with congestive heart failure is not clinically relevantly increased. No dose adjustment is necessary.

OVERDOSAGE: Single oral doses up to 480 mg and multiple doses up to 300 mg once daily for 5 days have been well tolerated in studies in healthy subjects. There is no specific antidote for tolvaptan intoxication. The signs and symptoms of an acute overdose can be anticipated to be those of excessive pharmacologic effect: a rise in serum sodium concentration, polyuria, thirst, and dehydration/hypovolemia. The oral LD50 of tolvaptan in rats and dogs is >2000 mg/kg. No mortality was observed in rats or dogs following single oral doses of 2000 mg/kg (maximum feasible dose). A single oral dose of 2000 mg/kg was lethal in mice, and symptoms of toxicity in affected mice included decreased locomotor activity, staggering gait, tremor and hypothermia.

If overdose occurs, estimation of the severity of poisoning is an important first step. A thorough history and details of overdose should be obtained, and a physical examination should be performed. The possibility of multiple drug involvement should be considered. Treatment should involve symptomatic and supportive care, with respiratory, ECG and blood pressure monitoring and water/electrolyte supplements as needed. A profuse and prolonged aquaresis should be anticipated, which, if not matched by oral fluid ingestion, should be replaced with intravenous hypotonic fluids, while closely monitoring electrolytes and fluid balance.

ECG monitoring should begin immediately and continue until ECG parameters are within normal ranges. Dialysis may not be effective in removing tolvaptan because of its high binding affinity for human plasma protein (>99%). Close medical supervision and monitoring should continue until the patient recovers.

PATIENT COUNSELING INFORMATION: As a part of patient counseling, healthcare providers must review the SAMSCA Medication Guide with every patient *[see FDA-Approved Medication Guide (17.3)]*.

Concomitant Medication: Advise patients to inform their physician if they are taking or plan to take any prescription or over-the-counter drugs since there is a potential for interactions.**Strong and Moderate CYP 3A inhibitors and P-gp inhibitors:** Advise patients to inform their physician if they use strong (e.g., ketoconazole, itraconazole, clarithromycin, telithromycin, nelfinavir, saquinavir, indinavir, ritonavir) or moderate CYP 3A inhibitors (e.g., aprepitant, erythromycin, diltiazem, verapamil, fluconazol) or P-gp inhibitors (e.g., cyclosporine) *[see Dosage and Administration (2.3), Contraindications (4.4), Warnings and Precautions (5.5) and Drug Interactions (7.1)]*.

Nursing: Advise patients not to breastfeed an infant if they are taking SAMSCA *[see Use In Specific Populations (8.3)]*.

For more information about SAMSCA, call 1-877-726-7220 or go to www.samsca.com.

Manufactured by Otsuka Pharmaceutical Co., Ltd., Tokyo, 101-8535 Japan

Distributed and marketed by Otsuka America Pharmaceutical, Inc., Rockville, MD 20850

SAMSCA is a registered trademark of Otsuka Pharmaceutical Co., Ltd., Tokyo, 101-8535 Japan

Otsuka

Otsuka America Pharmaceutical, Inc.

07US14L-0919B Rev. 02, 2014

ASN LEADING THE FIGHT AGAINST KIDNEY DISEASE

KidneyNews

ASN Kidney News is published by the American Society of Nephrology
1510 H Street NW, Suite 800, Washington, DC 20005. Phone: 202-640-4660

www.asn-online.org

Postmaster: Please send address changes to *ASN Kidney News*, c/o Customer Service, American Society of Nephrology 1510 H Street NW, Suite 800, Washington, DC 20005.

Publications mail agreement No. 40624074. Return undeliverable Canadian addresses to PO Box 503, RPO West Beaver Creek, Richmond Hill ON L4B 4R6

ASN Kidney News (ISSN print 1943-8044 and online 1943-8052) is an official publication of the American Society of Nephrology, 1510 H Street NW #800, Washington DC 20005, and is published monthly. Periodicals postage paid at Washington, DC and at additional mailing offices. Subscription rates: $12 per year. To order, please email bhenkel@asn-online.org. Subscription prices subject to change. Annual ASN membership dues include $12 for *ASN Kidney News* subscription.

ASN LEADING THE FIGHT AGAINST KIDNEY DISEASE

Corporate Supporters

The ASN Corporate Support Program recognizes supporters year round for their generous contributions to the Society. Through this program, supporters help ASN lead the fight against kidney disease. ASN gratefully acknowledges the following companies for their contributions in 2014.

Diamond Level

ALEXION

AMGEN

FRESENIUS MEDICAL CARE

KERYX BIOPHARMACEUTICALS, INC

Mallinckrodt Pharmaceuticals

Platinum Level

SANOFI RENAL

ASN Initiatives

Continued from page 1

Force included members from diverse geographic areas, programs, and educational roles (Table 1). The task force also surveyed training program directors and nephrology fellows.

The recommendations outlined below received the unanimous support of task force members, and were unanimously approved by the ASN Council.

Recommendation 1: ASN should continue its relationship with the National Resident Matching Program's (NRMP's) Specialties Match Service (SMS).

Task force discussions centered on the interests of applicants and the need to identify excellent candidates and ensure the best fit between programs and candidates. Members concluded that continued participation in the Match offers the best way to protect the rights of both the applicants and programs.

Recommendation 2: All Accreditation Council for Graduate Medical Education (ACGME)-accredited nephrology training programs should participate in the NRMP Match and offer all positions through the Match.

As the number of Nephrology fellowship applicants has declined, the number of Nephrology positions filled outside the Match has increased. This has created frustration among training program directors and undermined applicants' and program directors' trust in the Match. This also risks exacerbating declines in Match participation.

Task Force members recommended Nephrology adopt an "all-in" policy, *in which all accredited training programs participate and all positions must be filled in the NRMP Match*, concluding that this policy would best serve the fellowship applicants, training programs, and the discipline. The Task Force recommendation and resolution (www.asn-online.org/match) were unanimously approved by the ASN Council. NRMP will support ASN's policy, help monitor compliance, and apply sanctions in accordance with the NRMP Match Participation Agreement.

Recommendation 3: Nephrology programs should retain the ability to offer multiple tracks but offer only three options: "Clinical," "Research," and "Other."

Internal medicine specialties vary in use of program tracks in the Match. Discussions centered on which approaches are most supportive and least confusing for applicants and programs, and noted that programs can "revert" unfilled positions to be filled from their rank list for clinical tracks. The group unanimously recommended that diversity in program tracks should remain, but options reduced from four to three: "Clinical," "Research," and "Other," eliminating the "Basic" and "Clinical" research designations. The ASN Council also unanimously approved this recommendation.

Assessing Program Size

One of the most complex issues discussed centered on how individual programs and institutions determine the number of training slots. In future publications, ASN will address this challenge and provide self-assessment tools to help program leaders evaluate program size. During its retreat in May, the Nephrology Training Program Directors provided input regarding this challenge.

The Road Ahead

While outside the scope of this task force, broadening the appeal of nephrology is a priority for ASN: since 2010, the society has dedicated considerable resources to increasing interest in nephrology careers. The changes to the Match will help ensure that nephrology training programs continue to provide excellent candidates with high-quality educational experiences. The next generation of nephrologists must fuel advances to the complex and challenging care of patients with kidney disease.

To provide feedback or send questions about the Match, please write nephrologymatch@asn-online.org. More information on the Match is available at www.asn-online.org/match

Table 1. ASN Nephrology Match Task Force

Chair

Raymond C. Harris, MD, FASN
Ann and Roscoe Robinson Professor of Medicine
Chief, Division of Nephrology and Hypertension
Vanderbilt University School of Medicine

Members

Nancy Day Adams, MD
Professor of Medicine
Chief, Division of Nephrology
Nephrology Training Program Director
University of Connecticut School of Medicine

Sharon G. Adler, MD, FASN
Professor of Medicine
Associate Chief, Division of Nephrology
David Geffen School of Medicine
University of California at Los Angeles
Nephrology Training Program Director
Harbor UCLA Medical Center

Gregory L. Braden, MD
Professor of Medicine
Tufts University School of Medicine
Chief, Division of Nephrology
Nephrology Training Program Director
Baystate Medical Center

Gary V. Desir, MD
Professor of Medicine
Interim Chair, Department of Medicine
Yale University School of Medicine

Chi-yuan Hsu, MD
Professor of Medicine
Chief of Nephrology
University of California, San Francisco, School of Medicine

Mark D. Okusa, MD
John C. Buchanan Distinguished Professor of Medicine
Chief, Division of Nephrology
University of Virginia School of Medicine

Mark G. Parker, MD
Clinical Associate Professor
Tufts University School of Medicine
Director, Nephrology Division
Nephrology Training Program Director
Maine Medical Center

Mark E. Rosenberg, MD
Professor of Medicine and Vice Dean for Education
University of Minnesota School of Medicine

Michael J. Ross, MD, FASN
Associate Professor of Medicine
Nephrology Training Program Director
Icahn School of Medicine at Mt. Sinai
Chief of Nephrology, James J. Peters VA Medical Center

Rebecca J. Schmidt, DO, FASN
Professor of Medicine
Chief, Nephrology Section
West Virginia University School of Medicine

Paul G. Schmitz, MD
Professor of Internal Medicine
St. Louis University School of Medicine

Matthew A. Sparks, MD, FASN
Medical Instructor in the Department of Medicine
Duke University School of Medicine

Karen M. Warburton, MD
Associate Professor of Clinical Medicine
Perelman School of Medicine, University of Pennsylvania

Hormone and Bone Tests

Continued from page 1

artery calcification was lower in patients who reported exercising compared with those who did not, which is a novel finding in dialysis patients but in agreement with studies done in adults without CKD.

While these baseline findings are important for gaining a better understanding of the factors that contribute to the prevalence of coronary artery calcification in patients on dialysis, they don't necessarily help clinicians predict which patients will experience progression.

Dr. Malluche and his colleagues found that at 1 year, independent risk factors for progression of coronary artery calcification were age, baseline total or whole parathyroid hormone level greater than 9 times the normal value, and osteoporosis. Bone mineral density of the total hip, femoral neck, and spine was shown for the first time in dialysis patients to correlate with baseline coronary artery calcification as well as a diagnosis of osteoporosis by t scores.

"We discovered that high parathyroid hormone and the consequential bone loss are major risk factors for progression of vascular calcifications," Malluche said. "These two factors were heretofore not appreciated and were independent from traditional known risk factors." The researchers noted that patients who started and stayed within recommended parathyroid hormone ranges over the course of the study had the least progression of calcification.

The findings indicate that important information can be gained from monitoring parathyroid hormone levels and bone mass in patients on dialysis, to not only assess bone health but cardiovascular health as well. Additional controlled prospective studies are needed to evaluate the effects on coronary artery calcification of different therapies that are marketed to target osteoporosis or parathyroid hormone levels.

"This study adds a different perspective on mechanisms associated with vascular calcification in CKD that is different from the previously described associations of low bone turnover and low parathyroid hormone levels and increased risk of vascular disease in CKD," said Paul Miller, MD, who was not involved with the research and is a Distinguished Clinical Professor of Medicine at the University of Colorado Health Sciences Center and the Medical Director of the Colorado Center for Bone Research, in Lakewood.

Study co-authors include Gustav Blomquist, MD, Marie-Claude Monier-Faugere, MD, Thomas Cantor, and Daniel Davenport, PhD.

Disclosures: The authors reported no financial disclosures.

The article, entitled "High Parathyroid Hormone Level and Osteoporosis Predict Progression of Coronary Artery Calcification in Patients on Dialysis," is available at http://jasn.asnjournals.org/content/early/2015/04/01/ASN.2014070686.abstract.

Findings

High Rate of Repeat ED Visits for Kidney Stones

Eleven percent of patients seen in the emergency department (ED) for kidney stones make a repeat ED visit within 30 days, reports a study in *Academic Emergency Medicine*.

Using a California ED database, the researchers identified 128,564 patients with initial treat-and-release visits to EDs for kidney stones in 2008 to 2009. Of those, 13,684 patients made at least one additional ED visit for their kidney stones within 30 days: a rate of 11 percent. Repeat visits were more frequent for younger patients, for patients receiving Medicaid, and in rural areas with a lower workforce supply of urologists. The rates of repeat visits varied substantially among hospitals.

Twenty-nine percent of patients with repeat visits either were hospitalized or underwent an urgent procedure. These outcomes were more likely for patients aged 75 or older, odds ratio (OR) 3.90; for women, OR 1.82; and for patients living in areas with a higher supply of urologists, OR 1.77. Repeat visits were less likely for patients who had a white blood cell count at their initial ED visit, OR 0.86.

Kidney stones are a common reason for ED visits, and more than 90

percent of patients are treated and released. Preventing repeat visits is important to reduce the "excruciating pain" of kidney stones and to reduce health care costs.

The findings suggest that that one of nine patients makes a repeat ED visit for kidney stones. Close to one-third of these repeat visits result in hospitalization or an urgent procedure. Markers of access and quality of care may be useful targets for efforts to reduce high-cost, high-acuity repeat visits for kidney stones [Scales CD Jr., et al. Emergency department revisits for patients with kidney stones in California. *Acad Emerg Med* 2015; 22:468–474].

Urine Test for Early Detection of Renal Cell Carcinoma?

Measuring levels of two urine proteins may provide a noninvasive approach for early detection of renal cell carcinoma (RCC), reports a study in JAMA Oncology.

Urine specimens were obtained from a convenience sample of 720 patients undergoing abdominal computed tomography (CT) for various indications, and from 19 patients with pathologically confirmed RCC and 80 healthy control individuals. Two urine proteins—aquaporin-1 (AQP1) and perilpin-2 (PLIN2)—were evaluated as biomarkers of early RCC.

Continued on page 8

Findings

Urine Test

Continued from page 7

Previous studies showed that these proteins are elevated in patients with RCC but not in those with nonmalignant kidney disease. Renal masses and RCC were confirmed by CT scans and postnephrectomy examination, respectively.

The median urine AQP1 level was 225.0 ng/mg urine creatinine in patients with confirmed RCC versus 1.1 ng/mg in healthy control individuals. The values for PLIN2 were 37.8 versus 3.1 absorbance units/mg creatinine, respectively. In the screening population, the median AQP1 value was 0.5 ng/mg, and the median PLIN2 value was 0 absorbance units/mg.

For the two biomarkers alone or in combination, the area under the receiver operating characteristic curve was at least 0.990. Sensitivity was at least 95 percent and specificity at least 91 percent in comparison with control individuals and the screening population. Three patients in the screening population had biomarker levels suggesting RCC. All three had a renal mass shown by CT scan, and two had pathologically confirmed RCC.

The results validate the clinical utility of urine AQP1 and PLIN2 as biomarkers for early and noninvasive detection and screening for RCC. These proteins may also be useful for the differential diagnosis of renal masses seen on imaging studies [Morrissey JJ, et al. Evaluation of urine aquaporin-1 and perilipin-2 concentrations as biomarkers to screen for renal cell carcinoma: a prospective cohort study. *JAMA Oncol* Published online March 19, 2015. doi:10.1001/jamaoncol.2015.0213].

Continued on page 10

Introducing KSAP

The Kidney Self-Assessment Program (KSAP) is a new CME and Part 2 MOC product designed to help you review the essentials of nephrology. The program is composed of challenging, clinically-oriented questions that will refresh your understanding of the core elements of nephrology.

Based on the American Board of Internal Medicine (ABIM) nephrology examination blueprint, KSAP provides excellent preparation for fellows preparing for initial certification or practicing nephrologists preparing for recertification.

Refresh your nephrology knowledge and earn 25 Maintenance of Certification (MOC) points and 15 *AMA PRA Category 1 Credits*™.

Learn more and get started at www.asn-online.org/ksap

Education | The ASN Advantage
www.asn-online.org/ksap

ASN LEADING THE FIGHT AGAINST KIDNEY DISEASE

Findings

Spironolactone with TMP-SMX Linked to Sudden Death

Older adults taking spironolactone are at increased risk of sudden death after being prescribed trimethoprim-sulfamethoxazole (TMP-SMX), suggests a study in the *Canadian Medical Association Journal*.

Using Ontario health databases, the researchers identified about 207,000 older adults (66 or older) treated with spironolactone from 1994 through 2011. Of those, 11,968 died suddenly while taking spironolactone. A nested case-control analysis included 328 patients with sudden death within 14 days after being prescribed TMP-SMX or one of four other antibiotics: amoxicillin, ciprofloxacin, norfloxacin, or nitrofurantoin. Each patient was matched to as many as four control individuals. Associations between sudden death and exposure to each antibiotic were compared with amoxicillin, with adjustment for predictors of sudden death.

Most patients were aged 85 or older. The risk of sudden death for a person taking spironolactone was more than twice as high for patients taking TMP-SMX compared with amoxicillin: adjusted odds ratio (OR) 2.47. Ciprofloxacin and nitrofurantoin were also associated with an increased risk of sudden death: OR 1.55 and 1.70, respectively. On sensitivity analysis, the associations were weaker but still significant for TMP-SMX, OR 1.94, and ciprofloxacin, OR 1.40. In about 29,000 courses of TMP-SMX in patients receiving spironolactone, the rate of death within 14 days was 0.74 percent.

The results suggest a twofold increase in the risk of sudden death after prescriptions for TMP-SMX in older adults taking spironolactone. This risk likely reflects "terminal hyperkalemia" resulting from the known interaction between these two drugs. The study also notes a less pronounced but still significant interaction with ciprofloxacin [Antoniou T, et al. Trimethoprim-sulfamethoxazole and risk of sudden death among patients taking spironolactone. *CMAJ* 2015; 187:E138–E143].

High Mortality in Pediatric ESRD, but Lower with Transplantation

The 1-year mortality rates for children and adolescents with ESRD remain high but are substantially lower for patients receiving a kidney transplant compared with those who continue to receive dialysis, reports a study in the *American Journal of Nephrology*.

Using the US Renal Data System database, the researchers created annual cohorts of period-prevalent pediatric (younger than 19 years) ESRD patients from 1995 to 2010. The cohorts averaged about 1200 maintenance hemodialysis patients—60 percent using hemodialysis and 40 percent using peritoneal dialysis—and 1100 transplant recipients. Trends and patterns in 1-year mortality were assessed, including the effects of type of treatment and age group.

About half of the patients were aged 15 to 18, and 55 percent were male. Congenital, reflux, or obstructive causes of ESRD were present in 55 percent of patients and glomerulonephritis in 30 percent.

The unadjusted 1-year mortality per 100 patient-years was about 4.4 in dialysis patients, compared with 0.7 in transplant recipients. Except for a modest decline for peritoneal dialysis patients, the 1-year mortality rates did not consistently decline during the study period. On adjusted analysis, the odds of yearly survival were better for older patients, male patients, and those with glomerulonephritis as the cause of ESRD. Within yearly cohorts, race did not affect the odds of survival.

The 1-year mortality among children and adolescents with ESRD has not changed considerably since the 1990s. Mortality is about six times higher for dialysis patients than for transplant recipients. Efforts to reduce mortality from pediatric ESRD will require further improvement in dialysis procedures, early transplantation, and management of cardiovascular disease [Chavers BM, et al. One-year mortality rates in US children with end-stage renal disease *Am J Nephrol* 2015; 41:121–128].

Social Network Affects Diabetic Kidney Disease Risk

Lifestyle factors other than diet—including a high "social network score" (SNS)—are associated with a lower risk of chronic kidney disease (CKD) in patients with type 2 diabetes, reports a study in *Kidney International*.

The study included 6972 patients with type 2 diabetes but without macroalbuminuria, representing all such patients enrolled in the "Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial" (ONTARGET). During 5.5 years of follow-up, CKD progression was assessed in terms of more than a 5 percent annual decline in GFR, development of ESRD, microalbuminuria, or macroalbuminuria.

Various lifestyle and social factors were evaluated for association with CKD progression, including tobacco and alcohol use, physical activity, stress, financial worries, and the SNS as an indicator of the size of the social network. The analysis was adjusted for known risk factors and considered competing causes of death.

At follow-up, 31 percent of patients had incident or progressive CKD, and 15 percent had died. A higher SNS was independently associated with a lower risk of CKD and death: when the third tertile was compared with the first tertile of SNS, the odds ratios were 0.89 and 0.78, respectively.

Stress and financial worries were not related to CKD, but education was. The risk of CKD was lower for patients with moderate alcohol consumption and those with regular physical activity.

Information on modifiable risk factors is needed to lower the risk of progressive diabetic CKD, especially in the early stages. This study identifies lifestyle and social factors associated with a lower risk of CKD in high-risk diabetic patients—notably including a larger social network. This, along with physical activity and moderate alcohol intake, may be a useful target for disease prevention studies [Dunkler D, et al. Modifiable lifestyle and social factors affect chronic kidney disease in high-risk individuals with type 2 diabetes mellitus. *Kidney Int* 2015; 87:784–791].

Long-Term Allopurinol Improves CKD and Cardiovascular Outcomes

In patients with asymptomatic hyperuricemia, long-term treatment with allopurinol may slow the progression of chronic kidney disease (CKD) while reducing the risk of cardiovascular disease, reports the *American Journal of Kidney Diseases*.

In the original randomized trial, 113 patients with stable CKD were assigned to 2 years of allopurinol, 100 mg/day, or usual care. That study found a 47 percent reduction in progression of CKD in the allopurinol group, along with a decreased risk of cardiovascular events, reduced inflammatory markers, and fewer hospitalizations.

One hundred seven patients were followed up for as long as 5 additional years while they continued their assigned treatment. The rates of renal events (starting dialysis, doubling of serum creatinine, a 50 percent or greater reduction in estimated GFR, or a combination of these) and cardiovascular events were compared between groups.

During long-term follow-up, 12 of 56 patients in the treatment group stopped taking allopurinol, and 10 of 51 control individuals started allopurinol. At a total follow-up time of 84 months, renal events occurred in nine patients in the allopurinol group versus 24 in the control group.

The hazard ratio for renal events with allopurinol was 0.32, after adjustment for age, sex, baseline kidney function, uric acid level, and use of renin-angiotensin-aldosterone system blockers. The allopurinol group was also at lower risk of cardiovascular events: 16 versus 23 patients, adjusted hazard ratio 0.43.

The post hoc analysis suggests long-term benefits of allopurinol for patients with CKD. The results show reduced CKD progression along with lower cardiovascular risks for patients continuing allopurinol. The findings support large-scale controlled trials of uric acid–lowering therapy to prevent CKD progression [Goicoechea M, et al. Allopurinol and progression of CKD and cardiovascular events: long-term follow-up of a randomized clinical trial. *Am J Kidney Dis* 2015; 65:543–549].

KIDNEYWEEK 2015

San Diego, CA • Nov 3-8

Submit your abstract for ASN Kidney Week® 2015: The world's premier nephrology meeting

Kidney Week is the premier educational and scientific event in the nephrology community and offers you the opportunity to present your research to more than 13,000 nephrology professionals.

NEW FOR 2015

- Nonmembers can submit abstracts without ASN member sponsorship.
- ASN will accept an abstract submission if the abstract has been submitted for publication but not yet accepted for publication by June 3, 2015.
- The submission deadline is 2:00 p.m. EDT on June 3, 2015.

IMPORTANT DATES (2015)

ABSTRACTS

Wednesday, April 8
Abstract Submission Site Opens

Wednesday, June 3
Abstract Submission Site Closes
(2:00 p.m. EDT)

Wednesday, July 22
Late-Breaking Clinical Trial Submission Site Opens

Wednesday, September 23
Late-Breaking Clinical Trial Submission Site Closes
(2:00 p.m. EDT)

The full list of abstract categories and their descriptions are available at www.asn-online.org/kidneyweek.

Please note that ALL abstract authors (including co-authors) must have current disclosures on file with ASN at time of submission.

ASN LEADING THE FIGHT AGAINST KIDNEY DISEASE

Policy Update

ASN and AAKP Band Together for Kidney Health Advocacy Day 2015

By Grant Olan

On April 23, the ASN Public Policy Board and Board of Advisors joined patient advocates from the American Association of Kidney Patients (AAKP) for Kidney Health Advocacy Day 2015. Participants divided into teams of three or four and met with nearly 70 congressional offices to discuss two legislative priorities that would improve kidney care and patient health: 21st Century Cures and the Chronic Kidney Disease Improvement in Research and Treatment Act of 2015 (H.R.1130/S.598).

This marks the third consecutive year ASN and AAKP have partnered together for advocacy days. "When the world's largest professional kidney organization partners with America's oldest and largest kidney patient organization, Congress listens," AAKP President Paul T. Conway remarked. "ASN and AAKP appreciate the access congressional leaders and their staffs allow us as we promote legislation aimed at addressing gaps in chronic kidney disease research funding and barriers to kidney transplantation."

Chronic Kidney Disease Improvement in Research and Treatment Act of 2015 (H.R.1130/S.598)

Introduced in the House of Representatives by Rep. Tom Marino (R-PA)—a three-time kidney cancer survivor and co-chair of the Congressional Kidney Caucus—and Rep. John Lewis (D-GA), and in the Senate by U.S. Senators Ben Cardin (D-MD) and Mike Crapo (R-ID), ASN and AAKP highlighted the three sections of the Chronic Kidney Disease Improvement in Research and Treatment Act of 2015 (H.R.1130/S.598) calling for federal reports that would address key needs for patients with kidney disease.

1. Section 101: Identifying Gaps in Kidney Research

If passed by Congress, H.R.1130/S.598 would expedite a report Rep. Marino requested from the U.S. Government Accountability Office (GAO) in 2014 on the adequacy of federal investments in kidney research compared to federal expenditures for kidney care. This bill requires a report within one year after enactment.

An ASN analysis showed that the federal government invests less than 1% of what it spends on kidney care in kidney research. An analysis from an independent and respected body, such as the GAO, would provide validation and identify gaps in kidney research where additional investments could spur innovation and new therapies for improving patient care.

2. Section 103: Understanding the Progression of Kidney Disease and Treatment of Kidney Failure in Minority Populations

H.R.1130/S.598 would also require the Secretary of the U.S. Department of Health and Human Services (HHS) to submit a report to Congress—also within one year after enactment—on the social, behavioral, and biological factors leading to kidney disease; national efforts to slow the progression of kidney disease in minority populations disproportionately affected by such disease; and treatment patterns associated with providing care to minority populations disproportionately affected by kidney failure.

Why are African Americans more than three times as likely as Caucasians to develop kidney failure and up to 10 times as likely to develop kidney failure due to hypertension? Why are Hispanics and Native Americans nearly twice as likely as Caucasians to develop kidney failure? A HHS report would illuminate the legislative and regulatory steps needed to better understand and reduce disparities.

3. Section 104: Identifying Barriers or Payment Disincentives for Transplant and Posttransplant Care

The statistics are startling: in impoverished neighborhoods African Americans are 57% less likely to be waitlisted for a kidney transplant than their Caucasian counterparts and African Americans, Hispanics, and Native Americans wait approximately twice as long as Caucasians (commonly more than four years) to receive a kidney transplant.

H.R.1130/S.598 would require the Secretary of HHS—no later than two years after enactment—to submit a report to Congress on any disincentives in the Medicare payment systems that create barriers to kidney transplantation and posttransplant care for beneficiaries with kidney failure.

21st Century Cures

Launched in 2014 by House Commerce and Energy Committee (E&C) Representative Fred Upton (D-CO) and E&C Subcommittee on Oversight and Investigations Ranking Member Diana DeGette (D-CO), the goal of 21st Century Cures is to spur medical research and innovation. After nearly a year of hearings, the committee organized to gather feedback from the public and regulators. A draft bill was released earlier this year that includes three provisions ASN and AAKP advocated for that would benefit patients with kidney disease. The committee is in the process of drafting language for each of the provisions.

1. Patient-Focused Drug Development

This provision would help facilitate the inclusion of patient preferences in the regulatory process, which is an important goal that has been recognized by patients, the U.S. Food and Drug Administration, and other stakeholders. No one understands a particular condition or disease better than patients living with it. Meaningfully incorporating patient experience data into decision-making, such as patient assessments of desired benefits and tolerable risks associated with new treatments, is an important objective for increasing available therapies.

2. Expansion of Telehealth

Patients at every stage of kidney disease—from those with early-stage chronic kidney disease who may be at risk to progressing, to those who are on dialysis, to those who have received a kidney transplant or donated a kidney—would benefit from the expansion of telehealth opportunities that this provision seeks to facilitate. However, rigorous testing to evaluate whether telehealth services achieve their intended goals is imperative.

3. Supporting Young NIH Investigators

One of the biggest challenges to developing new cures is that young scientists have a hard time getting their research funded by the National Institutes of Health (NIH). That is especially troubling now that NIH's funding rate is at historic lows with only 1 in 6 grant applications funded. This provision would allow NIH to keep funding shifted from the agency's budget to benefit other HHS programs—which added up to $700 million in 2013—and reserve it for researchers applying for their first or second grant.

"ASN is pleased to again partner with AAKP to amplify the voices of patients with kidney disease, one of the most vulnerable patient populations," said ASN President Jonathan Himmelfarb, MD, FASN. "We urge Congress to pass the Chronic Kidney Disease Improvement in Research and Treatment Act of 2015 (H.R.1130/S.598) and to support the 21st Century Cures initiative, which would advance research, improve treatment, and save lives."

Join ASN and AAKP in promoting H.R.1130 and S.598 by visiting ASN's Legislative Action Center at http://www.asn-online.org/policy/ and sending your members of Congress a pre-composed message telling them how important this bill is for patients with kidney disease.

Rare Bipartisan Effort Finally Repeals Flawed Medicare Payment System

In an historic, overwhelmingly bipartisan vote on April 14, 2015, the U.S. Senate passed legislation to permanently replace the flawed Sustainable Growth Rate (SGR) system. President Obama signed the bill—H.R. 2, the Medicare Access and CHIP Reauthorization Act of 2015—into law shortly thereafter, ending years of uncertainty for physicians and patients participating in the Medicare system and finally putting this longstanding legislative goal to rest.

As Rep. Michael Burgess, MD, (R-TX) reflected "I've worked to resolve this issue my entire congressional career, and I extend my deepest thanks to everyone who played a part in making the burdensome SGR formula a relic of the past. May we never speak of it again."

The new law calls for an annual 0.5% update to physician payments for the next five years, combines three existing quality programs (the Physician Quality Reporting System [PQRS], Meaningful Use, and Value-Based Purchasing) into one program, and incentivizes the use of Alternative Payment Models. ASN will work closely with the Centers for Medicare & Medicaid Services (CMS) to advocate on behalf of nephrologists and the patients they serve as the agency begins to roll out these and other components of the new law.

Repealing and replacing the SGR formula has been a top public policy priority of ASN for years, so passage of H.R. 2 marks a long-anticipated advocacy victory for the society. ASN worked closely with the Senate Finance Committee and the House Ways and Means and Energy and Commerce committees in shaping the H.R. 2 package, as well as in collaboration with a united physician advocacy community led by the American College of Physicians and the American Medical Association.

Congress tried for years to repeal the SGR, which was widely acknowledged as a broken and unsustainable formula. But it had been unable to do away with the formula wholesale and instead each year passed temporary legisla-

tion postponing reductions to physician payments that the SGR formula called for. Both parties in the House and Senate were in agreement regarding the fundamental policy changes needed to the SGR owing to legislation drafted by the previous Congress (which failed to pass due to disagreements regarding how to pay for the cost of the bill).

So, what changed this spring? Because much of the "heavy lifting" in terms of policy was already complete when Congress reconvened in January 2015, the only remaining barrier was the cost. Conventional wisdom used to be that Congress had to come up with a way to pay for the cost of replacing SGR. Replacing SGR was a very big ticket item, and lawmakers had long been stymied as to where the money should come from.

Then in March, House Speaker John Boehner (R-OH) and House Minority Leader Nancy Pelosi (D-CA) began to suggest that Congress should consider passing a bill to replace SGR that wasn't totally "paid for" through cuts or spending reductions elsewhere. Among other reasons, Congress had spent more money and time on temporary postponements to SGR over the years than they would spend on just repealing the law itself. Building on Reps. Boehner's and Pelosi's leadership and with unified urging from the physician community, the chairs and ranking members of all three Medicare authorizing committees as well as Senate Majority and Minority leaders rallied to support this concept.

Although the legislation was in the end a rare moment of bipartisan collaboration, passage was not at all certain in the days and weeks leading up to the Senate vote. The Senate left for a two-week recess shortly after the House sent H.R. 2 over for consideration, leaving it with just two days to take action until Medicare would—as instructed by the SGR formula—cut physician payments by nearly 25%. Liberals in the Senate raised concerns about entitlement reforms included in H.R. 2, such as higher Medicare premiums for wealthier Americans, while fiscal conservatives in the Senate vociferously opposed passing a bill without offsets to cover the entire cost. Ultimately, the bill passed 92-8, a remarkable vote in a polarized Washington.

While repealing the SGR formula was an historic advocacy victory, considerable work remains to implement the law, which like every new law will bring its own benefits and challenges. Stay tuned to *ASN Kidney News* to learn more as CMS begins to roll our components of the new law.

Research Reveals How Heme Oxygenase-1 Directs the Immune Response after Acute Kidney Injury

New research indicates that an enzyme known to be important in the body's response to kidney injury exerts its protective effects in part by affecting the myeloid cells of the immune system. The findings, which are published in the *Journal of the American Society of Nephrology*, may lead to new kidney-protective treatments.

Heme oxygenase-1 (HO-1) is a cytoprotective enzyme that regulates the inflammatory response to tissue injury by converting highly reactive free heme molecules into carbon monoxide, iron, and biliverdin. People with HO-1 deficiency often experience severe hemolysis, dysregulated inflammation, kidney abnormalities, and premature death.

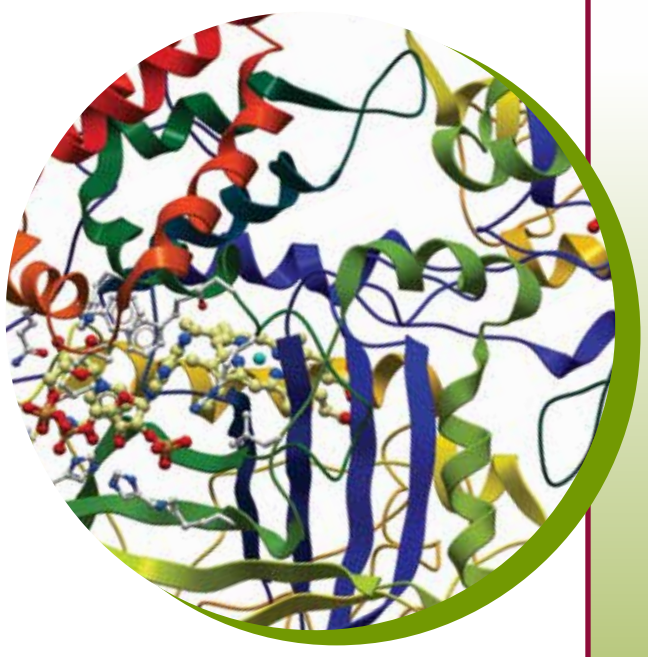
In an effort to uncover the effects of HO-1 after acute kidney injury (AKI), a team of researchers led by Anupam Agarwal, MD, of the University of Alabama at Birmingham, studied mice lacking expression of HO-1 systemically or in certain immune cells.

In age-matched male wild-type and HO-1–knockout mice that underwent bilateral renal ischemia for 10 minutes, ischemia-reperfusion injury resulted in significantly worse renal structure and function and increased mortality in the knockout mice. In addition, there were more macrophages and neutrophils in the knockout mice's kidneys after ischemia-reperfusion but a significant decrease in the population of intrarenal resident dendritic cells. Immunofluorescence experiments revealed increased migration of the resident dendritic cell population from the kidneys to the peripheral lymphoid organs in knockout mice compared with wild-type mice. This effect on renal dendritic cell migration was corroborated in myeloid-specific HO-1 knockout mice subjected to bilateral ischemia. These mice also evidenced impaired kidney recovery and increased fibrosis after injury.

"We utilized HO-1 transgenic mice and cell tracking experiments to demonstrate that HO-1 expression within renal cells is important to protect in the early period after injury, while myeloid expression of HO-1 regulates how these cells traffic throughout the body after injury," said Agarwal.

David Ferenbach, MD, PhD, who was not involved in the study and is a clinical fellow at the University of Edinburgh, noted that an accumulating field of evidence now points to the role of HO-1 as an important protector against AKI and that these latest results offer valuable new information. "Whilst not the headlined finding of the paper, important new data is shown that demonstrates that in animals with a targeted deletion of HO-1 in only myeloid cells, there is still worsened later injury and increased subsequent fibrosis compared to controls," he said. "This validates earlier studies suggesting that despite the widespread tubular induction of HO-1 in response to drugs, the renal macrophage/dendritic cell may be the key cell population mediating the protective effects of HO-1 expression."

Ferenbach noted that some evidence shows that aged mice have reduced levels of HO-1 in kidney cells and an increased susceptibility to renal injury. "It would be very useful to explore in human samples whether there are similar situations where HO-1 levels may fall, and whether these produce injury and scarring problems analogous to those seen in this paper," he said.



If the study's findings are validated in humans, HO-1 could be an important target in preventing the transition of AKI to chronic kidney disease, said Agarwal. HO-1–based treatments may also have broader clinical applications, although it is important to consider that HO-1 can have disparate functions in different cell types.

"Given the human relevance of HO-1 in AKI and the growing understanding of the myeloid cells in renal health and disease, these studies… provide the foundation for a whole new area of AKI research," noted Gilbert Kinsey, PharmD, PhD, of the University of Virginia, in an accompanying editorial.

Industry Spotlight

Ups and Downs in Clinical Trial Results

Several kidney-related drug trials have recently yielded results. ProMetic Life Sciences (Laval, Quebec), announced that it had successfully completed its phase 1b clinical trial of PBI-4050 in patients with chronic kidney disease (CKD).

The randomized double-blind, placebo-controlled, multidose trial was designed to demonstrate the safety and tolerability of PBI-4050, an orally active antifibrotic drug candidate. The trial also determined the pharmacokinetic profile of PBI-4050 while monitoring multiple oral doses during 10 days in patients with stage 3b or 4 stable renal impairment. The trial was performed in a group of eight patients: six patients received PBI-4050, and two received a placebo.

"We are pleased to see that the safety and pharmacokinetic profiles of our lead drug candidate remain unaffected by the severely impaired renal function in the patients tested," said chief medical officer John Moran. "Since fibrosis is the pathological pathway leading to organ failure and death in many diseases of differing etiologies … we plan to test the efficacy of this drug in several fibrosis-related conditions." Phase II trials in patients with metabolic syndrome and resulting in type 2 diabetes were expected to begin patient enrollment in April 2015.

Pharmalink AB, a specialty pharmaceutical company based in Sweden, has announced that a phase 2b trial of Nefecon for the treatment of primary IgA nephropathy has met its primary efficacy endpoint at a planned interim analysis. The trial was stopped early with respect to statistical analysis of the endpoint.

The randomized double-blind, placebo-controlled clinical trial assessed the safety and efficacy of two different doses of Nefecon, a new oral modified-release capsule of the corticosteroid budesonide. The corticosteroid was administered daily during a 9-month treatment period to patients with primary IgA nephropathy having persistent proteinuria despite optimized standard-of-care therapy. The trial was conducted in 62 centers in 10 European countries and was originally intended to recruit 90 patients, but 150 eventually were included.

Bengt Fellström, MD, PhD, professor of nephrology at Uppsala University Hospital, and principal investigator of the Nefecon trial, said, "IgA nephropathy is the most common inflammatory renal disease and in real need of new treatment options. Existing options are insufficient to prevent a significant proportion of patients from progressing to renal failure, with a devastating impact on patients' quality of life."

Zacks Equity reported the results of a phase 2a trial that failed to meet its primary endpoint of progression-free survival in patients with advanced renal cell carcinoma. Shares of Lpath, based in San Diego, "plunged in after-market trading" after the company's announcement of results from a phase 2a study of oncology candidate Asonep, Zacks wrote. The company will decide on the future of the candidate upon completion of the renal cell carcinoma trial.

Industry Spotlight

Hydra Biosciences Teams with Boehringer for Renal Research

Hydra Biosciences, Inc., a leader in the field of transient receptor potential channel modulation, and Boehringer Ingelheim announced that they have entered into a worldwide research collaboration and license agreement to identify small-molecule transient receptor potential inhibitors, to focus on renal disease treatments.

Hydra Biosciences, a biopharmaceutical company based in Cambridge, MA, develops drugs to treat several conditions involving ion channels.

Hydra's high-throughput screening platforms and integrated pharmacology and chemistry infrastructure allow the company to identify and develop drug candidates that address unmet medical needs.

"This partnership between Boehringer Ingelheim and Hydra Biosciences provides an excellent opportunity to maximize the potential of novel targets that may offer meaningful improvements in the treatment of chronic kidney diseases and other related diseases and disorders," said Russell Herndon, president and CEO of Hydra Biosciences.

"Renal diseases and disorders are of increasing importance to Boehringer Ingelheim as part of our CardioMetabolic Diseases Research area, and our dedicated renal disease research unit based in Ridgefield, CT, is constantly expanding its network of partnerships in this field," said Michel Pairet, senior corporate vice president of research and nonclinical development at Boehringer Ingelheim. "This new collaboration agreement with Hydra Biosciences reflects the importance and value Boehringer Ingelheim places in developing strong research partnerships to discover new treatments for renal diseases and related disorders."

The companies' researchers will work together to identify and advance candidate inhibitors. Boehringer Ingelheim is responsible for the global development and commercialization of the inhibitors that come from the collaboration. Hydra will receive an undisclosed upfront payment and is eligible to receive milestone payments and tiered royalty payments based on future product sales.

Detective Nephron

Detective Nephron, world-renowned for his expert analytic skills, trains budding physician-detectives in the diagnosis and treatment of kidney diseases. L.O. Henle, a budding nephrologist, presents a new case to the master consultant.

Nephron My apprentice, what do you have for me?

Henle No medical student or resident today. Not many are taking electives these days.

Nephron *(smiling)*: Time will come, my dear apprentice, when nephrology will be sought after. Don't give up your hopes. Keep doing what you love. After all, we want nephrologists who enjoy what they do!

Henle Glad to be on board. I am getting involved in the nephrology online journal club these days—nephJC.com—and it's been a fruitful experience.

Nephron *(interrupting)*: Social media—forget that! Let's get to the case!

Henle We have a case of hypophosphatemia.

Nephron Oh, come on! Is that real? Likely severe malnourishment…replete the patient intravenously and by mouth, and call it a day.

Henle *(with a smile)*: She is a 55-year-old woman who had been doing well until 3 months ago, when she had abdominal distention and pain. She had been eating well until just 1 week ago, when she noticed fatigue and worsening distention and was admitted. She has ovarian cancer according to the primary team.

Nephron *(angrily)*: Too much information. I am more concerned about what her urine looks like.

Henle Well, let's make it simple. Hypophosphatemia usually happens in three ways—increased urinary excretion or decreased intestinal absorption or a cellular shift.

Nephron Ahh! That is a simplistic look. I like things simple and not too complex. I don't want to confuse medical students these days! Nephrology can be made very simple if taught properly.

Henle Shifts are less likely here. I understand that refeeding is a possibility, but she was eating well until about a week ago, so that's less likely in this case. Other causes could be insulin secretion, but her blood glucose levels have been normal and not low. Last, another cause of shifts could be hungry bone syndrome, which is not possible because she has not had any recent parathyroid surgery, and no such findings are on my history or physical examination. No acute respiratory alkalosis either; that could cause a shift.

Nephron *(getting bored)*: Good work. So is this an intestinal problem or a kidney problem?

Henle Well, the urinary phosphorus is very high, and the fractional excretion of phosphate is 30 percent. I don't think the kidney is doing the right thing here. In the setting of low serum phosphorus, the kidney should be retaining phosphorus and not wasting it. The fractional excretion of phosphate should be less than 5 percent. I think this is renal phosphate wasting.

Nephron *(happy)*: Ahh! Now that is interesting! Are you sure that there is no vitamin D deficiency or diarrhea or intake of any binders that the patient might be taking, such as niacin, aluminum, antacids?

Henle Yes, we checked for all those, and she is not taking any such medications.

Nephron Good work, my apprentice. How do we want to investigate this phosphate wasting problem?

Henle The problem is related to the kidneys, so it's either a hormonal problem or a direct tubular defect. Let me start with the tubular defects first. They could be defects leading to solitary hypophosphaturia from drugs, or a Fanconi syndrome from… hmmm, she is not using anything specifically that could cause that…she hasn't received any chemotherapy yet, or any antibiotics that could cause that.

Nephron *(chewing)*: Want some cashews or almonds?

Henle No, thanks.

Pause.

Henle Well, there are no signs of a complete Fanconi syndrome—no glucosuria, uricosuria, hypokalemia, or any combination of those. In addition, her serum free light chains are normal, ruling out a paraprotein-mediated disease. I doubt she would have two malignancies at the same time.

Nephron Good work, my friend. Let's move on to the hormones. What hormones are we planning to discuss here?

Henle Two that are commonly associated with this entity are parathyroid (PTH) hormone and vitamin D. If this was primary hyperparathyroidism, there would be hypercalcemia and an elevated PTH level as well. She did have slightly elevated calcium, but her PTH level was in the low to normal range. Could she have secondary hyperparathyroidism? That's less likely because her renal function is normal, and her calcium is not low.

Nephron Good thus far.

Henle Yes, I know. In addition, she had a low 1,25-OH vitamin D3, moderately low to normal 25-OH vitamin D3, and normal PTHrP (parathyroid hormone-related protein) as well. But clearly, she doesn't have a profound vitamin D deficiency.

Nephron What happens in the kidney with vitamin D?

Henle Well, if the kidney is working well, the 25-OH vitamin D3 should get converted to 1,25-OH vitamin D3, and the levels should be relatively good. Hmm, so why is her 1,25-OH vitamin D3 low? I thought hypophosphatemia results in stimulation of calcitriol levels, which would tend to raise the serum phosphate by increasing intestinal phosphate absorption and perhaps by bone resorption.

Nephron Good question, Henle. Why?

Pause.

Nephron Want to eat some tofu?

Henle *(surprised)*: No, sir. What's with the food today? No coffee...let's get back to the case.

Nephron So, my dear apprentice, where do we stand now? You have hypophosphatemia, low 1,25 vitamin D level, low normal PTH level, and normal renal function. Is this still a urinary loss of phosphorus?

Henle Yes. I think so. I think we might have another hormone that might be involved here: fibroblast growth factor (FGF-23). It's a phosphaturic hormone, and perhaps this patient has an elevated FGF-23 level.

Nephron Good work, Henle. Why don't we get a serum FGF-23 level and rule it out? Meanwhile, make sure you are replenishing the phosphorus with aggressive measures to keep this patient from being symptomatic.

Henle exits, and Nephron decides to have a cola drink today instead of his usual coffee.

Nephron Nothing better than a nice jolt of phosphorus.

Three days later, Henle enters with a smile.

Nephron So, what do we have, sir?

Henle A strikingly elevated FGF-23 level was noted.

Nephron *(shocked)*: Henle, how do you explain the low 1,25 vitamin D in this instance?

Henle FGF-23 is an important hormone that is synthesized by osteocytes and osteoblasts. I believe that FGF-23 has one major function—to get that phosphorus out of the body. Hence, it will do anything in its power to increase excretion and decrease absorption. It is still an enigma as to how FGF-23 downregulates renal phosphate reabsorption, but it likely happens in the proximal tubule. FGF-23 also indirectly decreases the intestinal absorption of phosphate. In addition, it also decreases intestinal sodium phosphate transporters. But it also inhibits calcitriol synthesis in the kidney and stimulates the catabolism of active vitamin D sterols, so it will lower the 1,25 vitamin D levels in this case.

Nephron Very likely explanation. So that could explain the phosphaturia. The low 1,25 vitamin D with normal renal function might have been the clue in her case that FGF-23 was the real culprit. Good work. But why does she have elevated FGF-23?

Henle There are many possible causes of an elevated FGF-23 level. Given that her renal function is normal, the excretion of FGF-23 is not affected. In chronic kidney diseases, FGF-23 concentrations increase as GFR declines. In addition, a high-phosphate diet can induce a high FGF-23 state, but clearly that is not happening here. So that leaves me with causes of elevations in FGF-23 that are due to increased production. An active primary production of this hormone seems to be happening in her body. Intravenous iron use can cause it, but she never received that. Other genetic causes such as hypophosphatemic rickets are less likely. I think this is a paraneoplastic FGF-23 production from the ovarian cancer.

Nephron That is a nice chain of thought, Henle. What you are referring to is tumor-induced osteomalacia, a rare paraneoplastic syndrome characterized by elevated phosphatonins (FGF-23), renal phosphate wasting, and abnormal vitamin D metabolism, usually seen in benign mesenchymal tumors and head and neck cancers. To me, perhaps any cancer can cause it. Interestingly, although serum FGF-23 concentrations are also elevated in patients with advanced-stage ovarian cancer, low serum phosphorus is not usually observed. But it looks as if this did occur in your case. Fascinating! Please treat her cancer because that might improve her electrolyte disorder.

Henle Yes, sir!

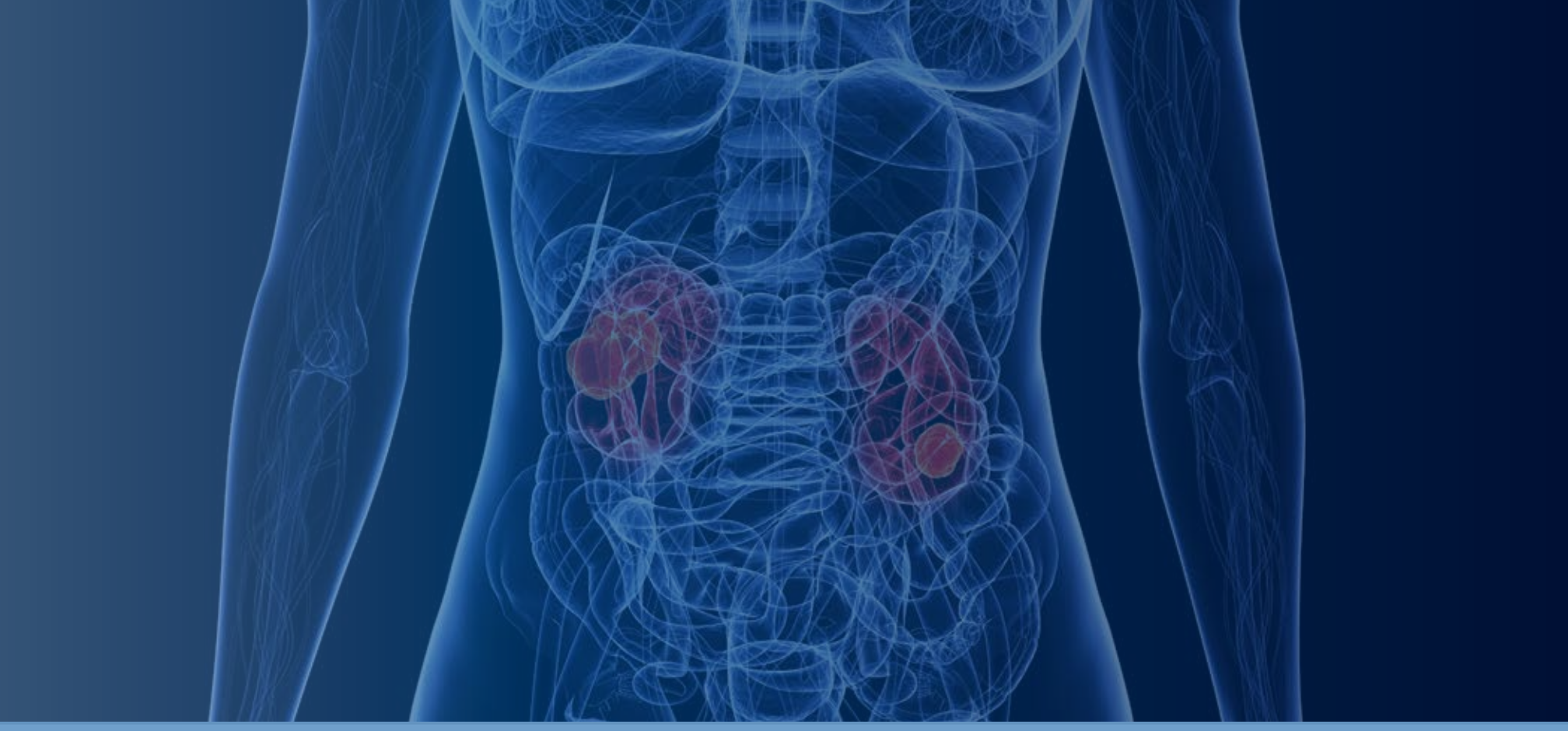
Three days later, Henle enters.

Nephron How did she respond to chemotherapy?

Henle Imaging confirmed metastatic ovarian malignancy, and the patient elected for hospice care. Despite repletion with high doses of intravenous and oral phosphate and vitamin D, normalizing her phosphate was challenging because her underlying malignancy was progressive and untreated: unfortunately, not an ending we were hoping for.

Nephron My dear apprentice, you did what you could. I understand her choices, and we must respect that. Henle, you have stumped me this time with a great case of an electrolyte abnormality that was a paraneoplastic syndrome associated with metastatic cancer. Again, nephrologists can always be amazing detectives. Let's go have some New York–style pizza. I feel like having a high-phosphorus diet today.

Detective Nephron was developed by Kenar Jhaveri, MD, associate professor of medicine at Hofstra North Shore LIJ School of Medicine. Thanks to Dr. Rimda Wanchoo, assistant professor of medicine at Hofstra North Shore LIJ School of Medicine, for her editorial assistance.



ASN Board Review Course & Update

July 25–31, 2015 | Chicago, IL
Fairmont Chicago, Millennium Park

Registration now open

Face the boards with *confidence*

Maximize your readiness for the ABIM nephrology examination.

ASN's Board Review Course & Update is designed for fellows and practicing physicians preparing for certification or recertification in nephrology. Each topic and its time allocation are patterned after the ABIM nephrology examination, giving you the most efficient preparation. Lectures, interactive case discussions, and panel Q&A sessions contribute to ASN's unparalleled review course.

Earn CME credits.

ASN designates this live activity for a maximum of 69 *AMA PRA Category 1 Credits*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

The best choice for your board preparation.

- Free post-course access to BRCU Online
- 270 practice exam questions
- Exam-focused curricula
- Renowned expert faculty
- Comprehensive syllabus with lecture outlines, explanatory text, and key slides

Learn more and register at www.asn-online.org/brcu.

Education | The ASN Advantage
www.asn-online.org/brcu

ASN LEADING THE FIGHT AGAINST KIDNEY DISEASE

Classified Ads

Kidney News
Classified Advertising Information

Classified space is for advertising positions available, open faculty positions, course announcements, seminars, meetings and educational courses.

Display Advertising Rates

Ad Size	1x	3x
Full Page	**$2,525**	**$2,345**
1/2 Page	$1,665	$1,485
1/3 Page	**$1,435**	**$1,375**
1/4 Page	$1,205	$1,090
1/6 Page	**$1,035**	**$1,025**

Line Advertising Rates

Please contact for rate information

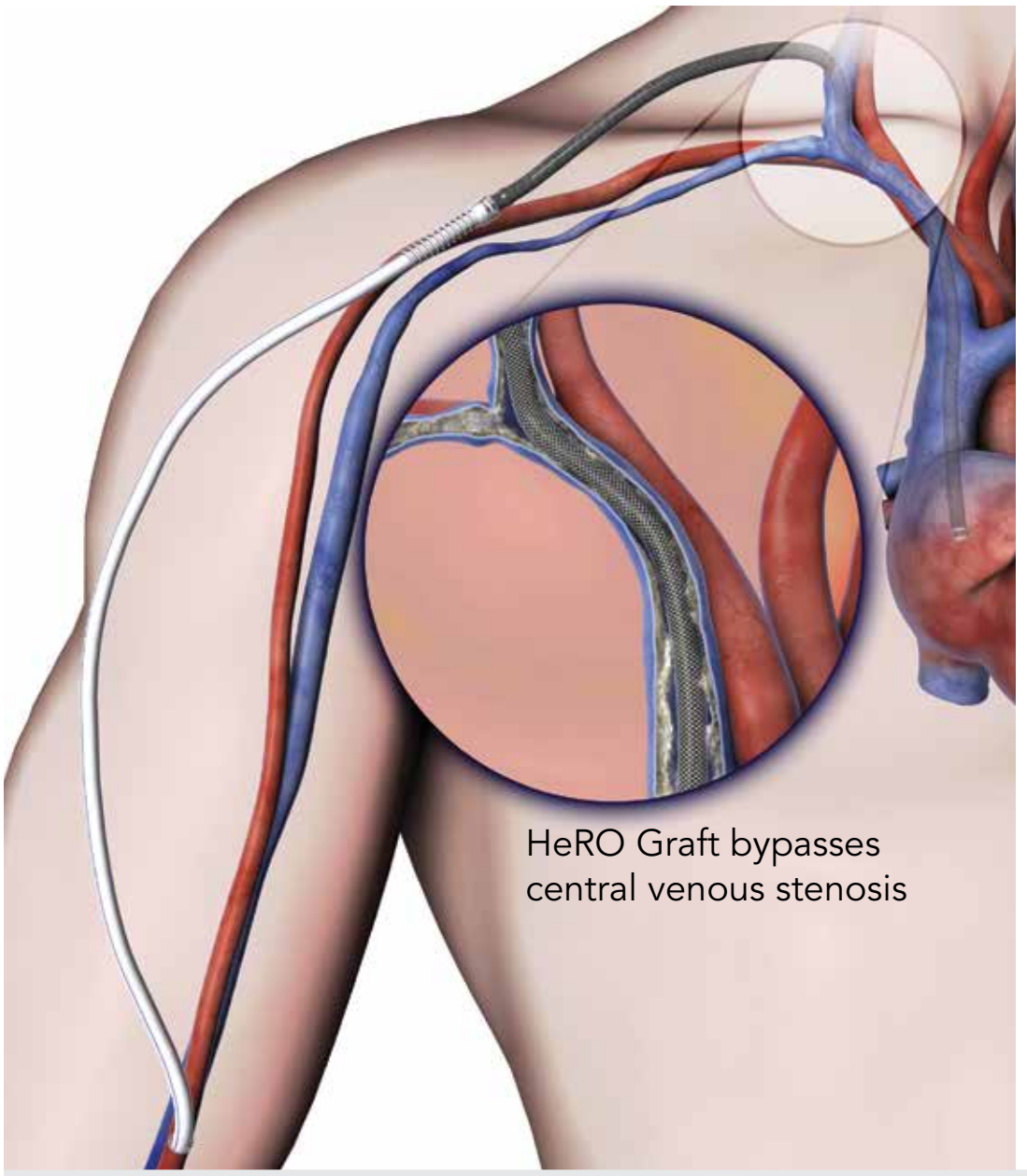
Closing Date & Cancellations:

Copy must be received four weeks in advance of the month in which the ad is to appear. Cancellation requests must be made in written form by fax, e-mail or postal mail and will be honored for the earliest applicable issue.

All Ads Must be Prepaid

Contact:
Rhonda Truitt
rhonda.truitt@wt-group.com
P: 443-512-8899 x. 106 F: 443-512-8909

Index to Advertisers



HeRO Graft bypasses central venous stenosis

HeRO (Hemodialysis Reliable OutFlow) Graft is the **ONLY** fully subcutaneous AV access solution clinically proven to maintain long-term access for hemodialysis patients with **central venous stenosis.**

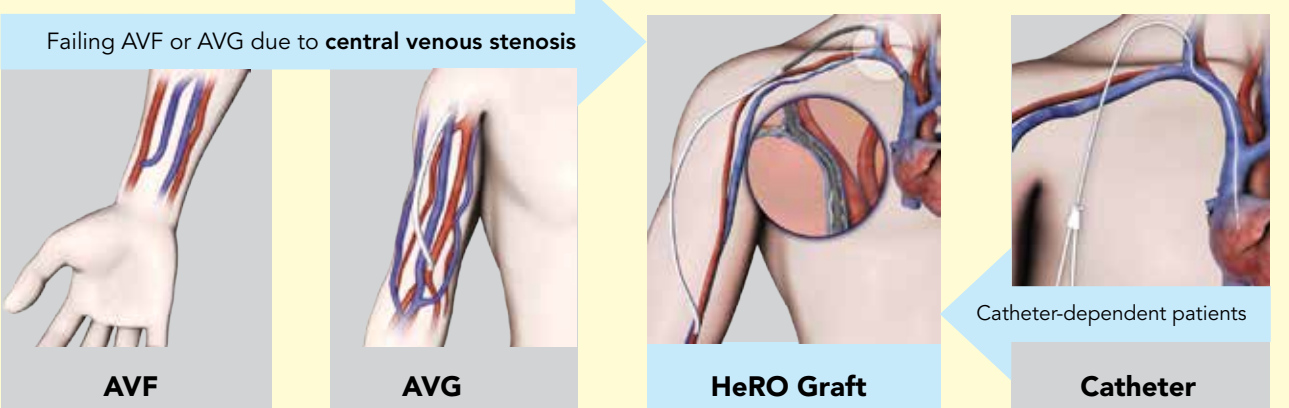
- **Fewer Infections:** 69% reduced infection rate compared with catheters[1]
- **Superior Dialysis Adequacy:** 1.7 Kt/V, a 16% to 32% improvement compared with catheters[1]
- **High Patency Rates:** Up to 87% cumulative patency at 2 years[1, 2]
- **Cost Savings:** A 23% average savings per year compared with catheters[3]

Reducing Catheter Dependency

HeRO Graft Candidates

- Catheter-dependent or approaching catheter-dependency
- Failing AVF or AVG due to central venous stenosis

Treatment Algorithm



Learn more at **www.herograft.com**
Order at: **888.427.9654**

References:
1) Katzman et al., J Vasc Surg 2009. 2) Gage et al., EJVES 2012. 3) Dageforde et al., JSR 2012.

Indications for Use: The HeRO Graft is indicated for end stage renal disease patients on hemodialysis who have exhausted all other access options. See Instructions for Use for full indication, contraindication and caution statements. Rx only.

HeRO Graft is classified by the FDA as a vascular graft prosthesis.

1. Download the App
2. Scan the code with your mobile device to watch video

Get the free mobile app at
http://gettag.mobi

1655 Roberts Boulevard, NW • Kennesaw, Georgia 30144 • Phone (888) 427-9654 • (770) 419-3355

CryoLife®
Life Restoring Technologies®